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A concise total synthesis of arizonins B1 and C1

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ABSTRACT

A concise and efficient total synthesis of arizonins B1 and C1 is reported. A key building block alkyne is synthesized from D-glucono-δ-lactone and used in the Dötz benzannulation reaction to construct the naphthalene unit. An oxa-Pictet–Spengler reaction gave the pyran ring while an H_2SO_4 mediated isomerization set the correct stereochemistry of the target molecules. Alternatively, a direct *anti*-pyran stereochemistry was prepared in a TFA solvent. The synthesis is competitive to previous reports and marks the first enantioselective synthesis of arizonin B1.

1. Introduction

Hochlowski et al.[1] isolated six new anti-Gram-positive antibiotics from the fermentation broth of *Actinoplanes arizonaensis* sp. nov. strain AB660D-122. These are known as arizonins A1, A2, B1, B2, C1, and C3 **1**–**6** (Fig. 1). Their structures were elucidated by spectroscopic and analytical techniques including the X-ray studies of arizonin A1 **3**. The absolute stereochemistry for arizonin B1 **1** was ascertained by comparing the ORD curves with that of nanaomycin D **7** and kalafungin **8** (Fig. 1).[2] Based on this study and a comparison of spectroscopic data, the stereochemistry of other members was determined.[1] Karwowski et al.[3] carried out bioactivity studies of the above strain of antibiotics and found arizonins A1 and B1 to exhibit moderate to potent in vitro antimicrobial activity against Gram-positive bacteria. The first synthetic attempt to prepare these molecules was by Brimble et al.[4a] who reported on a racemic synthesis of 5-*epi*-arizonin B1 and 5-*epi*-arizonin C1 involving a furo-furan to furo-pyran rearrangement. Later the same group reported[4b] on the racemic synthesis of arizonin C1 **2** involving an earlier strategy and a late stage BBr_3 mediated C-5 epimerization. However, this led to the complete demethylation of the C-7,8 methoxy groups. Remethylation completed the synthesis of (±)-arizonin C1. Recently, Brückner et al.[5] reported on the first enantioselective synthesis of (−)-arizonin C1 **2** by employing a Dötz benzannulation and asymmetric dihydroxylation. As part of our research program involving the stereoselective synthesis of various pyranonaphthoquinones and related molecules,[6] we herein report a concise enantioselective total synthesis of arizonins B1 **1** and C1 **2**. Our strategy relies on the synthesis of a key building block alkyne from a chiral pool material (D-glucono-δ-lactone),

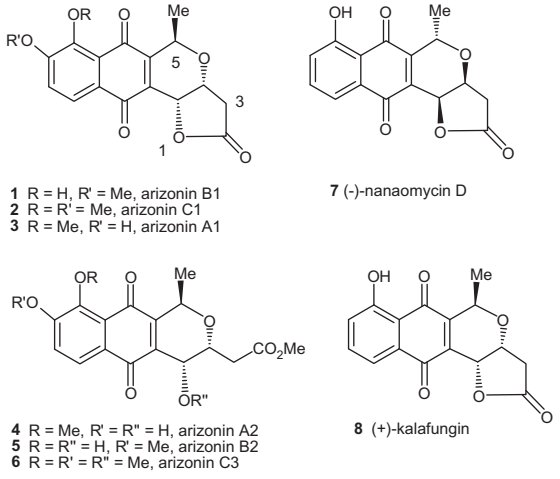

Figure 1. Structures of arizonins **1**–**6** and related molecules.

Dötz benzannulation, oxa-Pictet–Spengler reaction, and H_2SO_4 mediated epimerization/demethylation.

2. Results and discussion

Our retrosynthetic approach to arizonins B1 **1** and C1 **2** is shown in Scheme 1. The key building block alkyne **11** could be derived from the chiral pool material D-glucono-δ-lactone **13** through the intermediate diol **12** by the usual functional group manipulations.[6j] The Dötz benzannulation of Fischer carbene **10** with alkyne **11** would produce the naphthalene unit of **9** with the β-hydroxy-γ-lactone moiety installed. The oxa-Pictet–Spengler reaction of **9** would install the pyran ring of the target molecules.

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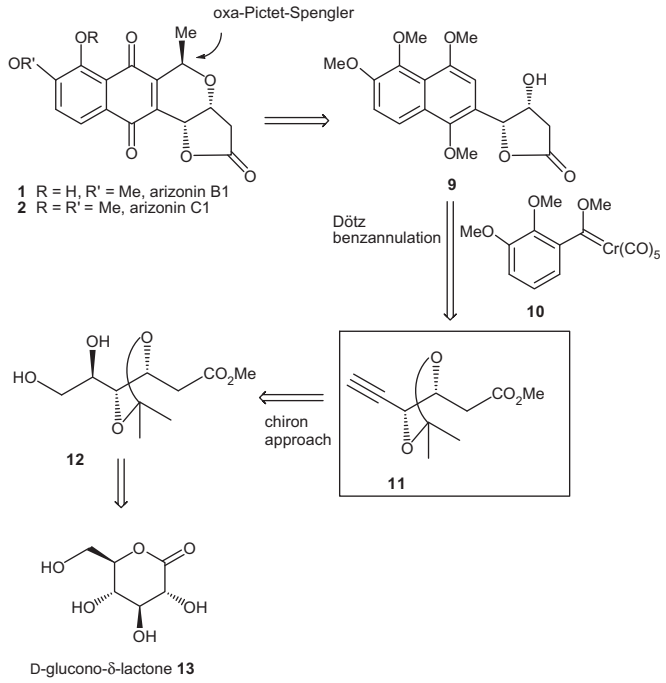
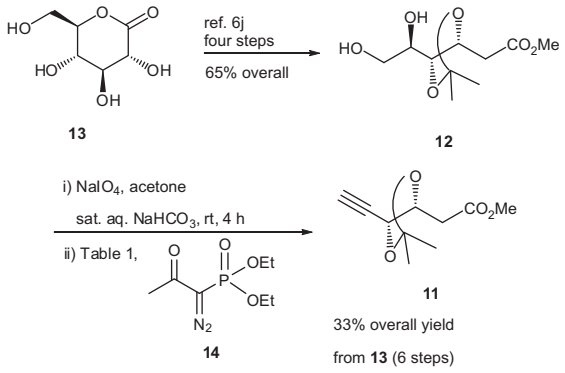


Scheme 1. Retrosynthesis of arizonins B1 **1** and C1 **2**.

