Synthesis and Absolute Structure of (−)-Umtatin

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A new preparation of 2-(hydroxymethyl)chromones was developed via the new regio-selective six-membered cyclization of 1-[*o*-(*tert*-butyldimethylsiloxy)phenyl]but-2-yn-1-ones by a three-step treatment with 1) diethylamine (activation of the γ-position), 2) KF-18-crown-6 (deprotection), and 3) silica-gel (cyclization). A naturally occurring chiral hydroxymethylfurochromone, (−)-umtatin, was synthesized starting from chiral (*R*)-(−)-2-isopropenyl-4,6-dimethoxy-2,3-dihydrobenzofuran, and the absolute structure was determined to R.

Many naturally occurring chiral isopropenyldihydrobenzofurans were isolated from various kinds of plants. There are different types, *R* or *S*, of absolute configurations,[1] and these showed the different types of cyclization which exists in different kinds of plants. Our interests were focused on the chemotaxonomy, is there any relationship between the absolute configurations and the origin.

Dean et al. isolated a chiral furochromone, (−)-umtatin (**1**), from *Ptaeroxylon obliquum* (Meliaceae),[2] and proposed the structure of 4-hydroxy-7-(hydroxymethyl)-2-isopropenyl-2,3-dihydro-5*H*-furo[3,2-*g*][1]benzopyran-5-one, shown in Figure 1, but the absolute configuration was left to be ambiguous.

Kondo and Takemoto isolated (+)-cimifugin, having a similar dihydrofurochromone structure of 7-(hydroxymethyl)-2-(1-hydroxy-1-methylethyl)-4-methoxy-2,3-dihydro-5*H*-furo-[3,2-*g*][1]benzopyran-5-one, from *Cimicifuga simplex* (Ranunculaceae), and showed S configuration.[3] The optical rotation suggested that naturally occurring (−)-umtatin has the opposite configuration to naturally occurring (+)-cimifugin. To clear this, the synthesis of chiral (−)-umtatin was needed. But, there was no report about the synthesis of umtatin, not only chiral but also racemic. In this paper, the synthesis of umtatin, both racemic and chiral, and the absolute structure of chiral (−)-umtatin is described.

We already reported the effective chromone-ring formation using 2,2-dimethoxy-*N*,*N*-dimethylethylamine.[4] As shown in Scheme 1, the 7-methyl analog **2** was synthesized from 5-acetyl-4-(*t*-butyldimethylsiloxy)-6-hydroxy-2-isopropenyl-2,3-dihydrobenzofuran (**4d**) using 2,2-dimethoxy-*N*,*N*-dimethylethylamine, as described next. Racemic remirol, 5-acetyl-4-hydroxy-2-isopropenyl-6-methoxy-2,3-dihydrobenzofuran (**4b**), was prepared from 2-isopropenyl-4,6-dimethoxy-2,3-dihydrobenzofuran (**3**) according to the reported procedure,[5] and then

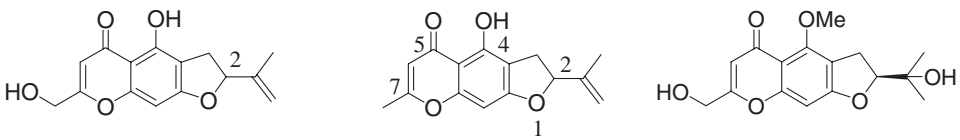
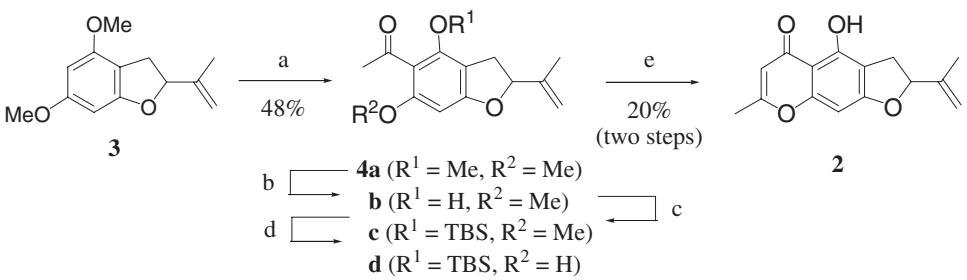


Figure 1. Chiral (−)-umtatin (**1**), the 7-methyl analog **2**, and chiral (+)-cimifugin.



