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SYNTHESIS OF (+)-MYRTOPSINE, (+)-7,8-DIMETHOXYMYRTOPSINE, AND RELATED 2,3-DIHYDRO-3-HYDROXY-2-(1-HYDROXY-1-METHYLETHYL)BENZOFURAN NATURAL PRODUCTS

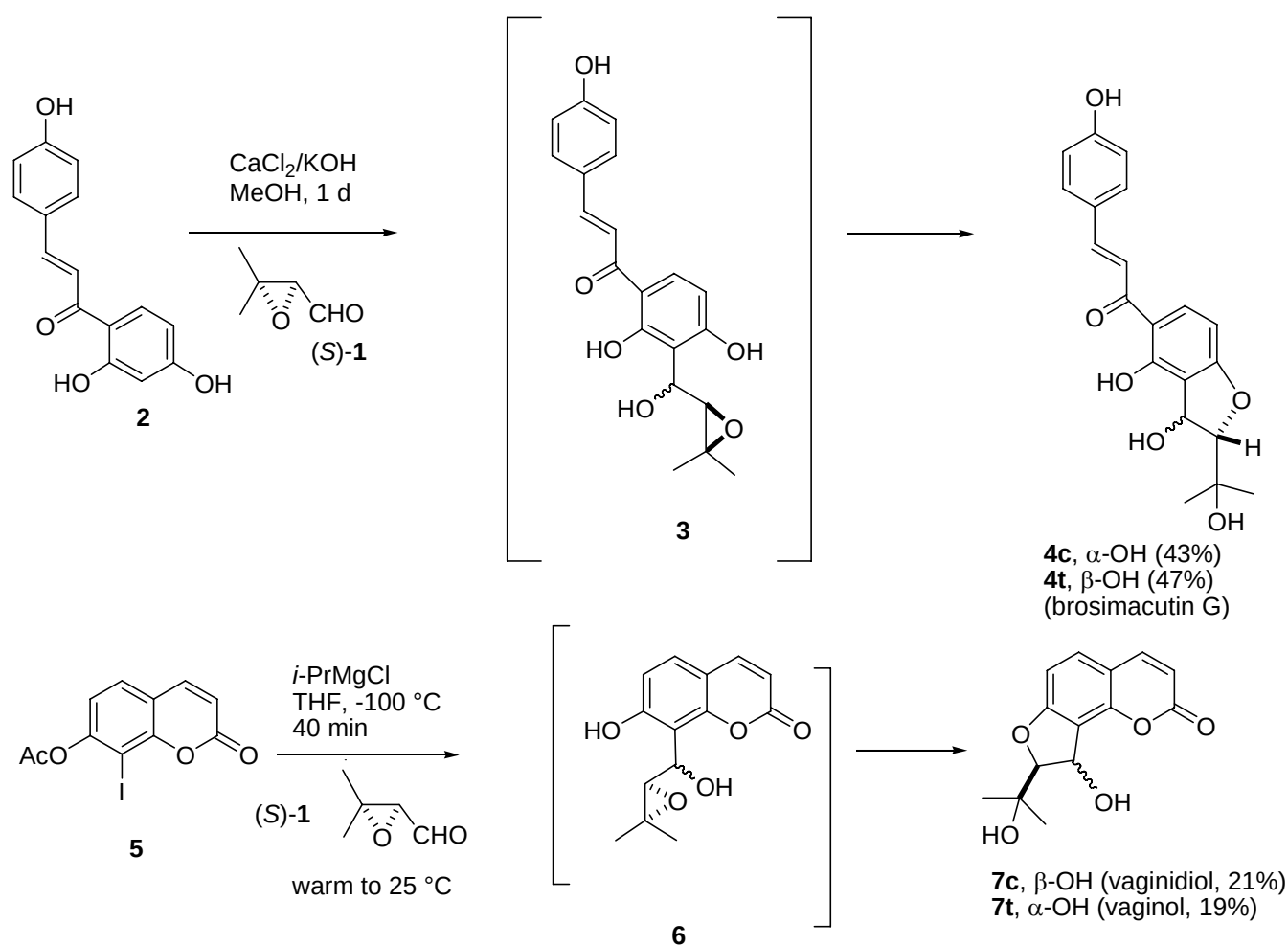
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Abstract – The first syntheses of myrtopsine (**8t**) and 7,8-dimethoxymyrtopsine (**9t**) have been carried out by halogen-metal exchange of 3-iodo-4-methoxyquinolin-2(1*H*)-ones (**15**) and (**21**) with *i*-PrMgCl followed by addition of 3,3-dimethyloxirane-2-carboxaldehyde (**1**). A two-step sequence leads selectively to *trans*-2,3-dihydro-3-hydroxy-2-(1-hydroxy-1-methylethyl)benzofurans (**7t**), (**8t**), (**9t**), (**28**), and (**32**) by conversion of a 2-iodophenol or a 3-iodo-4-methoxyquinolin-2(1*H*)-one to an aryl Grignard reagent and addition of 3-methyl-2-butenal, followed by threo selective epoxidation of the resulting allylic alcohol and cyclization with inversion.

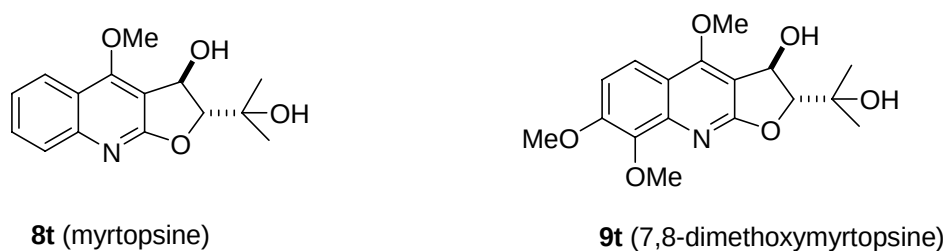
INTRODUCTION

We recently reported two practical one-step syntheses of 2,3-dihydro-3-hydroxy-2-(1-hydroxy-1-methylethyl)benzofurans from readily available α,β -epoxy aldehyde (**1**).¹ The first route involves the reaction of electron-deficient resorcinols with epoxy aldehydes using either Cs₂CO₃ in DMF or KOH/CaCl₂ in MeOH. For instance, reaction of epoxy aldehyde (*S*)-(**1**) with resorcinol (**2**), CaCl₂, and KOH in MeOH for 1 d afforded epoxy alcohol (**3**), which cyclized to brosimacutin G (**4t**) in 47% yield and the *cis* isomer (**4c**) in 43% yield (see Scheme 1). The second route involves the reaction of **1** with a 2-acetoxyaryl Grignard reagent. For instance, halogen-metal exchange of iodoacetoxy coumarin (**5**) with *i*-PrMgCl in THF at -100 °C by Knochel's procedure² gave the Grignard reagent, which was treated with (*S*)-**1** and warmed to 25 °C to complete the first synthesis of vaginol (**7t**) in 19% yield and vaginidiol (**7c**) in 21% yield via epoxy alcohol (**6**). Smyrindiol, xanthoarnol and avicenol A were prepared similarly.¹



Scheme 1. Synthesis of brosimacutin G (**4t**), vaginidiol (**7c**), and vaginol (**7t**)