The key building block alkyne **11** for the anticipated Dötz benzannulation was synthesized from chiral pool material D-glucono-δ-lactone **13** as shown in Scheme 2. Compound **13** was processed through four steps to give diol **12** (overall 65% yield).[6j] For the installation of the desired alkyne moiety, the well known Corey–Fuchs[7] procedure resulted in the decomposition of the aldehyde derived from the cleavage of diol **12**. Hence we opted for an alternative procedure using the Bestmann–Ohira reagent **14**.[8] The optimization of this reaction [6j] is given in Table 1.



Scheme 2. Synthesis of alkyne **11**.

The cleavage of diol **12** to the corresponding aldehyde and subsequent reaction under standard Bestmann–Ohira's conditions over a 12 h reaction led to the decomposition of the intermediate aldehyde (Table 1, entry 1). Changing the base to Cs_2CO_3 gave similar results (entry 2). Reduction in reaction time to 2 h, it furnished alkyne **11** in 18% yield (entry 3). Lowering the reaction temperature to 0 °C resulted in an improved yield of **11** (24%, entry 4). Lowering of base concentration from 2.5 to 1.5 equiv and then to 1.2 equiv furnished alkyne **11** in improved yields of 38% and 51%, respectively (entries 5 and 6). Changing the base to NaOMe did not give better results (30%, entry 7). The overall synthetic

Table 1
Bestmann–Ohira's reaction for the synthesis of alkyne **11** using reagent **14** and an aldehyde from **12**

Entry	Reaction conditions	**11** (yield)[a]
1	**14** (1.5 equiv), K_2CO_3 (2.5 equiv), MeOH, rt, 12 h	Decomp.
2	**14** (1.5 equiv), Cs_2CO_3 (2.5 equiv), *i*-PrOH, rt, 12 h	Decomp.
3	**14** (1.5 equiv), K_2CO_3 (2.5 equiv), MeOH, rt, 2 h	18%
4	**14** (1.5 equiv), K_2CO_3 (2.5 equiv), MeOH, 0 °C, 1 h, rt, 2 h	24%
5	**14** (1.5 equiv), K_2CO_3 (1.5 equiv), MeOH, 0 °C, 1 h, rt, 2 h	38%
6	**14** (1.5 equiv), K_2CO_3 (1.2 equiv), MeOH, 0 °C, 1 h, rt, 8 h	51%
7	**14** (1.5 equiv), NaOMe (1.5 equiv), THF, 0 °C, 2 h	30%

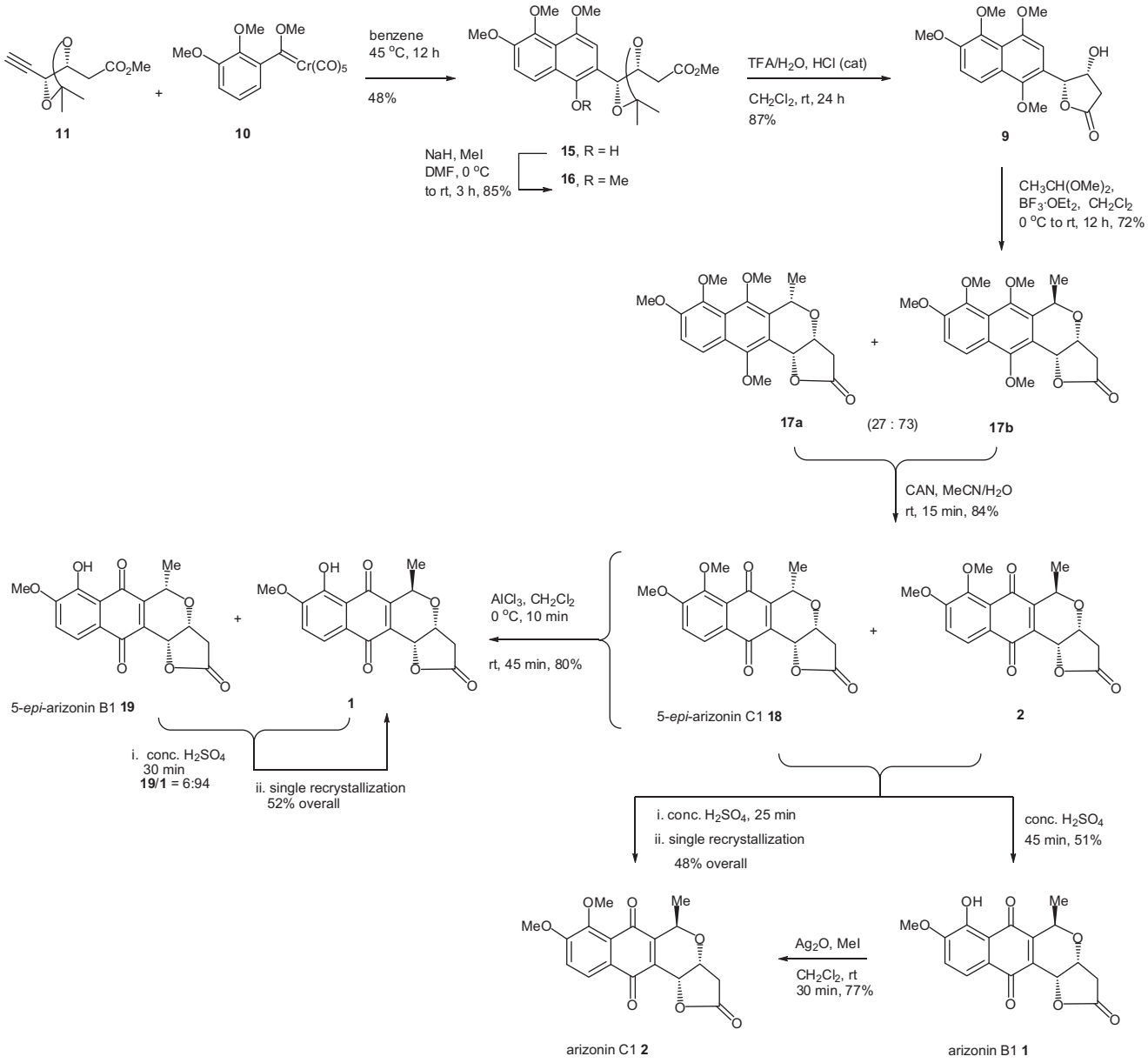
[a] Yields are from compound **12** including aldehyde formation.

sequence from D-glucono-δ-lactone **13** to alkyne **11** required six steps and resulted in 33% overall yield.