Reaction conditions: a) CH_3CO_2H, $(CF_3CO)_2O$, room temperature, 1 h; b) MgI_2-OEt_2, benzene, reflux, 3 h, 82%; c) TBSCl, NaH, THF, room temperature, 30 min, 83%; d) MgI_2-OEt_2, benzene, reflux, 15 h, 82%; e) 1) $CH_3C(OMe)_2NMe_2$, xylene, reflux, 24 h; 2) 1 M TBAF, THF, room temperature, 1 h, 20% (two steps)

Scheme 1. Synthesis of methylfurochromones **2** from dimethoxydihydrobenzofuran **3**.

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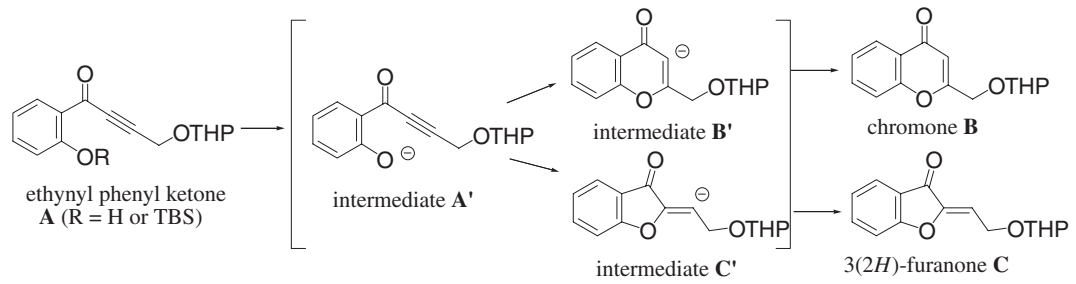
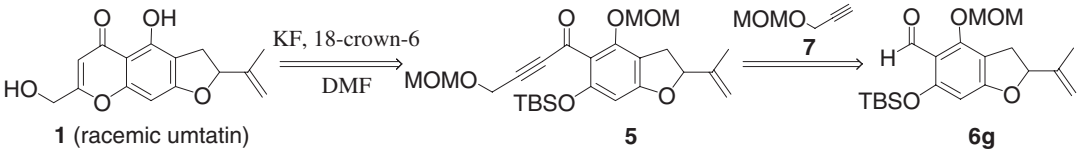
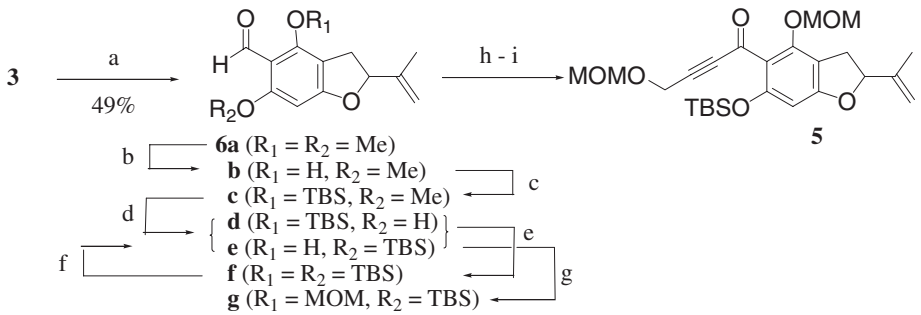


Scheme 2. Construction of 2-(hydroxymethyl)chromones.



Scheme 3. Synthetic strategy for racemic umtatin **1**.



Reaction conditions: a) DMF-$POCl_3$, 50 °C, 1 h; b) MgI_2-OEt_2, benzene, reflux, 10 min, 99%; c) TBSOTf, 2,6-lutidine, dichloromethane, 0 °C, 45 min, 99%; d) $AlBr_3$, acetonitrile, room temperature, 30 min, **6d** (39%), **6e** (43%); e) TBSCl, NaH, THF, room temperature, 40 min, 94%; f) MgI_2-OEt_2, benzene, 60 °C, 20 min, 99%; g) MOMCl, NaH, THF, room temperature, 1 h, 91%; h) **7**, *n*-BuLi, THF, -78 °C, 30 min, 74%; i) MnO_2, dichloromethane, room temperature, 32 h, 89%

Scheme 4. Preparation of 1-(dihydrobenzofuran-5-yl)butynone **5** via benzofuran-5-carbaldehyde **6**.