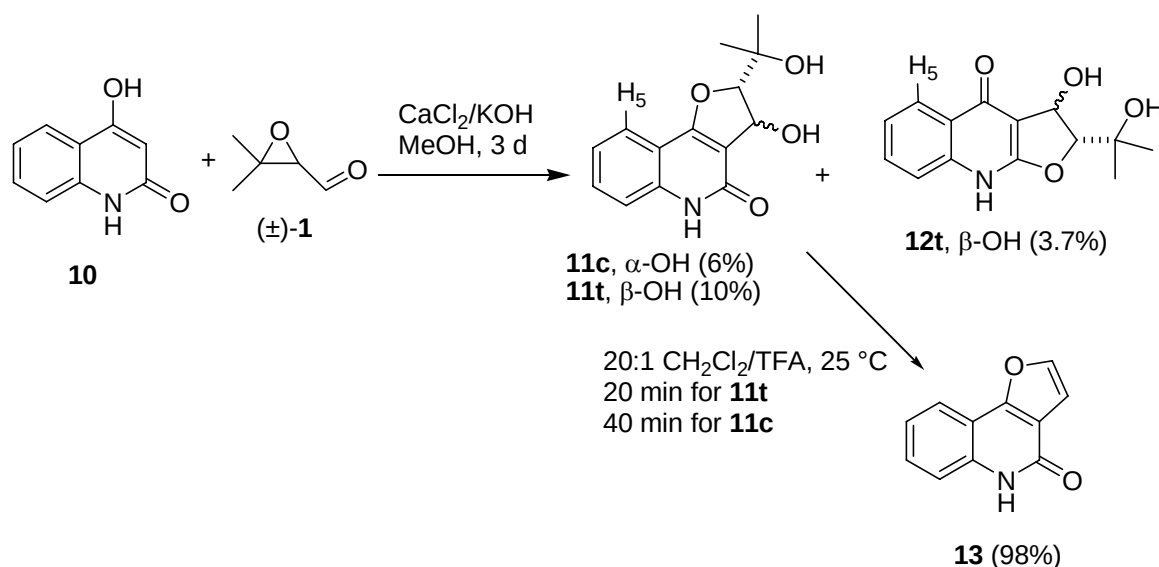
Two related natural products myrtopsine (**8t**)³⁻⁵ and 7,8-dimethoxymyrtopsine (**9t**)⁶⁻⁷ with the 2,3-dihydro-3-hydroxy-2-(1-hydroxy-1-methylethyl)furans linearly fused to a 4-methoxyquinoline have been reported (see Scheme 2). Myrtopsine was isolated from *Myrtopsis sellingii*^{3,4} and *Halophyllum foliosum*,⁵ while 7,8-dimethoxymyrtopsine was isolated from *Dutailleya Bauduinii*⁶ and *Melicope semecarpifolia*⁷ and shown to have significant antiplatelet aggregation activity in vitro.⁷ We decided to explore whether either of the above two routes could be used to prepare these natural products.



Scheme 2.

RESULTS AND DISCUSSION

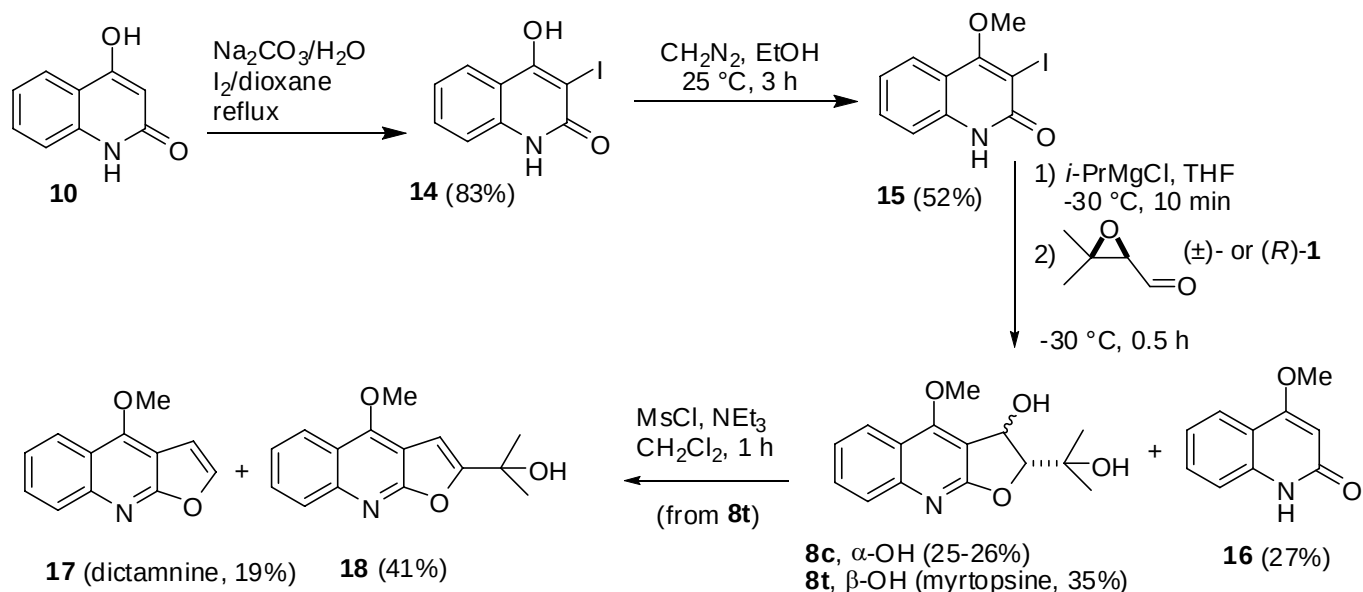
Reaction of 4-hydroxy-quinolin-2(1*H*)-one (**10**), 1.1 equiv of ($\pm$)-**1**,⁸ 1.1 equiv of CaCl₂ and 1-2 equiv of KOH in MeOH for 3 d at 25 °C followed by flash chromatography on silica gel gave 6% of **11c** and 17% of 2:1 mixture of **11t** and **12t** (see Scheme 3). Reverse phase HPLC gave pure **11t** and **12t**. The stereochemistry was assigned based on the 6.4 Hz vicinal coupling constant in cis isomer (**11c**) and 3.7 Hz and 3.1 Hz coupling constants in trans isomers (**11t**) and (**12t**), respectively.¹ H₅ in the linear isomer (**12t**) absorbs at δ 8.24 while H₅ in the angular isomers (**11c**) and (**11t**) absorb at δ 7.81 and 7.85 respectively, as observed in related systems.⁹ Treatment of **11c** with 20:1 CH₂Cl₂/TFA for 40 min at 25 °C afforded furoquinoline (**13**) in 98% yield by an acid catalyzed fragmentation.¹ The trans isomer (**11t**) reacted about twice as fast to give **13** cleanly. The spectral data of **13** are identical to those previously reported,¹⁰ and quite different from those of the linear analogue.¹¹ This establishes that the major products (**11c**) and (**11t**) are angularly fused and that only the minor product (**12t**) has the correct linearly fused geometry needed for the preparation of myrtopside. Reaction of 4-hydroxy-quinolin-2(1*H*)-one (**10**), 1.1 equiv of ($\pm$)-**1**,⁸ 1.1 equiv of Cs₂CO₃ in DMF for 3 d at 25 °C proceeded in even poorer yield giving only 3% of **11c**, 3% of a 2:1 mixture of **11t** and **12t**, and 8% of an uncharacterized 2:1 adduct. The failure of this direct route to provide practical quantities of **12t** led us to explore the second route using 3-iodo-4-methoxy-quinolin-2(1*H*)-one (**15**). Introduction of the methyl group before the coupling step will preclude the formation of the undesired angular products (**11**).



Scheme 3. Conversion of **1** and **10** to **11** and **12**

This second approach provides a very direct route to myrtopside. Iodination of 4-hydroxy-quinolin-2(1*H*)-one (**10**) with iodine in aqueous dioxane by the literature procedure¹¹ afforded **14** in 83% yield (see Scheme 4). Reaction of **14** with excess diazomethane in EtOH for 3 h at 25 °C as previously described^{13,14} provided the desired aryl iodide (**15**) in 52% yield. *i*-PrMgCl (3 equiv) was added to a

solution of **15** in THF at $-30\text{ }^{\circ}\text{C}$ and the solution was stirred for 10 min to effect halogen-metal exchange.² Epoxy aldehyde ($\pm$)-(**1**) (3.1 equiv) was added and the solution was stirred for 30 min to give myrtopisine (**8t**) in 35% yield, the cis isomer (**8c**) in 25% yield and byproduct (**16**)¹⁵ resulting from protonation of the intermediate aryl Grignard reagent in 27% yield. The stereochemistry was assigned based on a vicinal coupling constant of 1.8 Hz in **8t** and 5.5 Hz in **8c** as expected.¹ At least two equivalents of Grignard reagent are needed since reaction with the NH consumes one equivalent. We found that optimal results were obtained using three equivalents of both *i*-PrMgCl and epoxy aldehyde. Comparable or worse yields were obtained by using one equivalent of MeMgBr or PhMgCl to deprotonate **15**, followed by one equivalent of *i*-PrMgCl to effect halogen-metal exchange.² Apparently, deprotonation of the NH with *i*-PrMgCl is faster than halogen-metal exchange. Preparation of the Grignard reagent from **5** must be carried out at $-100\text{ }^{\circ}\text{C}$ because it contains an aryl acetate.¹ The Grignard reagent formed from **15** is more stable and can be prepared at $-30\text{ }^{\circ}\text{C}$. A similar reaction with (*R*)-**1**¹⁶ gave (+)-myrtopisine (**8t**, $[\alpha]_{\text{D}} +10.4^{\circ}$) in 35% yield and **8c**, ($[\alpha]_{\text{D}} -100.4^{\circ}$) in 26% yield. Therefore natural myrtopisine ($[\alpha]_{\text{D}} -5.0^{\circ}$)² is the enantiomer of **8t**.