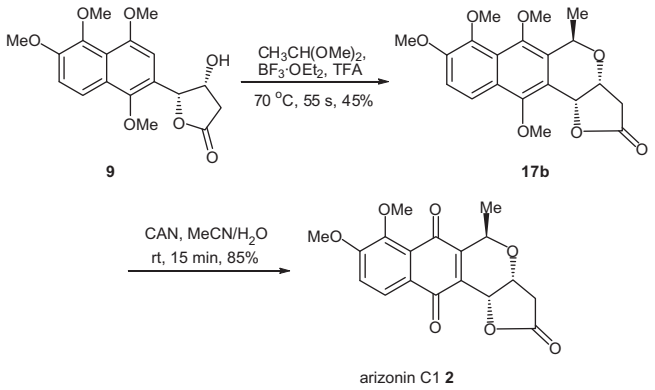
We continued our synthesis with further steps as shown in Scheme 3. The Dötz benzannulation[9] of alkyne **11** with the Fischer carbene **10**[5,10] in benzene solvent gave single regioisomeric naphthol **15** isolated in 48% yield. The methylation of **15** to **16** (85% yield) and a further one-pot acetonide deprotection and lactonization with trifluroacetic acid/catalytic conc. HCl furnished lactone **9** in 87% yield, $[\alpha]_D^{25} = -4.6$ (*c* 0.5, $CHCl_3$), lit.[5] $[\alpha]_D^{25} = -3.5$ (*c* 0.46, $CHCl_3$). The oxa-Pictet–Spengler[11] reaction of **9** with acetaldehyde dimethylacetal catalyzed by TMSOTf provided the *syn*/*anti* diastereomers **17a** and **17b** (65:35 by ^{1}H NMR, 68%) as an inseparable mixture (reaction conditions not shown in Scheme 3, see Section 4). However, the same reaction when catalyzed by $BF_3{\cdot}OEt_2$, reversed the stereoselectivity to give *syn*/*anti* diastereomers **17a** and **17b** (27:73 by ^{1}H NMR, 72%) as an inseparable mixture (Scheme 3). Further cerium ammonium nitrate (CAN) oxidation provided *syn*/*anti*-quinones, 5-*epi*-arizonin C1 **18**, and arizonin C1 **2** (27:73, 84%). Regioselective $AlCl_3$ mediated demethylation of the mixture gave a **19**/**1** mixture in 80% yield. Stirring this mixture with conc. H_2SO_4 over 30 min resulted in C-5 epimerization to give **19**/**1** in a 6:94 ratio. A single recrystallization provided arizonin B1 **1** in 52% yield from the mixture. Alternatively, when the mixture of **18**/**2** was stirred with conc. H_2SO_4 over 45 min a remarkable regioselective C-7 demethylation occurred in addition to the C-5 epimerization directly providing arizonin B1 **1** in 51% isolated yield, $[\alpha]_D^{25} = +137$ (*c* 0.108, MeOH), lit.[1] $[\alpha]_D^{25} = -53$ (*c* 0.112, MeOH). A slight charring of the material was observed which accounts for the lower yield. Methylation of the C-7 phenolic OH group using Ag_2O/MeI provided arizonin C1 **2** in 77% yield. If conc. H_2SO_4 treatment of the **18**/**2** mixture was carried over 25 min, it gave only the C-5 epimerized product (**18**/**2** = 6:94 ratio). A single recrystallization then provided arizonin C1 **2** in 48% yield, $[\alpha]_D^{25} = +75.3$ (*c* 0.7, MeOH), lit.[1] $[\alpha]_D^{25} = -84.3$ (*c* 1.017, MeOH), lit.[5] $[\alpha]_D^{25} = -86.5$ (*c* 0.7, MeOH). The spectroscopic data (^{1}H NMR, ^{13}C NMR, HRMS, IR) were in excellent agreement with those reported in the literature.[1,5]

In an oxa-Pictet–Spengler reaction of hydroxylactone **9** in trifluoroacetic acid (TFA) as the solvent and $BF_3{\cdot}OEt_2$ as the Lewis acid in less than 1 min (55 s) we isolated the single *anti*-pyran diastereomer **17b** in 45% yield (Scheme 4). The lower yield was attributed to the considerable charring of the material. We believe lowering the electron density on the naphthalene ring through protonation with TFA would lead to a ring closure through the oxocarbenium ion intermediate to give the more stable *anti*-pyran ring product **17b**.[12] Further quinone formation with CAN gave arizonin C1 **2** in 85% yield, $[\alpha]_D^{25} = +73.9$ (*c* 0.15, MeOH). This represents a direct synthesis of *anti*-pyran products without the need for C-5 epimerizations.

We noted a discrepancy in the specific rotations of the compounds synthesized by us in comparison to the natural materials and also those synthesized by Brückner et al.[5]of the same absolute



Scheme 3. Synthesis of arizonins B1 **1** and C1 **2**.

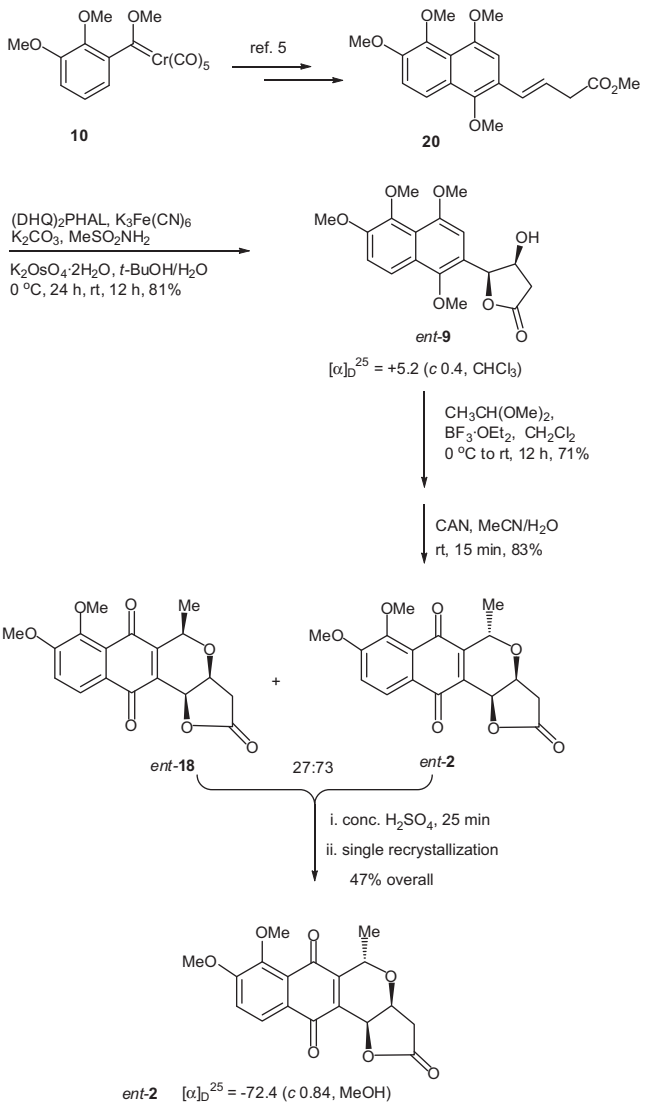


Scheme 4. Alternative synthesis of arizonin C1 **2**.