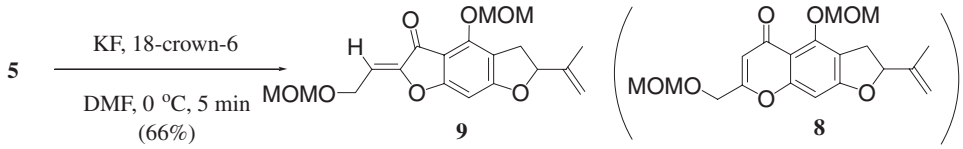
converted to **4d** by TBS protection followed by demethylation. The chromone-ring construction of **4d** effectively gave the 7-methyl analog **2** by treating with 2,2-dimethoxy-*N*,*N*-dimethylethylamine in refluxing xylene followed by deprotection with TBAF. However, any side-chain conversion of **2** caused the oxidation on the dihydrofuran ring and the result was unsuccessful.

Garcia et al. reported, in the cyclization of 1-(*o*-hydroxyphenyl)butynone **A** (R = H), as shown in Scheme 2, both five- and six-membered cyclization might be possible to give a mixture of 3(2*H*)-furanone **C** (as a kinetically favored product) and chromone **B** (as a thermodynamically favored product).[6] But recently, Nakatani et al. reported the regio-selective cyclization by treating 1-[*o*-(*t*-butyldimethylsiloxy)phenyl]butynone **A** (R = TBS) with potassium fluoride–18-crown-6 to give corresponding chromones **B**.[7]

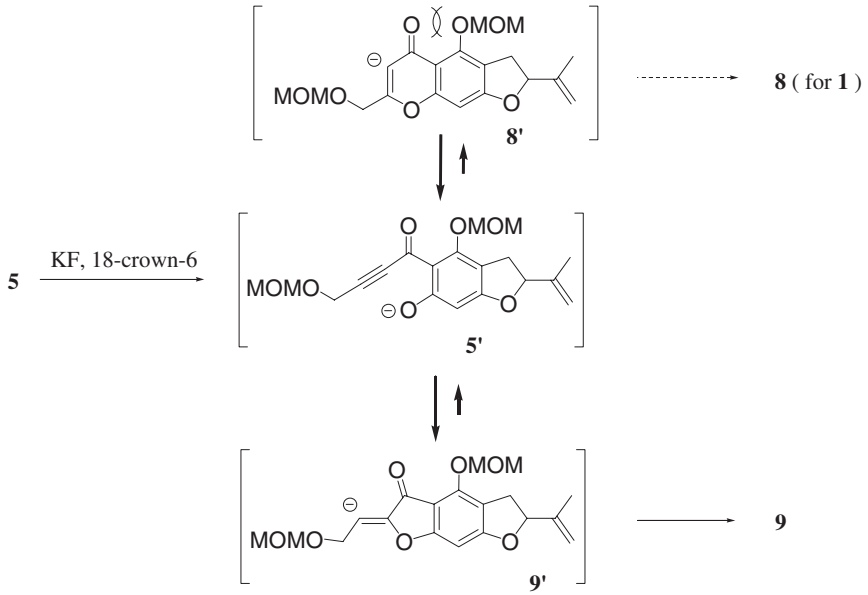
So, a new strategy for racemic umtatin **1** was planned, as shown in Scheme 3, using the Nakatani's regio-selective cyclization. The racemic umtatin **1** might be obtained by the cyclization of 1-[6-(*t*-butyldimethylsiloxy)dihydrobenzofuran-5-yl]-butynone **5**, which might be prepared by the propynylation of 6-(*tert*-butyldimethylsiloxy)-4-(methoxymethyloxy)dihydrobenzofuran-5-carbaldehyde **6g** with 3-(methoxymethyloxy)-1-propyne (**7**) followed by oxidation with manganese dioxide.

Similarly to the conversion from **4a** to **4d**, the starting substrate **6g** was prepared, as shown in Scheme 4, from 4,6-dimethoxy-2,3-dihydrobenzofuran-5-carbaldehyde **6a**, described next.