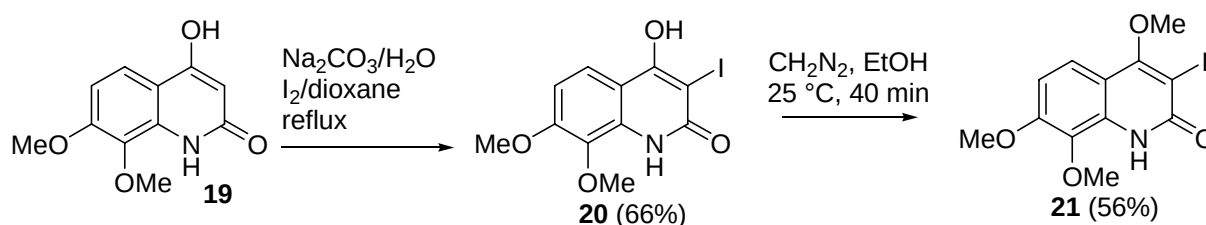


Scheme 4. Preparation of myrtopisine (**8t**)

We were quite surprised to find that **8t** did not undergo acid catalyzed fragmentation to afford dictamnine (**17**) as we had observed in the efficient conversion of **11** to **13** above. Fragmentation is initiated by protonation of the secondary alcohol. The 4-methoxyquinoline moiety of **8** is much more basic than the quinolin-2(1*H*)-one of **11**.¹⁷ Apparently, protonation of **8** on the nitrogen prevents the fragmentation because protonation of the secondary alcohol would form an unstable dication. Conversion of the secondary alcohol of **8** to a good leaving group should permit this fragmentation to proceed under the basic conditions that are standard for Grob fragmentations. Treatment of **8t** with 2 equiv of Et_3N and 1

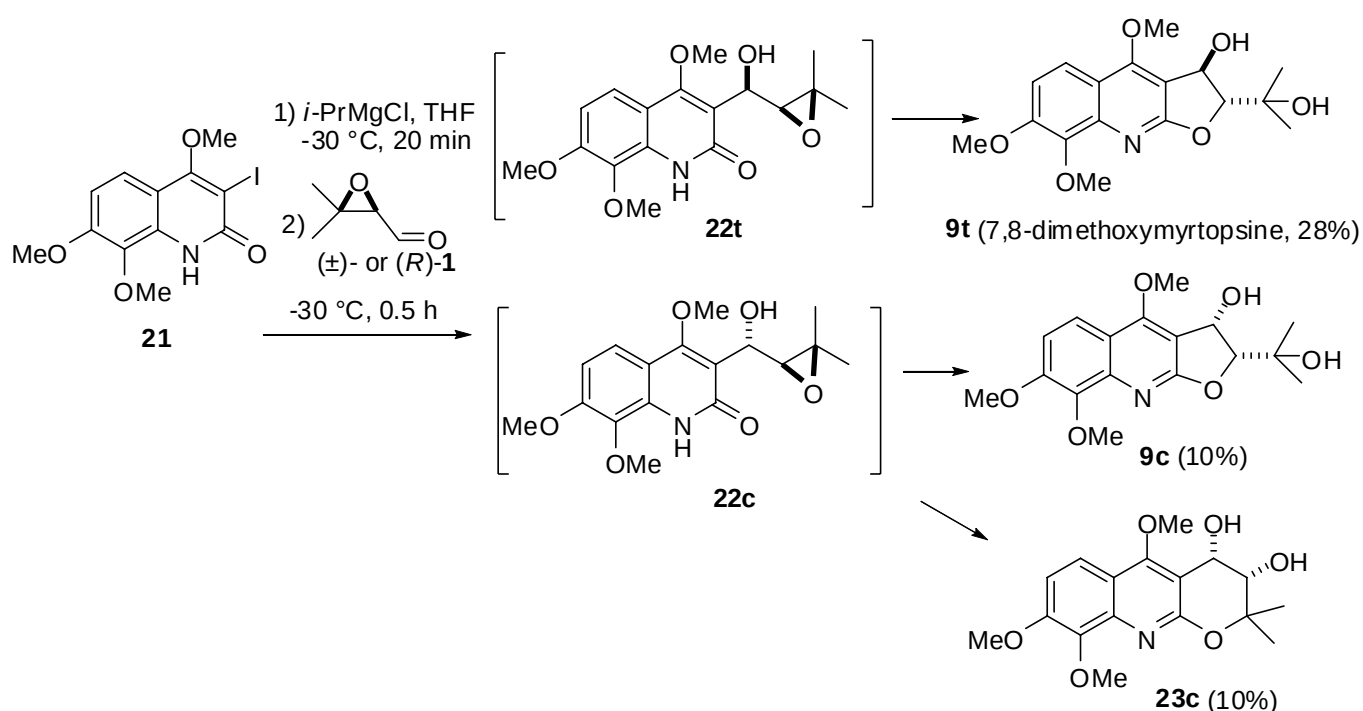
equiv of MsCl in CH₂Cl₂ for 1 h afforded dictamnine (**17**) in 19% yield and the elimination product (**18**) in 41% yield. The spectral data for dictamnine did not correspond with those reported,¹⁸ but fit exactly with those of a commercial sample.¹⁹ The spectral data of **18** fit well with the literature data except for slight systematic differences due to sample referencing.¹⁴ Although the conversion of **8** to **17** and **18** is not efficient, it serves to correlate these compounds confirming that they are all linearly fused.

Reaction of 2,3-dimethoxyaniline with malonic acid and POCl₃ afforded 4-hydroxy-7,8-dimethoxy-2-quinolone (**19**),²⁰ which was treated with iodine in aqueous dioxane to give iodoquinolone (**20**) in 66% yield (see Scheme 5). Reaction with diazomethane in ethanol gave 7,8-dimethoxymyrtopside precursor (**21**) in 56% yield and the bis methylated product 3-iodo-2,4,7,8-tetramethoxyquinoline in 14% yield.



Scheme 5. Preparation of 21

Reaction of **21** in THF at -30 °C with 3 equiv of *i*-PrMgCl for 20 min followed by the addition of 3 equiv of epoxy aldehyde (**1**) afforded 7,8-dimethoxymyrtopside (**9t**)^{6,7} in 28% yield, the *cis* analogue (**9c**) in 10% yield, and dihydropyran derivative (**23c**) in 10% yield (see Scheme 6). The stereochemistry was

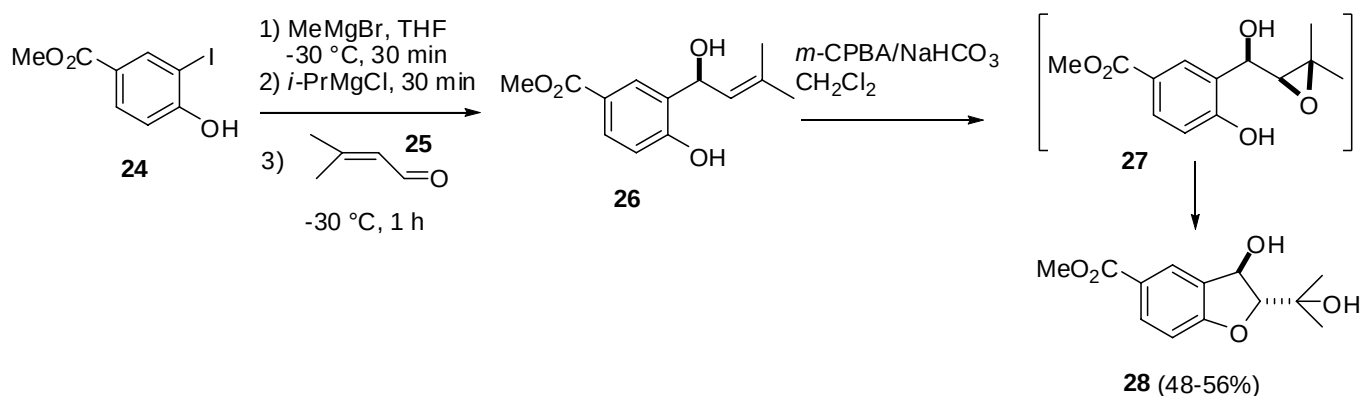


Scheme 6. Preparation of 7,8-dimethoxymyrtopside (9t)