configurations as shown herein. The natural arizonin B1 has $[\alpha]_D^{25} = -53$ (*c* 0.112, MeOH) and arizonin C1 $[\alpha]_D^{25} = -84.3$ (*c* 1.017, MeOH).[1] Synthesized arizonin C1 has $[\alpha]_D^{20} = -86.5$ (*c* 0.7, MeOH).[5] Our specific rotation values at different concentrations are given in Table 2. We were surprised with these differences, especially when the intermediate compound **9** synthesized by us had matching specific rotation and spectroscopic data with that reported.[5] The synthetic sequence from this lactone to the target molecules is similar.[13] The discrepancy was observed for both arizonins B1 and C1. We synthesized the enantiomer of arizonin C1 *ent*-**2** following the literature method (using asymmetric dihydroxylation to induce chiral elements, Scheme 5).[5] This showed a specific rotation of $[\alpha]_D^{25} = -72.4$ (*c* 0.84, MeOH); see Table 2 for values at different concentrations.[14] This matches that of the natural isolate. We also recorded CD spectra of a series of compounds (Figs. 2 and 3). By analogy, the arizonins B1 and C1 CD spectra match with those of kalafungin and they should have the same absolute stereochemistry (Fig. 2). However the compounds

Table 2
Optical rotations of arizonins B1, C1, and *ent*-C1 at different concentrations

Arizonin	Natural[1]	Brückner[5]	This work
B1	−53 (*c* 0.112, MeOH)	—	+137.0 (*c* 0.108, MeOH) +168.0 (*c* 0.024, MeOH) +88.9 (*c* 0.011, MeOH) +166.6 (*c* 0.024, $CHCl_3$)
C1	−84.3 (*c* 1.017, MeOH)	−86.5 (*c* 0.7, MeOH)	+75.3 (*c* 0.7, MeOH) +88.2 (*c* 0.25, MeOH) +93.9 (*c* 0.04, MeOH) +112.0 (*c* 0.01, MeOH)
C1 (enantiomer)	—	—	−72.4 (*c* 0.84, MeOH) −79.2 (*c* 0.7, MeOH) −76.6 (*c* 0.35, MeOH) −77.2 (*c* 0.1, MeOH) −68.0 (*c* 0.01, MeOH)



Scheme 5. Synthesis of *ent*-**2** (naturally configured arizonin C1) on the route, which the literature[5] describes for the (supposedly) enantiomeric series.

synthesized with this absolute stereochemistry have a specific rotation opposite to that reported.[1,5] The synthesized *ent*-arizonin C1 shows an opposite CD curve to that of (+)-kalafungin **8** (Fig. 3). Kalafungin, $\{[\alpha]_D^{20} = +160.6$ (*c* 0.3, $CHCl_3\}$[2h] and arizonin B1, $\{[\alpha]_D^{25} = +166.6$ (*c* 0.024, $CHCl_3$) see Table 2} differ by only one methoxy group and it is possible that they may have the same sign of the specific rotation since the stereochemistry of chiral elements is the same although this is not a general rule. Recently, we have adopted a similar strategy[6j] from alkyne **11** toward the synthesis of kalafungin and frenolicin B where such discrepancies were not observed. This validates the correctness of this strategy. However, we were unable to explain this discrepancy. We believe a future

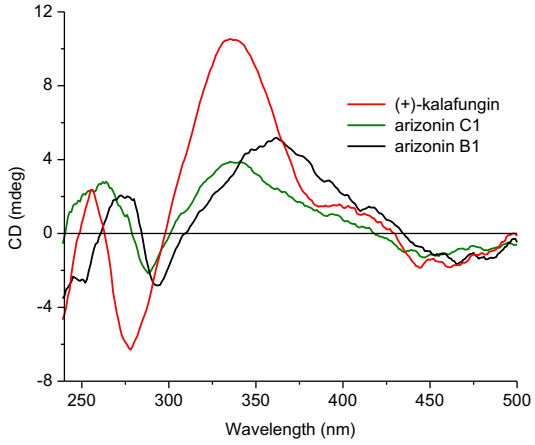


Figure 2. Circular dichroism spectra (MeOH) of (+)-kalafungin **8**, arizonin C1 **2**, and arizonin B1 **1**.

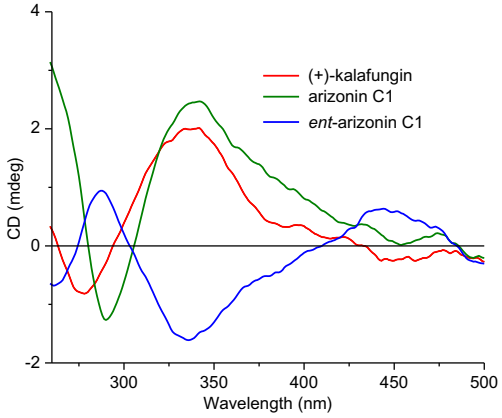


Figure 3. Circular dichroism spectra (MeOH) of (+)-kalafungin **8**, arizonin C1 **2**, and *ent*-arizonin C1.

report on the synthesis of these molecules through different approach may resolve these differences.[15]

3. Conclusions

In conclusion we have performed a concise and efficient total synthesis of arizonin B1 and arizonin C1. The key building block alkyne **11** was prepared from chiral pool material D-glucono-δ-lactone in six steps and 33% overall yield. Dötz benzannulation and oxa-Pictet–Spengler reaction provided the desired pyranonaphthoquinone structure while H_2SO_4 mediated epimerization led to the desired stereochemistry of the target molecules. A remarkable H_2SO_4 mediated regioselective demethylation in addition to C-5 epimerization was also observed. Secondly, a direct *anti*-pyran ring formation was also observed in TFA solvent catalyzed by $BF_3{\cdot}OEt_2$. Herein we have reported on the first asymmetric synthesis of arizonin B1. The use of alkyne **11**, which possesses the required stereoelements for the Dötz benzannulation constitutes as a new strategy that can be readily adopted for the synthesis of related pyranonaphthoquinones.