According to the reported procedure,[8] **6a** was prepared by Vilsmeier formylation of 2-isopropenyl-4,6-dimethoxy-2,3-dihydrobenzofuran (**3**), then converted to 4-(*t*-butyldimethylsiloxy)-6-methoxy-5-carbaldehyde **6c** by regio-selective demethylation with magnesium iodide etherate, giving 4-hydroxy-6-methoxy-5-carbaldehyde **6b** followed by TBS protection with *t*-butyldimethylsilyl trifluoromethanesulfonate. The demethylation of **6c** with magnesium etherate caused the removal of TBS to recover **6b** in major (80%), and the desired 4-(*t*-butyldimethylsiloxy)-6-hydroxy-5-carbaldehyde **6d** was



Scheme 5. Cyclization of 1-(dihydrobenzofuran-5-yl)butynone **5** in Nakatani's procedure.



Scheme 6. Cyclization mechanism of 1-(dihydrobenzofuran-5-yl)butynone **5**.

obtained in minor (trace). The demethylation of **6c** was, however, effective with aluminum tribromide in acetonitrile, but accompanied with a migration of *t*-butyldimethylsilyl group, to give a mixture of the desired 4-(*t*-butyldimethylsiloxy)-6-hydroxy-5-carbaldehyde **6d** and the TBS group migrated to afford 6-(*t*-butyldimethylsiloxy)-4-hydroxy-5-carbaldehyde **6e**. Being difficult to separate each component, the mixture was converted to 4,6-bis(*t*-butyldimethylsiloxy)-5-carbaldehyde **6f**, and then subjected to regio-selective deprotection with magnesium iodide etherate in mild condition to give the desired pure **6e**. 6-(*t*-Butyldimethylsiloxy)-4-hydroxy-5-carbaldehyde **6e**, thus obtained, was then treated with chloromethyl methyl ether to give **6g**, and converted to **5** by the propynylation with 3-(methoxymethyloxy)-1-propyne (**7**)–*n*-butyllithium followed by oxidation with manganese dioxide.

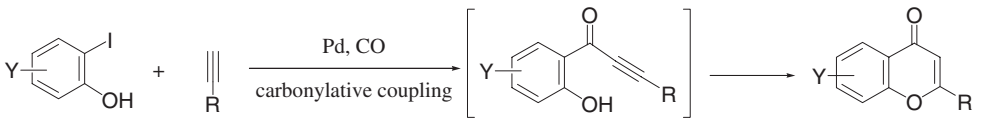
The 1-(dihydrobenzofuran-5-yl)butynone **5**, thus obtained, was then subjected to the six-membered chromone cyclization.[7] In spite of the use of the Nakatani's procedure, as shown in Scheme 5, the cyclization of **5** showed the five-membered cyclization to give only the undesired 3(2*H*)-benzodifuranone **9**, and none of the desired six-membered furochromone **8** was observed. Nakatani et al. described that the kinetic protonation causes the five-membered cyclization and the equilibrium leads the six-membered cyclization.

This might be explained by a steric repulsion between the bulky 4-methoxymethyl group and the carbonyl.[9] As shown in Scheme 6, the bulky 4-methoxymethyloxy group destabilizes the six-membered intermediate **8′** leading the furochromone **8**, and the equilibrium in the intermediates (**5′**, **8′**, and **9′**) might be favorable to the five-membered intermediate **9′** leading the benzodifuranone **9** in any condition.

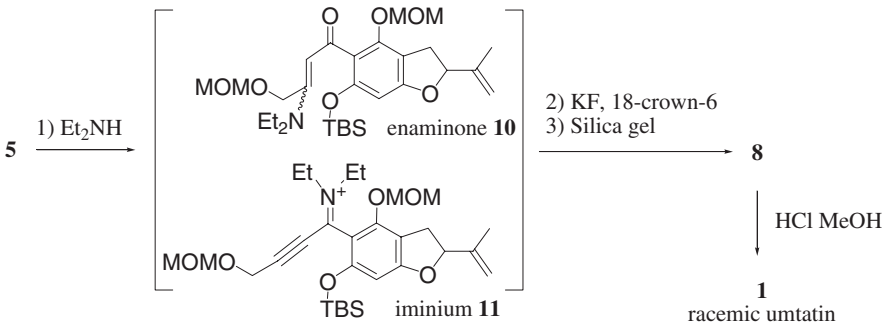
Recently, Torii et al. reported a new six-membered chromone cyclization via Pd-catalyzed carbonylation of *o*-iodophenols with acetylenes,[10] as shown in Scheme 7, where the use of diethylamine was effective for the six-membered cyclization of a supposed intermediate, 1-(2-hydroxyphenyl)butynone.