assigned based on a vicinal coupling constant of 2.4 Hz in **9t** and 6.1 Hz in **9c** as expected.¹ The reported coupling constant for 7,8-dimethoxymyrtopside is 3.0 Hz⁶ indicating that it is the trans isomer, although it has been assigned as the cis isomer based on NOE studies.⁷ The cis stereochemistry of **23c** follows from the 4.3 Hz vicinal coupling constant.²¹ Halogen-metal exchange of **21** and addition to epoxy aldehyde (**1**) gives a mixture of **22t**, which cyclizes to give **9t**, and **22c**, which cyclizes to give a mixture of **9c** and **23c**. In all the other cases we have examined, only the dihydrofurans are formed. It is not clear why **22c** gives both dihydrofuran (**9c**) and dihydropyran (**23c**). A similar reaction with (*R*)-**1**¹⁶ gave (+)-7,8-dimethoxymyrtopside (**9t**, $[\alpha]_D +17.0^\circ$) in 26% yield, **9c** ($[\alpha]_D -53.9^\circ$) in 9% yield, and **23c** ($[\alpha]_D -4.6^\circ$) in 10% yield. Therefore natural 7,8-dimethoxymyrtopside ($[\alpha]_D +16.2^\circ$)⁷ is **9t**.

Methyl 2,3-dihydro-3-hydroxy-2-(1-hydroxy-1-methylethyl)-benzofuran-5-carboxylate (**28**) was recently isolated from *Piper hispidum*.²² We attempted unsuccessfully to prepare it from the reaction of iodophenol (**24**) with *i*-PrMgCl and epoxy aldehyde (**1**). Knochel has recently shown that halogen-metal exchange can be carried out on free iodophenols using 1 equiv of MeMgBr and 1 equiv of LiCl in THF at -30 °C to generate the lithium phenoxide followed by treatment with 1 equiv of *i*-PrMgCl in THF at -30 °C to generate the aryl Grignard reagent.²³ Unfortunately, reaction of **24** with MeMgBr, LiCl and then *i*-PrMgCl, followed by epoxy aldehyde (**1**) also failed to give **28** in acceptable yields. Since Knochel had shown that the Grignard reagent prepared from **24** adds to benzaldehyde in 62% yield under these conditions,^{23b} we thought that epoxy aldehyde (**1**) might be incompatible with the LiCl or lithium phenoxide. We therefore decided to use 3-methyl-2-butenal (**25**) instead of **1** and to epoxidize the allylic alcohol after the coupling reaction.

Iodophenol (**24**) was treated with 1 equiv of MeMgBr and 1 equiv of LiCl in THF at -30 °C for 30 min. 1 equiv of *i*-PrMgCl was added and the solution was stirred for 30 min and treated with 1 equiv of **25** and stirred for 1 h to give the unstable crude allylic alcohol (**26**) (see Scheme 7). Flash chromatography gave a complex mixture including the 2,2-dimethyl-2*H*-chromene formed by dehydrative cyclization.²⁴ Fortunately, treatment of crude **26** with 1 equiv of *m*-CPBA and 1.5 equiv of NaHCO₃ in CH₂Cl₂ effected oxidation to give **27** and cyclization to give **28** in 56% overall yield from **24**. *m*-CPBA epoxidation of

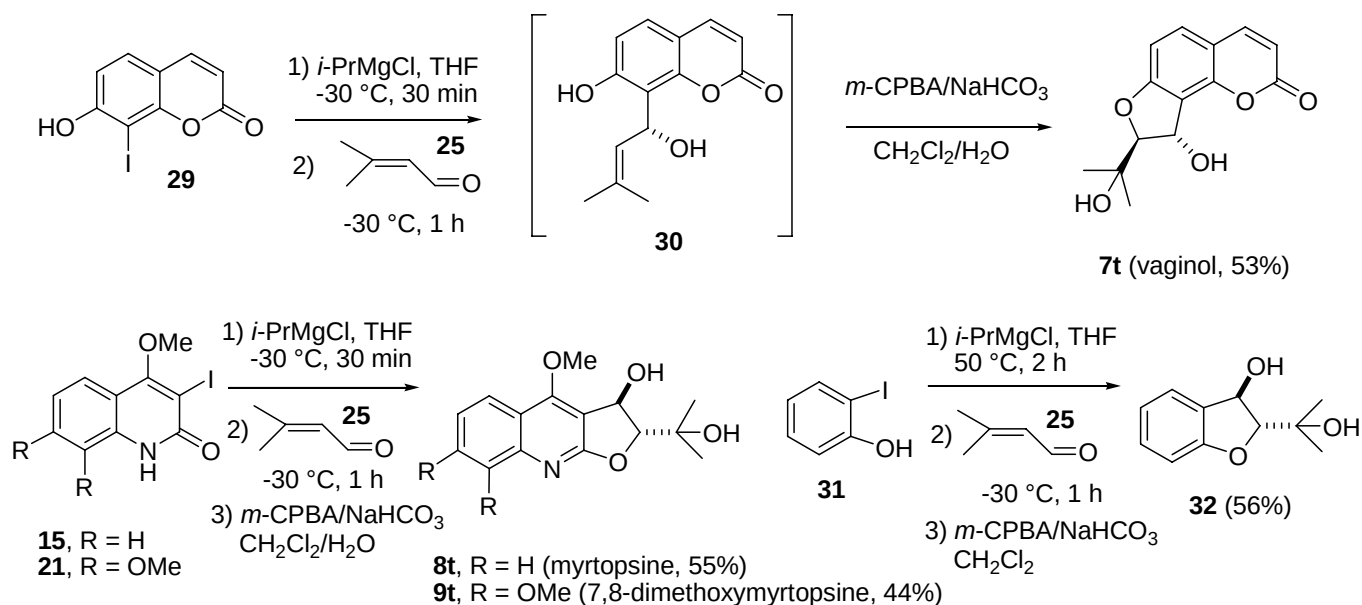


Scheme 7. Preparation of **28**

allylic alcohols with the substitution pattern of **26** is threo selective,²⁵ so that epoxidation of **26** gives mainly **27** which cyclizes with inversion to give the *trans*-dihydrobenzofuran (**28**). A similar sequence omitting the LiCl in the formation of **26** gave **28** in 48% overall yield.

The one-step procedure using epoxy aldehyde (**1**) provides a diastereomeric mixture of alcohols such as **22c** and **22t**, which leads to mixtures of *cis*- and *trans*-dihydrofurans. However, this procedure can be used to prepare optically pure products starting from optically pure epoxy aldehyde (**1**).^{1,16} The two-step sequence starting with α,β -unsaturated aldehyde (**25**) to give an allylic alcohol such as **26**, which undergoes a threo-selective cyclization to give **27**, gives only the *trans*-dihydrobenzofuran (**28**), but cannot be used to make optically pure products because addition of the Grignard reagent to the aldehyde gives a racemic mixture. We thought it would be useful to explore the scope of this reaction.

Reaction of **29** with 3 equiv of *i*-PrMgCl in THF at -30 °C for 30 min and addition of 3 equiv of **25** and stirring for 1 h afforded allylic alcohol **30**, which was treated with 4 equiv of NaHCO₃ and 2.6 equiv of *m*-CPBA in CH₂Cl₂ at -20 °C overnight to give vaginol (**7t**) in 53% overall yield (see Scheme 8). A similar sequence converted **15** to myrtopside (**8t**) in 55% overall yield, **21** to 7,8-dimethoxymyrtopside (**9t**) in 44% yield, and 2-iodophenol (**31**) to the parent dihydrobenzofuran (**32**) in 56% yield. These results indicate that the two-step sequence provides a general route to racemic *trans*-2,3-dihydro-3-hydroxy-2-(1-hydroxy-1-methylethyl)benzofurans in 44-56% overall yield.



Scheme 8.