4. Experimental

4.1. General

Flasks were oven or flame dried and cooled in a desiccator. Dry reactions were carried out under an atmosphere of Ar or N_2. Solvents and reagents were purified by standard methods. Thin layer chromatography was performed on EM 250 Kieselgel 60 F254 silica gel plates. The spots were visualized by staining with $KMnO_4$ or by UV lamp. ^1H NMR and ^{13}C NMR were recorded at 400 and 100 MHz, respectively, and chemical shifts are based on TMS peak at $\delta = 0.00$ ppm for proton NMR and $CDCl_3$ peak at $\delta = 77.00$ ppm (t) for carbon NMR. IR samples were prepared by evaporation from $CHCl_3$ on CsBr plates. High-resolution mass spectra were obtained using positive electrospray ionization. Compound **12** was prepared from **13** following literature procedures.[6j]

4.1.1. Methyl (3*R*,4*R*)-3,4-isopropylidenedioxyhex-5-ynoate 11

To a solution of **12** (1.80 g, 7.68 mmol, 1.0 equiv) in acetone (28 mL) were added satd aq $NaHCO_3$ (0.6 mL) and solid $NaIO_4$ (3.28 g, 15.36 mmol, 2.0 equiv). The resulting mixture was stirred at room temperature for 4 h. Acetone was then removed under reduced pressure and the residue was filtered through a small pad of silica gel, and washed with petroleum ether/EtOAc (7:3) to give a crude aldehyde (1.55 g). This was virtually pure and used for the next step.

To a solution of above crude aldehyde (1.55 g, 7.66 mmol, 1.0 equiv) in MeOH (25 mL) were added freshly prepared Bestmann–Ohira's reagent **14** (2.53 g, 11.5 mmol, 1.5 equiv) and K_2CO_3 (1.27 g, 9.2 mmol, 1.2 equiv) sequentially. The resulting solution was stirred at 0 °C for 1 h and then at room temperature for 8 h. It was then quenched with satd aq NH_4Cl (12 mL) and MeOH was removed under reduced pressure. The solution was extracted with EtOAc (3 × 35 mL) and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to afford alkyne **11** (0.777 g, 51% over two steps) as a colorless oil: $[\alpha]_D^{25} = +1.65$ (*c* 0.9, $CHCl_3$); IR ($CHCl_3$): $\nu = 3273, 2991, 2955, 2123, 1743, 1439, 1383, 1372, 1333, 1240, 1193, 1176, 1067, 995, 906, 846, 758, 668\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.40$ (s, 3H), 1.53 (s, 3H), 2.54 (d, $J = 2.0$ Hz, 1H), 2.63 (dd, $J = 15.5$, 7.0 Hz, 1H), 2.69 (dd, $J = 15.6$, 5.1 Hz, 1H), 3.72 (s, 3H), 4.38 (dt, $J = 7.4$, 2.0 Hz, 1H), 4.40 (dd, $J = 7.3$, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.2$, 27.0, 37.2, 51.9, 69.6, 75.0, 77.7, 79.9, 110.8, 170.4; HRMS *m*/*z* calcd for $[C_{10}H_{14}O_4+H]^+$ 199.097, found 199.0988.

4.1.2. Fischer carbene 10[5,10]

To a stirred solution of TMEDA (5.43 mL, 36.19 mmol, 1.0 equiv) in dry Et_2O (100 mL) at room temperature was added *n*-BuLi (22.6 mL, 36.19 mmol, 1.0 equiv, 1.6 M solution in hexane). The mixture was stirred for 10 min after which 1,2-dimethoxybenzene (5.0 g, 36.19 mmol) was added. The reaction mixture was stirred at room temperature for 2.5 h, then cooled to −78 °C and a solution of bromine (1.85 mL, 36.19 mmol, 1.0 equiv) in dry hexane (10 mL) was added. The reaction was maintained at −78 °C for 30 min and then allowed to warm to room temperature. It was then quenched with satd aq Na_2SO_3 (20 mL). The solution was extracted with EtOAc (3 × 30 mL) and the combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9.5:0.5 to 9:1) as eluent to give 1-bromo-2,3-dimethoxybenzene (6.68 g, 85%) as a colorless oil: IR ($CHCl_3$): $\nu = 3007, 2940, 2838, 1585, 1572, 1480, 1460, 1435, 1289, 1264, 1237, 1173, 1150, 1080, 1039, 1004, 910, 837, 769, 649\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 3.86$ (s, 3H), 3.87 (s, 3H), 6.85 (dd, $J = 8.3$, 1.5 Hz, 1H), 6.93 (t, $J = 8.1$ Hz, 1H), 7.13 (dd, $J = 8.0$, 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.8$, 60.3, 111.4, 117.5, 124.5, 124.8, 146.2, 153.7; HRMS *m*/*z* calcd for $[C_8H_9O_2Br+H]^+$ 216.9864, found 216.9873.

To a solution of the above 1-bromo-2,3-dimethoxybenzene (2.0 g, 9.21 mmol, 1.0 equiv) in dry Et_2O (35 mL) at −78 °C was added *n*-BuLi (6.0 mL 9.67 mmol, 1.05 equiv, 1.6 M solution in hexane) and the reaction mixture was stirred for 15 min. It was then transferred to a suspension of $Cr(CO)_6$ (2.23 g, 10.13 mmol, 1.1 equiv) in dry Et_2O (35 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then at room temperature for 2 h. Next, Et_2O was evaporated and the residue was dissolved in dry CH_2Cl_2 (30 mL). To this solution was added Me_3OBF_4 (2.04 g, 13.82 mmol, 1.5 equiv) in portions at 0 °C and the reaction mixture was stirred for 1 h. It was then warmed to room temperature and stirred for 2 h. The red colored reaction mixture was concentrated and purified by silica gel column chromatography using petroleum ether/CH_2Cl_2 (9:1 to 4:1) as eluent to give **10** (2.23 g, 65%) as a red solid: mp 81–83 °C. This was immediately used in the next step. Characterization data are the same as reported earlier.[5]