A similar cyclization was attempted after treating **5** with diethylamine (Scheme 8). The mixture of **5** and diethylamine was treated with potassium fluoride–18-crown-6, and the resulting mixture was then treated with silica gel to give the desired six-membered chromone **8**. This might be explained in the following three steps mechanism; 1) activation of the β-carbon of the conjugated ynone **5** either the regio-selective nucleophilic attach of diethylamine to form an enaminone **10** or the nucleophilic attach of diethylamine on the carbonyl carbon to form an iminium **11**, 2) deprotection of TBS, and 3) acidic cyclization. Acidic deprotection of **8** gave racemic umtatin **1**, which was identical with the natural (−)-umtatin in all reported spectra data.[2]

Either chiral 4,6-dimethoxydihydrobenzofuran (−)-**3** or (+)-**3** was needed for the synthesis of chiral (−)-umtatin. We already reported the effective preparation of both enantiomers using kinetic resolution of racemic 4,6-dimethoxydihydrobenzofuran **3**.[1d] (+)-Cimifugin, having a similar dihydrofurochromone structure of 7-(hydroxymethyl)-2-(1-hydroxy-1-methylethyl)-4-methoxy-2,3-dihydro-5*H*-furo[3,2-*g*]-[1]benzopyran-5-one, showed S configuration.[3] So, naturally occurring chiral (−)-umtatin, showing an opposite optical



Scheme 7. A new chromone cyclization via Pd-catalyzed carbonylation.



Scheme 8. Revised cyclization of 1-(dihydrobenzofuran-5-yl)butynone **5**.

rotation, was supposed to be R configuration, and the chiral (*R*)-(−)-**3** might be suitable as starting material.

The starting chiral material, (*R*)-(−)-**3** of 99%ee, was prepared by the kinetic resolution of racemic **3** using Sharpless asymmetric dihydroxylation, treating with $K_2[Os(OH)_4O_2]$, $K_3[Fe(CN)_6]$, K_2CO_3, $CH_3SO_2NH_2$, and chiral ligand $(DHQ)_2AQN$.[1d,11] Similarly to the conversion from racemic **3** to racemic **6c**, chiral (*R*)-(−)-**3** was converted chiral (*R*)-**6c** in three steps; 1) Vilsmeier formylation, 2) selective demethylation giving (*R*)-(−)-**6b**, and 3) TBS protection. And, the chiral umtatin was similarly synthesized from chiral (*R*)-**6c**, via mild demethylation with aluminum tribromide, TBS protection giving, 4) selective deprotection with magnesium iodide etherate giving (*R*)-**6e**,[12] and 5) methoxymethyl protection. Propynylation of (*R*)-**6g** with **7**–*n*-butyllithium following oxidation with manganese dioxide effectively gave chiral butynone (*R*)-**5**. Chiral (*R*)-**5** was treated with diethylamine and then with potassium fluoride–18-crown-6, and a final treatment with silica gel effectively gave the corresponding chromone, which was then deprotected to (*R*)-(−)-umtatin. The synthesized chiral (*R*)-(−)-umtatin was identical with the natural (−)-umtatin in all spectral data and showed the same rotation with the natural (−)-umtatin.[2] Naturally occurring (−)-umtatin was thus synthesized starting from chiral (*R*)-(−)-2-isopropenyl-4,6-dimethoxy-2,3-dihydrobenzofuran (**3**) in 5.5% (13 steps), and so the absolute structure of natural (−)-umtatin was determined to R.

Experimental

Cyclization of 5 by Treating with Potassium Fluoride–18-Crown-6. Under an argon atmosphere, to a soluition of **5** (45 mg, 0.87 mmol) in dry DMF (3 mL) was added 18-crown-6 (45 mg, 0.17 mmol) and potassium fluoride (10 mg, 12 mmol) at 0 °C, and the mixture was stirred at 0 °C for 5 min. The mixture was treated with aqueous ammonium chloride solution, and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified on a silica-gel column to give 6-isopropenyl-4-(methoxymethyloxy)-2-(2-methoxymethyloxyethylidene)-5,6-dihydrobenzo[1,2-*b*;5,4-*b*′]difuran-3-one (**9**) (23 mg, 66%).