In conclusion, we have completed the first syntheses of myrtopside (**8t**) and 7,8-dimethoxymyrtopside (**9t**) by halogen-metal exchange of 3-iodo-4-methoxyquinolin-2(1H)-ones (**15**) and (**21**) with *i*-PrMgCl followed by addition of epoxy aldehyde (**1**). We have also developed a two-step sequence that leads selectively to *trans*-dihydrobenzofurans (**7t**), (**8t**), (**9t**), (**28**), and (**32**) by addition of enal (**25**) to the

appropriate Grignard reagent followed by threo selective epoxidation of the resulting allylic alcohol and cyclization with inversion.

EXPERIMENTAL

General Procedure. NMR spectra were recorded at 400 MHz with chemical shifts reported in δ and coupling constants in Hz; IR spectra are reported in cm^{-1} .

cis-3,5-Dihydro-3-hydroxy-2-(1-hydroxy-1-methylethyl)furo[3,2-c]quinolin-4(2H)-one (11c), trans-3,5-Dihydro-3-hydroxy-2-(1-hydroxy-1-methylethyl)furo[3,2-c]quinolin-4(2H)-one (11t), and trans-3,9-Dihydro-3-Hydroxy-2-(1-hydroxy-1-methylethyl)furo[2,3-b]quinolin-4(2H)-one (12t). A solution of ($\pm$)-**1** (220 mg, 2.2 mmol), 4-hydroxyquinolin-2(1H)-one (**10**, 322 mg, 2 mmol), CaCl_2 (244 mg, 2.2 mmol), and KOH (123 mg, 2.2 mmol) in MeOH (40 mL) was stirred at 25 °C for 3 d. The reaction was neutralized with 10% citric acid to pH 5-6 and extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried (MgSO_4), and concentrated to yield 449.1 mg of crude product. Flash chromatography on MeOH-deactivated silica gel (50:1 to 20:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) yielded 30.3 mg (6%) of pure **11c** and 85.9 mg (17%) of a 2:1 mixture of **11t** and **12t** as determined by analysis of the ^1H NMR spectrum. Reverse phase preparative HPLC (Zorbex Eclipse XDB-C18 9.4 $\times$ 250 mm column, 3:1 $\text{H}_2\text{O}/\text{MeOH}$, flow rate = 5 mL/min) of about 5.0 mg of this mixture gave 1.1 mg of **12t** (t_R = 13.1 min) and 2.9 mg of **11t** (t_R = 39.8 min).

A solution of ($\pm$)-**1** (44 mg, 0.44 mmol), 4-hydroxyquinolin-2(1H)-one (**10**, 64.4 mg, 0.4 mmol), and Cs_2CO_3 (142 mg, 0.44 mmol) in dry DMF (10 mL) was stirred under N_2 at 25 °C for 3 d. The reaction was neutralized with 10% citric acid to pH 5-6 and extracted with EtOAc. The combined EtOAc extracts were washed with water and brine, dried (MgSO_4), and concentrated to yield 98.6 mg of crude product. Flash chromatography on MeOH-deactivated silica gel (50:1 to 20:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) yielded 3.4 mg (3%) of pure **11c**, 3.2 mg (3%) of a 2:1 mixture of **11t** and **12t**, and 15.0 mg (8%) of a two-to-one adduct generated from two molecules of 4-hydroxyquinolin-2(1H)-one and one molecule of ($\pm$)-**1**.

Data for **11c**: mp 169-170 °C; ^1H NMR (CD_3OD) 7.81 (dd, 1, J = 7.8, 1.2), 7.58 (ddd, 1, J = 7.8, 7.8, 1.2), 7.39 (d, 1, J = 7.8), 7.26 (dd, 1, J = 7.8, 7.8), 5.49 (d, 1, J = 6.4), 4.54 (d, 1, J = 6.4), 1.55 (s, 3), 1.52 (s, 3); ^{13}C NMR (CD_3OD) 167.7, 163.7, 141.6, 133.3, 124.2, 123.7, 117.2, 113.0, 112.9, 94.4, 73.3, 71.6, 27.3, 26.7; IR (KBr) 3274, 2977, 1658, 1623; HRMS (DEI) calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_4(\text{MH}^+)$ 262.1079, found 262.1070.

Data for **11t**: ^1H NMR (CD_3OD) 7.85 (dd, 1, J = 7.9, 1.2), 7.60 (ddd, 1, J = 7.9, 7.9, 1.2), 7.40 (d, 1, J = 7.9), 7.28 (dd, 1, J = 7.9, 7.9), 5.44 (d, 1, J = 3.7), 4.53 (d, 1, J = 3.7), 1.31 (s, 3), 1.30 (s, 3); ^{13}C NMR (CD_3OD) 168.0, 164.3, 141.7, 133.2, 124.2, 123.7, 117.1, 113.0, 111.9, 101.3, 72.4, 72.0, 25.34, 25.32; HRMS (DEI) calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_4(\text{MH}^+)$ 262.1079, found 262.1069.

Data for **12t**: ^1H NMR (CD_3OD) 8.24 (d, 1, $J = 7.9$), 7.78-7.72 (m, 2), 7.46-7.42 (m, 1), 6.35 (d, 1, $J = 3.1$), 5.81 (s, 1, OH), 4.56 (d, 1, $J = 3.1$), 1.37 (s, 3), 1.33 (s, 3); ^{13}C NMR (CD_3OD) 133.6, 127.1, 125.3, 117.1, 96.1, 88.3, 83.2, 71.1, 25.6, 25.1 (four quaternary carbons were not observed); HRMS (DEI) calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_4(\text{MH}^+)$ 262.1079, found 262.1069.

Two-to-one adduct: ^1H NMR (CD_3OD) 7.99 (d, 1, $J = 7.9$), 7.87 (dd, 1, $J = 7.9, 1.2$), 7.54 (ddd, 1, $J = 7.9, 7.9, 1.2$), 7.49 (ddd, 1, $J = 7.9, 7.9, 1.2$), 7.36 (d, 1, $J = 7.9$), 7.28 (dd, 1, $J = 7.9, 7.9$), 7.27 (d, 1, $J = 7.9$), 7.22 (dd, 1, $J = 7.9, 7.9$), 5.19 (d, 1, $J = 6.7$), 5.07 (d, 1, $J = 6.7$), 1.37 (s, 3), 1.31 (s, 3).

Furo[3,2-c]quinolin-4(5H)-one (13). TFA (0.20 mL) was added to a suspension of **11c** (38.6 mg, 0.15 mmol) in CH_2Cl_2 (4 mL) and the solution was stirred at 25 °C for 40 min. The solution was neutralized with 30% NaOH saturated with NaCl and extracted with EtOAc (3×5 mL). The organic layer was washed with water (2×2 mL), brine (2×2 mL), dried (MgSO_4) and concentrated to yield 30.8 mg of crude **13**. Flash chromatography on silica gel (1:1 hexanes/EtOAc) gave 26.8 mg (98%) of pure **13**: mp 245-247 °C (lit.¹⁰ mp 243-245 °C); ^1H NMR ($\text{DMSO}-d_6$) 8.08 (d, 1, $J = 1.8$), 7.91 (d, 1, $J = 7.8$), 7.51 (ddd, 1, $J = 7.8, 7.8, 1.2$), 7.45 (d, 1, $J = 7.8$), 7.28 (ddd, 1, $J = 7.8, 7.8, 1.2$), 7.07 (d, 1, $J = 1.8$); ^{13}C NMR ($\text{DMSO}-d_6$) 158.9, 155.4, 145.5, 137.0, 129.5, 122.3, 120.2, 116.0, 115.5, 111.2, 107.7. The ^1H NMR and ^{13}C NMR ($\text{DMSO}-d_6$) spectral data match the literature data.¹⁰

4-Hydroxy-3-iodoquinolin-2(1H)-one (14) was prepared by the literature procedure.¹² A solution of iodine (1.75 g, 6.9 mmol) in warm dioxane (10 mL) was added in portions during 5 min to a refluxing solution of **10** (1.0 g, 6.2 mmol) and Na_2CO_3 (1.25 g, 11.8 mmol) in water (25 mL). After refluxing for 22 h, the solution was cooled to 5 °C and acidified with AcOH. The precipitate was collected by filtration and dried at 70 °C for 12 h to give pure **14** (1.49 g, 83%): ^1H NMR (CD_3OD) 8.01 (d, 1, $J = 8.0$), 7.58 (dd, 1, $J = 8.0, 8.0$), 7.34 (d, 1, $J = 8.0$), 7.26 (dd, 1, $J = 8.0, 8.0$).