4.1.3. Methyl-(3*R*,4*R*)-4-(1-hydroxy-4,5,6-trimethoxynaphthalen-2-yl)-3,4-isopropylidenedioxybutanoate 15

To a freshly prepared Fischer carbene complex **10** (0.5 g, 1.343 mmol, 1.0 equiv) in dry and degassed benzene (10 mL) was added chiral alkyne **11** (0.320 g, 1.61 mmol, 1.2 equiv). The reaction mixture was then stirred at 45 °C for 12 h. It was then cooled to room temperature, exposed to air, and stirred for a further 30 min. The reaction mixture was concentrated and the residue purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 4:1) as an eluent to give **15** (0.26 g, 48%) as a yellow oil: $[\alpha]_D^{25} = +9.1$ (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): $\nu = 3367, 2989, 2928, 2854, 1743, 1661, 1603, 1464, 1384, 1277, 1172, 1065, 926, 853, 762\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.54$ (s, 3H), 1.68 (s, 3H), 2.66 (dd, $J = 15.3$, 7.1 Hz, 1H), 2.75 (dd, $J = 15.3$,4.0 Hz, 1H), 3.66 (s, 3H), 3.87 (s, 3H), 3.91 (s, 3H), 3.99 (s, 3H), 4.35–4.40 (m, 1H), 4.94 (d, $J = 8.9$ Hz, 1H), 6.48 (s, 1H), 7.30 (d, $J = 9.2$ Hz, 1H), 8.03 (d, $J = 9.2$ Hz, 1H), 8.31 (s, 1H, *OH*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 26.8$, 27.0, 36.1, 52.0, 56.9, 57.7, 61.7, 77.2, 82.1, 107.1, 109.0, 109.7, 114.5, 119.0, 122.4, 123.3, 143.6, 145.6, 149.0, 151.0, 170.7; HRMS *m*/*z* calcd for $[C_{21}H_{26}O_8+Na]^+$ 429.1525, found 429.1526.

4.1.4. Methyl-(3*R*,4*R*)-4-(1,4,5,6-tetramethoxynaphthalen-2-yl)-3,4-isopropylidenedioxybutanoate 16

To a solution of naphthol **15** (0.24 g, 0.59 mmol, 1.0 equiv) in dry DMF (7 mL) at 0 °C was added NaH (28.3 mg, 0.7086 mmol, 60% in mineral oil, 1.2 equiv). The reaction mixture was stirred at room temperature for 20 min, then cooled to 0 °C and MeI (0.074 mL, 1.18 mmol, 2.0 equiv) was added. The reaction mixture was stirred at 0 °C to room temperature for 3 h. It was then quenched with ice cold water (5 mL) and the solution was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with water, brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 4:1) as eluent to give **16** (0.211 g, 85%) as a yellow solid: mp 67–69 °C; $[\alpha]_D^{25} = +26.1$ (*c* 0.6, $CHCl_3$); IR ($CHCl_3$): ν = 3018, 2935, 2844, 1739, 1603, 1580, 1463, 1381, 1361, 1278, 1175, 1070, 852, 819, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.57 (s, 3H), 1.64 (s, 3H), 2.69 (dd, *J* = 16.1, 8.4 Hz, 1H), 2.78 (dd, *J* = 16.1, 3.4 Hz, 1H), 3.62 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 3.99 (s, 6H), 4.28 (td, *J* = 8.5, 3.4 Hz, 1H), 5.21 (d, *J* = 8.6 Hz, 1H), 6.91 (s, 1H), 7.32 (d, *J* = 9.2 Hz, 1H), 7.80 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.1, 27.2, 36.6, 51.7, 56.6, 57.1, 61.8, 62.4, 76.5, 78.5, 103.8, 109.5, 115.5, 118.8, 122.2, 122.6, 125.5, 144.7, 148.0, 150.8, 152.7, 171.1; HRMS *m*/*z* calcd for $[C_{22}H_{28}O_8+H]^+$ 421.1862 found 421.1861.

4.1.5. (4*R*,5*R*)-4-Hydroxy-5-(1,4,5,6-tetramethoxynaphth-2-yl)-dihydrofuran-2(3H)-one 9

To a solution of compound **16** (0.2 g, 0.475 mmol. 1.0 equiv) in CH_2Cl_2 (5 mL) were added TFA/H_2O (9:1, 0.5 mL) and 2 drops of conc. HCl. The resulting solution was stirred at room temperature for 24 h. It was then quenched with satd aq $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 4:1) as eluent to give **9** (0.144 g, 87%) as a pale yellow solid: mp 148–150 °C, lit.[5] mp 155–160 °C (decomp.); $[\alpha]_D^{25} = -4.6$ (*c* 0.5, $CHCl_3$), lit[5] $[\alpha]_D^{20} = -3.5$ (*c* 0.46, $CHCl_3$); IR ($CHCl_3$): ν = 3449, 3002, 2936, 2843, 1776, 1624, 1603, 1580, 1475, 1464, 1383, 1362, 1278, 1233, 1158, 1077, 1058, 1025, 1010, 973, 918, 898, 866, 819, 801, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 2.77 (d, *J* = 17.6 Hz, 1H), 2.97 (dd, *J* = 17.6, 5.4 Hz, 1H), 3.84 (s, 3H), 3.88 (s, 3H), 3.96 (s, 3H), 3.99 (s, 3H), 4.83 (dd, *J* = 4.9, 3.7 Hz, 1H), 5.85 (d, *J* = 3.5 Hz, 1H), 6.84 (s, 1H), 7.29 (d, *J* = 9.2 Hz, 1H), 7.71 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.5, 56.0, 56.6, 61.4, 62.1, 69.9, 81.3, 104.3, 114.5, 118.7, 119.4, 121.8, 124.3, 143.5, 146.5, 150.2, 151.4, 176.2; HRMS *m*/*z* calcd for $[C_{18}H_{20}O_7+H]^+$ 349.1289, found 349.1296.