6-Isopropenyl-4-(methoxymethyloxy)-2-(2-methoxymethyloxyethylidene)-5,6-dihydrobenzo[1,2-*b*;5,4-*b*′]difuran-3-one (**9**); pale yellow oil; IR (liquid film) 1703 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.76 (3H, s), 3.02 (1H, dd, $J = 7.3$ and 15.5 Hz), 3.37 (1H, dd, $J = 9.7$ and 15.5 Hz), 3.41 (3H, s), 3.52 (3H, s), 4.46 (2H, d, $J = 7.0$ Hz), 4.69 (2H, s), 4.96 (1H, br s), 5.09 (1H, br s), 5.32 (1H, dd, $J = 7.3$ and 9.7 Hz), 5.49 (2H, s), 6.05 (1H, t, $J = 7.0$ Hz), 6.32 (1H, s).

Conversion of 5 to Racemic Umtatin 1 by Cyclization Using Diethylamine, KF–18-crown-6, Silica Gel Followed by Deprotection. Under an argon atmosphere, to a solution of **5** (80 mg, 0.17 mmol) was added diethylamine (1 mL), and the mixture was stirred at room temperature for 5 min. The mixture was treated with 18-crown-6 (88 mg, 0.33 mmol) and potassium fluoride (23 mg, 0.40 mmol) at 0 °C, and stirred at room temperature for 1 h, and concentrated in vacuo. The residue was diluted with diethyl ether and stirred with silica gel (1.50 g) for 3.5 h. The mixture was filtered through a short celite pad, and concentrated in vacuo. The residue gave crude 2-isopropenyl-4-(methoxymethyloxy)-7-(methoxymethyloxymethyl)-2,3-dihydro-5*H*-furo[3,2-*g*]-[1]benzopyran-5-one (**8**) (40 mg, crude 65%).

2-Isopropenyl-4-(methoxymethyloxy)-7-(methoxymethyloxymethyl)-2,3-dihydro-5*H*-furo[3,2-*g*][1]benzopyran-5-one (**8**); colorless crystal; IR (liquid film) 1661 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.76 (3H, s), 3.14 (1H, dd, $J = 7.7$ and 16.0 Hz), 3.42 (3H, s), 3.49 (1H, dd, $J = 9.3$ and 16.0 Hz), 3.58 (3H, s), 4.42 (2H, s), 4.73 (2H, s), 4.96 (1H, br s), 5.10 (1H, br s), 5.18 (2H, s), 5.31 (1H, dd, $J = 7.7$ and 9.3 Hz), 6.23 (1H, s), 6.60 (1H, s).

Under an argon atmosphere, to a solution of crude **8** (40 mg, 0.083 mmol) in methanol (3 mL) was added a catalytic amount of concd hydrochloric acid at room temperature, and the mixture was refluxed for 30 min. After cooling, the mixture was concentrated in vacuo, and diluted with diethyl ether. The organic layer was washed with a saturated sodium hydrogencarbonate solution and brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was recrystallized from cyclohexane–ethyl acetate to give 4-hydroxy-7-(hydroxymethyl)-2-isopropenyl-2,3-dihydro-5*H*-furo[3,2-*g*][1]benzopyran-5-one (racemic

umtatin) (**1**) (14 mg, 31% in two steps).

4-Hydroxy-7-(hydroxymethyl)-2-isopropenyl-2,3-dihydro-5*H*-furo[3,2-*g*][1]benzopyran-5-one (**1**); colorless crystals; IR (liquid film) 3407 (OH) and 1674 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.77 (3H, s), 2.06 (1H, br s), 3.10 (1H, dd, $J = 7.3$ and 15.9 Hz), 3.35 (1H, dd, $J = 9.3$ and 15.9 Hz), 4.56 (2H, s), 4.95 (1H, br s), 5.09 (1H, br s), 5.33 (1H, dd, $J = 7.3$ and 9.3 Hz), 6.23 (1H, s), 6.34 (1H, s), 12.85 (1H, s); Mass (*m*/*z*): 274 (M^+), 259 ($M^+ - CH_3$), 233 ($M^+ - C_3H_5$).

This was identical with natural umtatin in all reported spectral data.[2]

Acetylation of 1. Under an argon atmosphere, to a solution of **1** (16 mg, 0.058 mmol) in dry dichloromethane (1 mL) and pyridine (0.010 mL, 0.15 mmol) was added acetic anhydride (0.01 mL, 0.12 mmol), and the mixture was stirred at room temperature for 6 h. After the reaction, the mixture was treated with brine, and extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified on a silica gel to give 7-acetoxymethyl-4-hydroxy-2-isopropenyl-2,3-dihydro-5*H*-furo[3,2-*g*][1]benzopyran-5-one, acetate of racemic umtatin, (16 mg, 89%).