3-Iodo-4-methoxyquinolin-2(1H)-one (15) was prepared by the literature procedure.^{13,14} A solution of **14** (1 g, 3.5 mmol) in EtOH (45 mL) was treated with a 4 molar excess of ethereal diazomethane and stirred at 25 °C for 3 h. Excess CH_2N_2 was destroyed by the addition of glacial AcOH. Evaporation of the solvent gave a gum which was dissolved in EtOAc (100 mL). The solution was washed with 1 M NaOH (3×20 mL) and water (2×20 mL), dried (MgSO_4), and concentrated to yield 1.09 g of crude **15**. Flash chromatography on silica gel (2:1 hexanes/EtOAc) yielded 0.55 g (52%) of **15**: ^1H NMR ($\text{DMSO}-d_6$) 7.76 (d, 1, $J = 7.9$), 7.59 (dd, 1, $J = 8.5, 7.3$), 7.37 (d, 1, $J = 8.5$), 7.24 (dd, 1, $J = 7.9, 7.3$), 3.94 (s, 3); ^{13}C NMR ($\text{DMSO}-d_6$) 166.8, 160.7, 138.8, 131.5, 122.7, 122.2, 115.59, 115.57, 88.8, 61.0. The ^1H NMR and ^{13}C NMR ($\text{DMSO}-d_6$) spectral data match the literature data.¹³

cis-2,3-Dihydro-3-hydroxy-4-methoxy- α,α -dimethylfuro[2,3-b]quinoline-2-methanol (8c), trans-2,3-Dihydro-3-hydroxy-4-methoxy- α,α -dimethylfuro[2,3-b]quinoline-2-methanol (myrtopsine, 8t), and 4-Methoxyquinolin-2(1H)-one (16). A solution of **15** (240 mg, 0.8 mmol) in dry THF (20 mL) was

stirred under N₂ at -30 °C for 5 min. *i*-PrMgCl (1.2 mL, 2 M in THF, 2.4 mmol, 3 equiv) was slowly added and the solution was stirred for 10 min. Epoxide (±)-(**1**) (248 mg, 2.48 mmol, 3.1 equiv) was added and the solution was stirred for 0.5 h. The reaction was then quenched with MeOH (1 mL) and the resulting solution was poured into a mixture of saturated aqueous NH₄Cl solution (2 mL) and water (2 mL). The mixture was extracted with CH₂Cl₂ and the organic layer was dried (MgSO₄) and concentrated to yield crude product. Flash chromatography on silica gel (50:1 to 20:1 CH₂Cl₂/MeOH) yielded 71.7 mg of impure **8c**, followed by 37.9 mg (27%) of **16**, and 74.5 mg (35%) of **8t**. Flash chromatography of impure **8c** on silica gel (3:2 hexanes/EtOAc) afforded 54.7 mg (25%) of **8c**.

Data for **16**: ¹H NMR (DMSO-*d*₆) 7.76 (d, 1, *J* = 7.9), 7.50 (dd, 1, *J* = 7.9, 7.9), 7.28 (d, 1, *J* = 7.9), 7.15 (dd, 1, *J* = 7.9, 7.9), 5.89 (s, 1), 3.92 (s, 3); ¹³C NMR (DMSO-*d*₆) 163.3, 163.2, 138.6, 131.0, 122.2, 121.4, 115.2, 114.5, 96.7, 56.1. The ¹H NMR and ¹³C NMR (DMSO-*d*₆) spectral data match the literature data.¹⁵

Data for **8c**: mp 169-171 °C; ¹H NMR (CD₃OD) 8.12 (d, 1, *J* = 7.9), 7.63-7.62 (m, 2), 7.38-7.34 (m, 1), 5.81 (d, 1, *J* = 5.5), 4.64 (s, 1, OH), 4.45 (s, 3), 4.34 (d, 1, *J* = 5.5), 1.53 (s, 3), 1.51 (s, 3); ¹³C NMR (CD₃OD) 170.1, 162.4, 148.8, 132.0, 126.8, 124.8, 124.3, 121.2, 106.4, 89.7, 73.0, 71.6, 59.1, 27.4, 26.3; IR (KBr) 3273, 2958, 1623, 1586; HRMS (DEI) calcd for C₁₅H₁₈NO₄ (MH⁺) 276.1236, found 276.1240.

Data for **8t**: mp 191-192 °C; ¹H NMR (CD₃OD) 8.13 (d, 1, *J* = 7.9), 7.62-7.60 (m, 2), 7.37-7.32 (m, 1), 5.72 (d, 1, *J* = 1.8), 4.52 (s, 3), 4.39 (d, 1, *J* = 1.8), 1.35 (s, 3), 1.27 (s, 3); ¹³C NMR (CD₃OD) 170.6, 162.8, 148.9, 131.9, 126.7, 124.7, 124.2, 121.3, 105.8, 96.7, 72.1, 71.4, 59.2, 26.2, 25.2; IR (KBr) 3228, 2976, 1632, 1587; HRMS (DEI) calcd for C₁₅H₁₈NO₄ (MH⁺) 276.1236, found 276.1241. The ¹H NMR spectral data correspond to the literature data.³

A similar sequence using **15** (192 mg, 0.64 mmol), *i*-PrMgCl (0.96 mL, 2 M in THF, 1.82 mmol, 3 equiv) and (*R*)-**1** (198.4 mg, 1.98 mmol, 3.1 equiv) gave 60.2 mg (35%) of (+)-**8t** and 46.3 mg (26%) of (-)-**8c**.

Data for (-)-**8c**: mp 158-159 °C; [α]_D²¹ -100.4° (*c* 0.5, CH₃OH); the ¹H NMR and ¹³C NMR spectral data are identical to those of racemic **8c**.

Data for (+)-**8t**: mp 199-200 °C (lit.,³ mp 208 °C, lit.,⁵ 201-202 °C); [α]_D²¹ +10.4° (*c* 0.6, CH₃OH) {lit.,^{3,5} for enantiomer [α]_D²⁰ -5.0° (*c* 1.0, CH₃OH)}; the ¹H NMR and ¹³C NMR spectral data are identical to those of racemic **8t**.

4-Methoxyfuro[2,3-*b*]quinoline (dictamnine, 17) and 4-Methoxy- α,α -dimethylfuro[2,3-*b*]quinoline-2-methanol (18). A solution of **8t** (27.8 mg, 0.1 mmol) in dry CH₂Cl₂ (40 mL) was treated with Et₃N (27.9 μ L, 0.20 mmol) and MsCl (9.1 μ L, 0.11 mmol) and then stirred at 25 °C under N₂ for 1 h. The organic solution was washed with water (2 $\times$ 10 mL), dried (MgSO₄) and concentrated to yield 26.1 mg of crude product. Flash chromatography on silica gel (4:1 to 2:1 hexanes/EtOAc) afforded **17** (3.8 mg, 19%) followed by **18** (10.7 mg, 41%).

Data for dictamnine (**17**): mp 131-132 °C (lit.,¹⁴ mp 132-134 °C, lit.,⁴ mp 128-130 °C); ¹H NMR (CDCl₃) 8.29 (d, 1, *J* = 7.8), 8.01 (d, 1, *J* = 7.8), 7.69 (dd, 1, *J* = 7.8, 7.8), 7.64 (d, 1, *J* = 2.8), 7.46 (dd, 1, *J* = 7.8, 7.8), 7.10 (d, 1, *J* = 2.8), 4.47 (s, 3); ¹³C NMR (CDCl₃) 163.8, 156.8, 145.6, 143.6, 129.6, 127.8, 123.7, 122.3, 118.7, 104.7, 103.4, 59.0. The ¹H NMR and ¹³C NMR (CDCl₃) spectral data match those of a sample purchased from Apin Chemicals LTD.

Data for **18**: ¹H NMR (CDCl₃) 8.26 (dd, 1, *J* = 7.9, 1.2), 7.98 (d, 1, *J* = 7.9), 7.67 (ddd, 1, *J* = 7.9, 7.9, 1.2), 7.44 (ddd, 1, *J* = 7.9, 7.9, 1.2), 6.90 (s, 1), 4.43 (s, 3), 1.72 (s, 6); ¹³C NMR (CDCl₃) 163.7, 161.8, 156.3, 145.2, 129.4, 127.7, 123.7, 122.3, 118.9, 104.6, 97.9, 69.5, 59.0, 28.6 (2 C). These data correspond to the literature data,¹⁴ except that our ¹H NMR data are 0.1 to 0.15 ppm downfield and our ¹³C NMR data are all about 1.2 ppm downfield.