4.1.6. (3a*R*,5*S*,11b*R*)-6,7,8,11-Tetramethoxy-5-methyl-3,3a,5,11b-tetrahydro-2*H*-benzo[*g*]furo[3,2-*c*]isochromen-2-one 17a and (3a*R*,5*R*,11b*R*)-6,7,8,11-tetramethoxy-5-methyl-3,3a,5,11b-tetrahydro-2*H*-benzo[*g*]furo[3,2-*c*]isochromen-2-one 17b

To a solution of lactone **9** (50 mg, 0.144 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at 0 °C were added acetaldehyde dimethylacetal (0.030 mL, 0.288 mmol, 2.0 equiv) and TMSOTf (0.039 mL, 0.216 mmol, 1.5 equiv). The reaction mixture was stirred at 0 °C for 2 h. It was then quenched with satd aq $NaHCO_3$ (5 mL) and the solution extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 1:1) as eluent to afford an inseparable mixture of *syn*/*anti* diastereomers **17a** and **17b** (36.5 mg, 68%, *syn*/*anti* = 65/35, ^1H NMR) as a colorless gummy solid: ^1H NMR (400 MHz, $CDCl_3$/TMS) for major diastereomer: δ = 1.75 (d, *J* = 6.3 Hz, 3H), 2.78 (d, *J* = 17.2, Hz, 1H), 2.92 (dd, *J* = 17.2, 4.4 Hz, 1H), 3.75 (s, 3H), 3.87 (s, 3H), 4.03 (s, 3H), 4.10 (s, 3H), 4.37 (dd, *J* = 4.2, 2.4 Hz, 1H), 5.09 (q, *J* = 6.3 Hz, 1H), 5.59 (d, *J* = 2.5 Hz, 1H), 7.36 (d, *J* = 9.3 Hz, 1H), 7.93 (d, *J* = 9.3 Hz, 1H); HRMS *m*/*z* calcd for $[C_{20}H_{22}O_7+H]^+$ 375.1444, found 375.1441.

4.1.7. (3a*R*,5*S*,11b*R*)-6,7,8,11-Tetramethoxy-5-methyl-3,3a,5,11b-tetrahydro-2*H*-benzo[*g*]furo[3,2-*c*]isochromen-2-one 17a and (3a*R*,5*R*,11b*R*)-6,7,8,11-tetramethoxy-5-methyl-3,3a,5,11b-tetrahydro-2*H*-benzo[*g*]furo[3,2-*c*]isochromen-2-one 17b

To a solution of lactone **9** (0.1 g, 0.29 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) at 0 °C were added acetaldehyde dimethylacetal (0.061 mL, 0.58 mmol, 2.0 equiv) and $BF_3{\cdot}OEt_2$ (0.073 mL, 0.58 mmol, 2.0 equiv). The reaction mixture was stirred at 0 °C to room temperature for 12 h. It was then quenched with satd aq $NaHCO_3$ (5 mL) and the solution extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 1:1) as eluent to afford an inseparable mixture of *syn*/*anti* diastereomers **17a** and **17b** (0.0774 g, 72%, *syn*/*anti* = 27/73, ^1H NMR) as colorless gummy solid: ^1H NMR (400 MHz, $CDCl_3$/TMS) for major diastereomer: δ = 1.57 (d, *J* = 6.8 Hz, 3H), 2.71 (d, *J* = 17.5, Hz, 1H), 2.96 (dd, *J* = 17.5, 4.9 Hz, 1H), 3.86 (s, 6H), 4.02 (s, 3H), 4.07 (s, 3H), 4.75 (dd, *J* = 4.8, 2.8 Hz, 1H), 5.39 (q, *J* = 6.7 Hz, 1H), 5.58 (d, *J* = 2.8 Hz, 1H), 7.34 (d, *J* = 9.3 Hz, 1H), 7.91 (d, *J* = 9.3 Hz, 1H); HRMS *m*/*z* calcd for $[C_{20}H_{22}O_7+H]^+$ 375.1444, found 375.1448.

4.1.8. Arizonin B1 1

To a stirred solution of a **17a** and **17b** mixture (27:73, 50 mg, 0.133 mmol, 1.0 equiv) in CH_3CN (5 mL) was added a solution of cerium(IV) ammonium nitrate (146 mg, 0.267 mmol, 2.0 equiv) in water (5 mL). The reaction mixture was stirred at room temperature for 15 min. It was then diluted with CH_2Cl_2 (15 mL) and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with water, brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 7:3) as eluent to afford an inseparable mixture of *syn*/*anti* diastereomers **18** and **2** (38.6 mg, 84%) as a yellow solid.

To a solution of the above **18** and **2** mixture (38.6 mg, 0.112 mmol, 1.0 equiv) in dry CH_2Cl_2 (15 mL) at 0 °C was added $AlCl_3$ (29.9 mg, 0.224 mmol, 2.0 equiv) in portions and the reaction mixture stirred for 15 min. The ice bath was removed and stirring was continued at room temperature for 45 min. It was then quenched with water (5 mL) and the solution extracted with CH_2Cl_2 (5 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel flash column chromatography using petroleum ether/EtOAc (9:1 to 7:3) as eluent to provide a mixture of **19** and **1** (29.6 mg, 80%) as an orange gummy solid. The mixture was treated with conc. H_2SO_4 (2 mL). The resulting mixture was stirred at room temperature for 30 min. Brine solution (5 mL) was added and reaction mixture extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with satd aq $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 1:1) as eluent to give a mixture of **1** and **19** (94:6, ^1H NMR). A single recrystallization (CH_2Cl_2/hexane) gave pure arizonin B1 **1** (15.4 mg, 52%) as an orange semi solid: $[\alpha]_D^{25} = +137$ (*c* 0.108, MeOH), lit.[1] $[\alpha]_D^{25} = -53$ (*c* 0.112, MeOH); IR ($CHCl_3$): ν = 3461, 3020, 2928, 2855, 1791, 1650, 1621, 1458, 1434, 1366, 1336, 1319, 1269, 1240, 1154, 1072, 1035, 995, 957, 921, 843, 670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.56 (d, *J* = 6.9 Hz, 3H), 2.68 (d, *J* = 17.7 Hz, 1H), 2.96 (dd, *J* = 17.7, 5.2 Hz, 1H), 4.00 (s, 3H), 4.68 (dd, *J* = 5.1, 3.0 Hz, 1H), 5.07 (q, *J* = 6.9 Hz, 1H), 5.25 (d, *J* = 2.9 Hz, 1H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H),

12.27 (s, 1H, *OH*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.5, 36.9, 56.5, 66.2, 66.4, 68.7, 114.8, 115.7, 121.4, 123.3, 135.8, 149.4, 152.4, 154.3, 174.0, 180.4, 188.5; HRMS *m*/*z* calcd for $[C_{17}H_{14}O_7+H]^+$ 331.0818, found 331.0827.

4.1.9. Synthesis of arizonin B1 1 from a mixture of 18 and 2 through direct epimerization of C-5 and regioselective demethylation

A mixture of **18** and **2** (16.7 mg, 0.049 mmol) was treated with conc. H_2SO_4 (2 mL). The resulting mixture was then stirred at room temperature for 45 min. Partial charring of the material was observed. Brine solution (5 mL) was then added and the reaction mixture extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with satd aq $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 1:1) as eluent to give arizonin B1 **1** (7.7 mg, 48%) as an orange semi solid: $[\alpha]_D^{25} = +135$ (*c* 0.11, MeOH). The spectroscopic data were the same as before.