7-Acetoxymethyl-4-hydroxy-2-isopropenyl-2,3-dihydro-5*H*-furo[3,2-*g*][1]benzopyran-5-one; pale yellow oil; ^1H NMR ($CDCl_3$): δ 1.77 (3H, s), 2.19 (3H, s), 3.01 (1H, dd, $J = 7.3$ and 15.8 Hz), 3.36 (1H, dd, $J = 9.5$ and 15.8 Hz), 4.95 (1H, br s), 4.96 (2H, s), 5.10 (1H, br s), 5.34 (1H, dd, $J = 7.3$ and 9.5 Hz), 6.22 (1H, s), 6.36 (1H, s), 12.74 (1H, s).

The acetate was also identical with the acetate of natural umtatin in all ^1H NMR data.[2]

Conversion of (*R*)-(−)-3 to (*R*)-6g. According to the reported procedure,[1d] chiral (*R*)-(−)-**3** was prepared by the kinetic resolution of racemic **3** via Sharpless dihydroxylation using potassium osmate(IV) dehydrate, $(DHQ)_2AQN$, potassium hexacyanoferrate(III).

According to the reported procedure,[8] chiral (*R*)-(−)-**3** (652 mg, 2.96 mmol, 99%ee) was formylated with DMF (647 mg, 8.86 mmol) and phosphoryl chloride (0.55 mL, 5.92 mmol) to give chiral (*R*)-(−)-**6a** (297 mg, 45%, 99%ee, $[\alpha]_D^{25}$ −35.4°) as pale yellow crystal. The optical purity was determined on a HPLC using chiral column OJ-H (eluent; 2-propanol in hexane).

According to the racemic conversion, the region-selective demethylation of chiral (*R*)-(−)-**6a** (751 mg, 3.03 mol) with a solution of anhydrous aluminum bromide (729 mg, 2.73 mmol) in dry acetonitrile (10 mL) at room temperature for 10 min, to give the chiral (*R*)-(−)-**6b** (510 mg, 72%, 96%ee, $[\alpha]_D^{25}$ −74.8°) as colorless crystal. The optical purity was determined by HPLC using chiral column OJ-H, 0.5% ethanol in hexane) The chiral of (*R*)-(−)-**6b** was identical with the racemic **6b** in IR and ^1H NMR spectra.

Then, chiral (*R*)-(−)-**6b** (510 mg, 2.18 mmol) was protected with TBSOTf (0.60 mL, 2.62 mmol) in dry dichloromethane (8 mL) at 0 °C for 45 min to give the chiral (*R*)-**6c** (763 mg, 99%) as a pale yellow oil.

Demethylation of chiral (*R*)-(−)-**6c** (763 mg, 2.19 mol), with a solution of anhydrous aluminum bromide (523 mg, 1.96 mmol) in dry acetonitrile (12 mL) at room temperature for 50 min, gave a mixture (365 mg, 50%) of chiral (*R*)-**6d** and (*R*)-**6e** (a pale yellow oil) and (*R*)-6-dihydroxy-4-methoxy-5-carbaldehyde (*R*)-**6b** (114 mg, 22%) was also recovered.

The solution of chiral (*R*)-**6d** and (*R*)-**6e** (365 mg, 1.09 mmol) in dry THF (5 mL) was treated with a suspension of 60% sodium hydride (73 mg, 1.64 mmol) in dry THF (10 mL) and then treated with TBSCl (196 mg, 1.31 mmol) under stirring at room temperature for 40 min to give crude chiral (*R*)-**6f** (602 mg, crude 123%).

The regio-selective deprotection of crude chiral (*R*)-**6f** (602 mg) with a magnesium iodide etherate solution, prepared from magnesium (turning, 52 mg, 2.18 mmol), dry diethyl ether (8 mL), dry benzene (4 mL), and iodine (282 mg, 1.09 mmol), under stirring at room temperature for 1 h gave chiral (*R*)-**6e** (305 mg, 84% in two steps from (*R*)-**6c**) as a pale yellow oil.