4-Hydroxy-3-iodo-7,8-dimethoxyquinolin-2(1*H*)-one (20). A solution of iodine (532 mg, 2.1 mmol) in warm dioxane (3 mL) was added in portions during 5 min to a refluxing solution of 7,8-dimethoxy-4-hydroxyquinolin-2(1*H*)-one (**19**,²⁰ 416 mg, 1.9 mmol) and Na₂CO₃ (767 mg, 7.2 mmol) in water (7.5 mL). After refluxing for 2 h, the solution was cooled to 5 °C and acidified with AcOH. The precipitate was collected by filtration and dried at 70 °C for 12 h to give 438 mg (66%) of pure **20**: mp 183-184 °C; ¹H NMR (CD₃OD) 7.74 (d, 1, *J* = 9.2), 7.03 (d, 1, *J* = 9.2), 3.97 (s, 3), 3.92 (s, 3); ¹H NMR (DMSO-*d*₆) 10.93 (br s, 1, NH), 7.70 (d, 1, *J* = 9.2), 7.00 (d, 1, *J* = 9.2), 3.83 (s, 3), 3.76 (s, 3); ¹³C NMR (DMSO-*d*₆) 162.9, 160.8, 153.5, 133.7, 132.8, 118.5, 109.3, 107.3, 74.6, 60.7, 56.2.

3-Iodo-4,7,8-trimethoxy-quinolin-2(1*H*)-one (21). A solution of **20** (420 mg, 1.21 mmol) in ethanol (70 mL) was treated with a 4 molar excess of ethereal diazomethane and stirred at 25 °C for 40 min. Excess CH₂N₂ was destroyed by the addition of glacial acetic acid. Evaporation of the solvent gave 458 mg of a gummy residue. Flash chromatography on silica gel (2:1 to 1:2 hexanes/EtOAc) yielded 64.4 mg (14%) of 3-iodo-2,4,7,8-tetramethoxyquinoline followed by 243 mg (56%) of **21**.

Data for 3-iodo-2,4,7,8-tetramethoxyquinoline: ¹H NMR (CDCl₃) 7.69 (d, 1, *J* = 9.2), 7.14 (d, 1, *J* = 9.2), 4.15 (s, 3), 4.13 (s, 3), 4.02 (s, 3), 4.01 (s, 3); ¹³C NMR (CDCl₃) 166.4, 160.4, 153.0, 142.2, 142.1, 117.6, 117.5, 112.0, 73.6, 61.8, 61.4, 56.8, 55.0.

Data for **21**: mp 218-220 °C; ¹H NMR (CD₃OD) 7.60 (d, 1, *J* = 9.2), 7.09 (d, 1, *J* = 9.2), 4.02 (s, 3), 3.98 (s, 3), 3.92 (s, 3); ¹H NMR (CDCl₃) 9.49 (br, 1, NH), 7.51 (d, 1, *J* = 9.2), 6.87 (d, 1, *J* = 9.2), 4.02 (s, 3), 3.98 (s, 6); ¹³C NMR (CDCl₃) 167.8, 161.3, 153.5, 133.9, 132.6, 118.7, 111.4, 107.9, 84.1, 61.3, 61.1, 56.2; HRMS (EI) calcd for C₁₂H₁₂NO₄I (M⁺) 360.9811, found 360.9816.

cis-2,3-Dihydro-3-hydroxy-4,7,8-trimethoxy- α,α -dimethylfuro[2,3-*b*]quinoline-2-methanol (9c), trans-2,3-Dihydro-3-hydroxy-4,7,8-trimethoxy- α,α -dimethylfuro[2,3-*b*]quinoline-2-methanol (7,8-dimethoxymyrtopside, 9t), and cis-3,4-Dihydro-5,8,9-trimethoxy-2,2-dimethyl-2*H*-pyrano[2,3-*b*]quinoline-3,4-diol (23c). A solution of **21** (72 mg, 0.2 mmol) in dry THF (5 mL) was stirred

under N₂ at -30 °C for 5 min. *i*-PrMgCl (0.3 mL, 2 M in THF, 0.6 mmol, 3 equiv) was slowly added and the solution was stirred for 20 min. Epoxide ((±)-**1**) (60 mg, 0.6 mmol, 3 equiv) was added and the solution was stirred for 0.5 h. The reaction was then quenched with 1 mL of MeOH and the resulting solution was poured into a mixture of saturated aqueous NH₄Cl solution (2 mL) and water (2 mL). The mixture was extracted with EtOAc and the organic layer was dried (MgSO₄) and concentrated to yield crude product. Flash chromatography on silica gel (50:1 to 20:1 CH₂Cl₂/MeOH) yielded 15.3 mg of a 1:1 mixture of **9c** and **23c**, followed by 19.0 mg (28%) of **9t**. Preparative TLC (20:1 CH₂Cl₂/MeOH) of the mixture afforded 6.8 mg (10%) of **9c** and 6.8 mg (10%) of **23c**.

Data for **9c**: ¹H NMR (CDCl₃) 7.82 (d, 1, *J* = 9.2), 7.06 (d, 1, *J* = 9.2), 5.72-5.70 (dd, 1, *J* = 7.3, 6.1), 5.28 (d, 1, *J* = 7.3, OH), 4.40 (s, 3), 4.30 (d, 1, *J* = 6.1), 4.03 (s, 3), 3.99 (s, 3), 1.60 (s, 6); ¹³C NMR (CDCl₃) 168.1, 160.9, 153.3, 143.5, 141.7, 118.7, 115.5, 110.3, 103.3, 86.2, 72.8, 71.0, 61.5, 58.3, 56.4, 28.9, 24.4. Data for **9t**: mp 194-196 °C; ¹H NMR (CDCl₃) 7.57 (d, 1, *J* = 9.2), 6.94 (d, 1, *J* = 9.2), 5.57 (br d, 1, *J* = 2.4), 4.49 (d, 1, *J* = 2.4), 4.41 (s, 3), 3.98 (s, 3), 3.97 (s, 3), 1.38 (s, 3), 1.33 (s, 3); ¹³C NMR (CDCl₃) 168.4, 161.5, 153.3, 143.2, 141.6, 118.5, 115.3, 110.5, 101.7, 94.7, 71.3, 70.9, 61.4, 58.3, 56.6, 25.5, 24.7; IR (KBr) 3350, 2970, 1626, 1581, 1488, 1366, 1270; HRMS (EI) calcd for C₁₇H₂₁NO₆ (M⁺) 335.1369, found 336.1371. The spectral data are identical to those reported for 7,8-dimethoxymyrtopside.^{6,7}

Data for **23c**: ¹H NMR (CDCl₃) 7.64 (d, 1, *J* = 9.0), 7.14 (d, 1, *J* = 9.0), 5.21 (br, 1), 4.13 (s, 3), 4.04 (s, 3), 4.00 (s, 3), 3.90 (d, 1, *J* = 4.3), 1.60 (s, 3), 1.42 (s, 3); ¹H NMR (CDCl₃ + D₂O) 5.21 (d, 1, *J* = 4.9), 3.89 (d, 1, *J* = 4.9); ¹³C NMR (CDCl₃) 165.6, 159.2, 153.0, 143.5, 142.1, 117.5, 116.2, 112.1, 108.1, 79.0, 70.7, 63.6, 62.4, 61.6, 56.7, 24.6, 23.8.

A similar sequence using **21** (72 mg, 0.2 mmol), *i*-PrMgCl (0.3 mL, 2 M in THF, 0.6 mmol, 3 equiv) and (*R*)-**1** (60 mg, 0.6 mmol, 3 equiv) gave 17.6 mg (26%) of (+)-**9t**, and 6.2 mg (9%) of **9c** and 6.5 mg (10%) of **23c**.

Data for (+)-**9t**: mp 166-168 °C; [α]_D²¹ +17.0° (c 0.165, CHCl₃) {lit.,⁷ [α]_D²³ +16.2° (c 0.165, CHCl₃)}; the ¹H NMR and ¹³C NMR spectral data are identical to those of racemic **9t**.