4.1.10. Arizonin C1 2 from arizonin B1 1

To a stirred solution of **1** (4 mg, 0.012 mmol) in CH_2Cl_2 (5 mL) was added silver(I) oxide (39.3 mg, 0.169 mmol, 14 equiv) and methyl iodide (0.015 mL, 0.24 mmol, 20 equiv) at room temperature and the reaction mixture stirred for 30 min at room temperature. The reaction mixture was filtered through a small pad of silica gel and the filtrate evaporated under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 1:1) as eluent to afford arizonin C1 **2** (3.2 mg, 77%) as an orange solid: mp 115−130 °C (decomp.), lit.[5] mp 110−135 °C (decomp.); $[\alpha]_D^{25} = +75.3$ (*c* 0.7, MeOH), lit.[5] $[\alpha]_D^{20} = -86.5$ (*c* 0.7, MeOH); IR ($CHCl_3$): ν = 3011, 2926, 2853, 1789, 1663, 1575, 1486, 1456, 1403, 1368, 1337, 1274, 1234, 1201, 1156, 1125, 1069, 1036, 993, 947, 905, 845, 820, 711, 669 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.55 (d, *J* = 6.9 Hz, 3H), 2.69 (d, *J* = 17.7 Hz, 1H), 2.96 (dd, *J* = 17.7, 5.2 Hz, 1H), 3.93, (s, 3H), 3.99 (s, 3H), 4.67 (dd, *J* = 5.1, 3.1 Hz, 1H), 5.07 (q, *J* = 6.9 Hz, 1H), 5.26 (d, *J* = 3.0 Hz, 1H), 7.24 (d, *J* = 8.6 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.6, 37.0, 56.3, 61.2, 66.3, 66.7, 68.9, 116.1, 124.9 (2C), 125.2, 133.1, 149.5, 150.5, 159.2, 174.2, 181.3, 182.4; HRMS *m*/*z* calcd for $[C_{18}H_{16}O_7+H]^+$ 345.0974, found 345.0979.

4.1.11. Synthesis of arizonin C1 through H_2SO_4 mediated epimerization of a mixture of 18 and 2

A mixture of **18** and **2** (18.4 mg, 0.053 mmol) was treated with conc. H_2SO_4 (2 mL). The resulting mixture was then stirred at room temperature for 25 min. Brine solution (5 mL) was then added and the reaction mixture extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with satd aq $NaHCO_3$, brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 1:1) as eluent to give a mixture of **18** and **2** (6:94, ^{1}H NMR). A single recrystallization (CH_2Cl_2/hexane) gave pure arizonin C1 **2** (8.8 mg, 48%) as an orange solid: $[\alpha]_D^{25} = +75.4$ (*c* 0.65, MeOH). The spectroscopic data were the same as before.

4.1.12. (3a*R*,5*R*,11b*R*)-6,7,8,11-Tetramethoxy-5-methyl-3,3a,5,11b-tetrahydro-2*H*-benzo[g]furo[3,2-*c*]isochromen-2-one 17b

To a preheated solution of $BF_3{\cdot}OEt_2$ (0.091 mL, 0.72 mmol, 10.0 equiv) in TFA (2 mL) was added a solution of lactone **9** (25 mg, 0.072 mmol, 1.0 equiv) and acetaldehyde dimethylacetal (0.031 mL 0.29 mmol, 4.0 equiv) in THF (0.5 mL) at 70 °C and stirred for 55 s. The reaction mixture was cooled to 0 °C and satd aq $NaHCO_3$ was slowly added for neutralization (pH 7). The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1 to 1:1) as eluent to afford **17b** (12.1 mg, 45%) as a colorless solid: mp 176–178 °C; $[\alpha]_D^{25} = +120.8$ (*c* 0.25, $CHCl_3$); IR ($CHCl_3$): ν = 2931, 2852, 1786, 1740, 1613, 1599, 1507, 1464, 1361, 1336, 1276, 1215, 1199, 1155, 1132, 1067, 1049, 1011, 981, 905, 668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.57 (d, *J* = 6.8 Hz, 3H), 2.72 (d, *J* = 17.6, Hz, 1H), 2.99 (dd, *J* = 17.6, 4.9 Hz, 1H), 3.87 (s, 6H), 4.03 (s, 3H), 4.07 (s, 3H), 4.76 (dd, *J* = 4.7, 2.8 Hz, 1H), 5.40 (q, *J* = 6.7 Hz, 1H), 5.58 (d, *J* = 2.8 Hz, 1H), 7.35 (d, *J* = 9.2 Hz, 1H), 7.92 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 37.9, 56.6, 61.9, 62.5, 64.2, 66.1, 67.9, 72.2, 114.4, 115.5, 119.8, 124.6, 125.1, 129.2, 142.7, 146.1, 151.2, 153.5, 175.4; HRMS m/z calcd for $[C_{20}H_{22}O_7+H]^+$ 375.1444, found 375.1445.

4.1.13. Arizonin C1 2

The title compound was prepared from **17b** (12 mg, 0.032 mmol, 1 equiv) by a similar procedure as described for the conversion of mixture of **17a** and **17b** to **18** and **2** to give **2** (9.4 mg, 85%) as a yellow solid: $[\alpha]_D^{25} = +73.9$ (*c* 0.15, MeOH). The spectroscopic data were the same as before.

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13. Isomerization of the C-5 centre is known in the literature to the more stable *anti*-pyran products either mediated by BBr_3 or H_2SO_4. However under the conditions employed and our own previous work,[6j] we ruled out epimerization at all stereogenic centres so as to reverse the sign of specific rotations. Also any other stereogenic centre epimerization should give a different diastereomer. The matching spectroscopic data of the final compounds also rule out this possibility.
14. These results are contradictory to previous report.[5]
15. Discrepancies in specific rotations is a known phenomenon, see for similar discrepancies in the case of a related pyranonaphthoquinone, thysanone (a) Singh, S. B.; Cordingley, M. G.; Ball, R. G.; Smith, J. L.; Dombrowski, A. W.; Goetz, M. A. *Tetrahedron Lett.* **1991**, *32*, 5279–5282; (b) Donner, C. D.; Gill, M. *Tetrahedron Lett.* **1999**, *40*, 3921–3924; (c) Donner, C. D.; Gill, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 938–948; (d) Sperry, J.; Brimble, M. A. *Synlett* **2008**, 1910–1912; (e) Sperry, J.; Tuen, T. Y.; Brimble, M. A. *Synthesis* **2009**, 2561–2569.