Also, the chiral (*R*)-**6e** (305 mg, 0.913 mmol) was protected by treating it with a suspension of 60% sodium hydride (61 mg, 1.37 mmol) in dry THF (13 mL) followed by treating it with MOMCl (0.08 mL, 1.10 mmol) at room temperature for 1.5 h, to give the crude chiral (*R*)-**6g** (257 mg, 74%) as a pale yellow oil. The chiral (*R*)-**6g** was identical with the racemic **6g** in IR and ^1H NMR spectra.

Conversion of Chiral (*R*)-6g to Chiral (*R*)-5. The chiral (*R*)-**6g** (257 mg, 0.68 mmol) was alkylated with the acetylide, prepared from propargyl MOM ether **7** (106 mg, 1.02 mmol) and 1.6 mol dm^{-3} *n*-butyllithium hexane solution (0.55 mL, 0.88 mmol) under stirring at −78 °C for 20 min to give the corresponding chiral (*R*)-alcohol (90 mg, 28%) as a pale yellow oil.

The chiral (*R*)-alcohol (90 mg, 0.19 mmol), thus obtained, was oxidized with manganese dioxide (534 mg, 6.1 mmol) under stirring at room temperature for 3 days to give the chiral (*R*)-**5** (77 mg, 87%) as a pale yellow oil. The chiral (*R*)-**5** was identical with the racemic **5** in IR and ^1H NMR spectra.

Conversion of Chiral (*R*)-5 to Chiral Umtatin (*R*)-1. The chiral 1-(dihydrobenzofuran-5-yl)butynone (*R*)-**5** (77 mg, 0.16 mmol) was treated with diethylamine (1 mL) under stirring at room temperature for 15 min. Then, the mixture was treated with 18-crown-6 (89 mg, 0.34 mmol) and potassium fluoride (23 mg, 0.40 mmol) under stirring at room temperature for 1 h. After dilution with a dry diethyl ether (1 mL), the mixture was treated with silica gel (3.5 g) at room temperature for 1 day, and filtered through a short celite pad. The filtrate was concentrated in vacuo to give crude chiral (*R*)-**8** (124 mg) as a pale yellow oil.

To the solution of chiral (*R*)-**8** (124 mg) in methanol (4 mL) was added a catalytic amount of concentrated hydrochloric acid, and the mixture was refluxed for 1 h. The chiral umtatin (*R*)-**1** (30 mg, 68%, $[\alpha]_D^{25}$ −48.6°) was obtained as colorless crystal. The chiral umtatin (*R*)-(−)-**1** was identical with the natural umtatin[2] and the synthetic racemic **1**, described above, in IR and ^1H NMR spectra. The natural umtatin showed $[\alpha]_D^{21}$ −56.3° and the optical purity of the synthesized chiral umtatin was 86%ee, and this showed that the partial racemization, through the ring-opening and the recyclization, might occur in acidic deprotections.

Supporting Information

Preparation of **4d** and the following chromone-ring formation with 2,2-dimethoxy-*N*,*N*-dimethylethylamine to **2a**. Preparation of **6g** and following conversion to **5**. This material is available free of charge on the web at http://www.csj.jp/journals/bcsj/.

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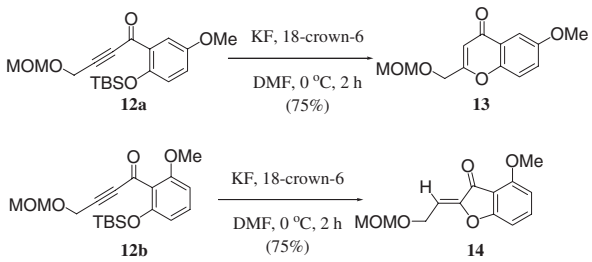
9 The steric repulsion effects in Nakatani's cyclization were also observed in the cyclizations of two phenyl butynones. As shown in scheme, the cyclization of 1-[2-(*t*-butyldimethylsiloxy)-5-methoxyphenyl]butynone **12a** showed the six-membered cyclization to give the corresponding chromone **13**, while the cyclization of 1-[2-(*t*-butyldimethylsiloxy)-6-methoxyphenyl]butynone **12b** showed the five-membered cyclization to give the corresponding 3(2*H*)-furanone **14**.



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12 Use of excess Lewis acids, magnesium iodide etherate or aluminium tribromide, caused partial racemization, due to a dihydrofuran-ring opening and a following re-cyclization.