Methyl *trans*-2,3-Dihydro-3-hydroxy-2-(1-hydroxy-1-methylethyl)benzofuran-5-carboxylate (26). MeMgBr (1.36 mL, 1.1 M in THF, 1.5 mmol) was added dropwise to a solution of methyl 4-hydroxy-3-iodobenzoate (**24**, 420 mg, 1.5 mmol) and LiCl (63.6 mg, 1.5 mmol) in dry THF (5 mL) under N₂ at -30 °C and the solution was stirred for 30 min. Then, *i*-PrMgCl (0.75 mL, 2 M in THF, 1.5 mmol) was slowly added and the mixture was stirred for 30 min at -30 °C. 3-Methyl-2-butenal (**25**, 0.15 mL, 1.5 mmol) was added and the solution was stirred for 1 h. The solution was poured into a mixture of saturated aqueous NH₄Cl solution (2 mL) and water (2 mL). The phases were separated and the aqueous phase was extracted with Et₂O. The combined organic layers were dried (Na₂SO₄) and aqueous

yield crude **26** that was used in the next step without purification.

A suspension of crude **26**, NaHCO₃ (189 mg, 2.2 mmol, 1.5 equiv), and *m*-CPBA (303 mg of 85% pure, 1.5 mmol, 1 equiv) in CH₂Cl₂ (15 mL) was stirred at 0 °C for 5 h. The reaction was quenched by adding saturated Na₂SO₃ (5 mL). The phases were separated and the aqueous phase was extracted with Et₂O (3 × 15 mL). The combined organic layers were washed with 1 M NaOH (3 × 10 mL) and brine, dried (MgSO₄) and concentrated to yield 452.5 mg of crude **28**. Flash chromatography on silica gel (2:1 hexanes/EtOAc to 1:1 hexanes/EtOAc) yielded 211.5 mg (56%) of **28**: ¹H NMR (CD₃OD) 8.03 (s, 1), 7.94 (d, 1, *J* = 8.2), 6.89 (d, 1, *J* = 8.2), 5.34 (d, 1, *J* = 4.3), 4.32 (d, 1, *J* = 4.3), 3.87 (s, 3), 1.27 (s, 6); ¹H NMR (acetone-*d*₆) 8.01 (br s, 1), 7.91 (dd, 1, *J* = 8.5, 1.8), 6.85 (d, 1, *J* = 8.5), 5.45 (d, 1, *J* = 4.2), 4.36 (d, 1, *J* = 4.2), 3.83 (s, 3), 1.28 (s, 3), 1.27 (s, 3); ¹³C NMR (acetone-*d*₆) 206.3, 167.0, 165.2, 132.9, 128.2, 123.5, 110.4, 99.1, 72.7, 71.1, 52.1, 25.9 (2 C); HRMS (DEI) calcd for C₁₃H₁₇O₅ (MH⁺) 253.1076, found 253.1088. The ¹H and ¹³C NMR (acetone-*d*₆) spectral data match those of the authentic sample provided by Prof. Jenett-Siems. The spectral data reported to be in CD₃OD are actually in acetone-*d*₆.^{22,26}

Preparation of Vaginol (7t) from 25 and 29. *i*-PrMgCl (0.3 mL, 2 M in THF, 0.6 mmol, 3 equiv) was added dropwise to a solution of **29** (58 mg, 0.2 mmol) in dry THF (3 mL) under N₂ at -30 °C and the solution was stirred for 30 min. Enal (**25**) (60 μL, 0.6 mmol, 3 equiv) was added and the solution was stirred for 1 h. The solution was poured into a mixture of saturated aqueous NH₄Cl solution (1 mL) and water (1 mL). The phases were separated and the aqueous phase was extracted with Et₂O. The combined organic layers were dried (Na₂SO₄) and concentrated to yield crude **30** that was used in the next step without purification.

To a suspension of crude **30** and NaHCO₃ (69 mg, 0.8 mmol, 4 equiv) in H₂O (1 mL) at -20 °C was added under stirring a solution of *m*-CPBA (104 mg of 85% pure, 0.51 mmol, 2.6 equiv) in CH₂Cl₂ (4 mL). The reaction was stirred overnight at -20 °C and quenched by adding saturated Na₂SO₃ (1 mL). The phases were separated and the aqueous phase was extracted with Et₂O. The combined organic layers were washed with 1 M NaOH (3 × 2 mL) and brine, dried (MgSO₄) and concentrated to yield crude product. Flash chromatography on MeOH-deactivated silica gel (1:1 hexanes/EtOAc) yielded 27.8 mg (53%) of vaginol (**7t**) identical to that obtained from **1**.¹

Preparation of Myrtopsine (8t) from 15 and 25. Reaction of **15** (60 mg, 0.2 mmol, 1 equiv), *i*-PrMgCl (0.3 mL, 2 M in THF, 0.6 mmol, 3 equiv), and 3-methyl-2-butenal (**25**) (60 μL, 0.6 mmol, 3 equiv) was carried out using the procedure for preparation of **7t** from **29**. Epoxidation of the resulting crude allylic alcohol with *m*-CPBA (104 mg of 85% pure, 0.51 mmol, 2.6 equiv) and NaHCO₃ (69 mg, 0.8 mmol, 4 equiv) in CH₂Cl₂/H₂O (4 mL/1 mL) at -20 °C gave 30.2 mg (55%) of myrtopsine (**8t**) identical to that obtained from **15** and **1**.

Preparation of 7,8-Dimethoxymyrtopsine (9t) from 21 and 25. Reaction of **21** (21.7 mg, 0.06 mmol),

i-PrMgCl (0.09 mL, 2 M in THF, 0.18 mmol, 3 equiv), and 3-methyl-2-butenal (18 μ L, 0.18 mmol, 3 equiv) was carried out using the procedure for the preparation of **7t** from **29**. Epoxidation of the resulting crude allylic alcohol with *m*-CPBA (37 mg of 85% pure, 0.18 mmol, 3 equiv) and NaHCO₃ (20 mg, 0.24 mmol, 4 equiv) in CH₂Cl₂/H₂O (2 mL/0.5 mL) at -20 °C gave 8.9 mg (44%) of 7,8-dimethoxymyrtosine (**9t**) identical to that obtained from **21** and **1**.

trans-2,3-Dihydro-3-hydroxy- α,α -dimethylbenzofuran-2-methanol (32). *i*-PrMgCl (1.0 mL, 2 M in THF, 2 mmol, 2 equiv) was added dropwise to a solution of 2-iodophenol (**31**, 220 mg, 1 mmol) in dry THF (2 mL) under N₂ at 25 °C and the solution was stirred at 50 °C for 2 h. The exchange was complete as indicated by TLC and the solution was cooled to -30 °C. Enal (**25**) (97 μ L, 1 mmol) was added and the solution was stirred for 1 h. The solution was poured into a mixture of saturated aqueous NH₄Cl solution (1 mL) and water (1 mL). The phases were separated and the aqueous phase was extracted with Et₂O. The combined organic layers were dried (Na₂SO₄) and concentrated to yield crude product that was used in the next step without purification.

A suspension of the crude allylic alcohol, NaHCO₃ (130 mg, 1.5 mmol, 1.5 equiv), and *m*-CPBA (202 mg of 85% pure, 1 mmol) in CH₂Cl₂ (10 mL) was stirred at 0 °C for 5 h. The reaction was quenched by adding saturated Na₂SO₃ (5 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 $\times$ 15 mL). The combined organic layers were washed with 1 M NaOH (3 $\times$ 10 mL) and brine, dried (MgSO₄) and concentrated to yield crude product. Flash chromatography on silica gel (2:1 hexanes/EtOAc) yielded 109.1 mg (56%) of **32**: ¹H NMR (CDCl₃) 7.37 (d, 1, *J* = 7.9), 7.26 (dd, 1, *J* = 8.5, 7.3), 6.95 (dd, 1, *J* = 7.9, 7.3), 6.85 (d, 1, *J* = 8.5), 5.36 (d, 1, *J* = 4.5), 4.28 (d, 1, *J* = 4.5), 1.34 (s, 3), 1.27 (s, 3); ¹³C NMR (CDCl₃) 159.7, 130.5, 128.5, 125.3, 121.2, 110.2, 96.7, 73.6, 71.3, 25.6, 24.4; HRMS (DEI) calcd for C₁₁H₁₄O₃Na (MNa⁺) 217.0841; found 217.0842.

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