

Total Synthesis of (+)-Rutamarin

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Abstract: The first enantioselective total synthesis of (+)-rutamarin (**1**) is described. The synthetic route features the highly enantioselective construction of the stereogenic center *via* the Sharpless asymmetric dihydroxylation (99% *ee*), the facile assembly of quaternary carbon-centered 3-substituted side chain and high synthetic efficiency from readily available start-

ing materials. Furthermore, the synthetic strategy could be readily adopted for the synthesis of (+)-rutamarin analogues.

Keywords: asymmetric synthesis; furanocoumarins; rutamarin; Sharpless asymmetric dihydroxylation

Introduction

Given their structural diversity, complexity, and novelty, natural products continue to serve as a rich source in the discovery of biologically interesting molecules.^[1] In the recent past, furanocoumarins have received considerable attention as results of their broad spectrum of intriguing bioactivities. (+)-Rutamarin, 3-substituted 6,7-furanocoumarin (**1**) (Figure 1), isolated from the *Ruta graveolens* L.^[2] exhibited an inhibitory spasmogenic effect on isolated smooth muscle organs.^[3] Recently, (+)-rutamarin (**1**) was found to possess anti-cancer activities against a variety of tumor cell lines at micromolecular concentrations.^[4] Importantly, more recently, we found that (+)-rutamarin (**1**) possesses new biological implications. It strongly sensitized insulin in the GLUT4 translocating assay,^[5] indicating its promising anti-diabetic activity. These results underline the significant potential of (+)-rutamarin (**1**) as a lead compound for the development of novel therapeutic agents. Unfortunately, a major obstacle to further development has been its limited availability. To date, surprisingly, since its reported isolation, only one synthesis of rutamarin has been described by Massanet and co-workers.^[6] However, the Massanet synthesis was racemic, and that ru-

tamarin had not previously been submitted to asymmetric synthesis. Inspired by the intriguing anti-diabetic activity of (+)-rutamarin, we devised a strategy toward its first asymmetric synthesis. Notably, the synthetic route features the highly enantioselective construction of the stereogenic center *via* the Sharpless asymmetric dihydroxylation (99% *ee*), the facile assembly of the quaternary carbon-centered 3-substituted side chain and high synthetic efficiency from readily available starting materials. Furthermore, the general synthetic strategy can be readily elaborated for the synthesis of (+)-rutamarin analogues.

Results and Discussion

Despite the fact that (+)-rutamarin (**1**) has a relatively simple structure, the development of an efficient approach to this molecule and a general route for the preparation of its analogues faces several challenges (Figure 1). First, the versatile and facile construction of the 3-substituted coumarin moiety is a difficult task. The widely used approach relies on the Claisen or Ireland–Claisen rearrangement.^[7] We hypothesized that the coumarin motif could be constructed *via* an aldol condensation between **2** and **3**. Such a strategy

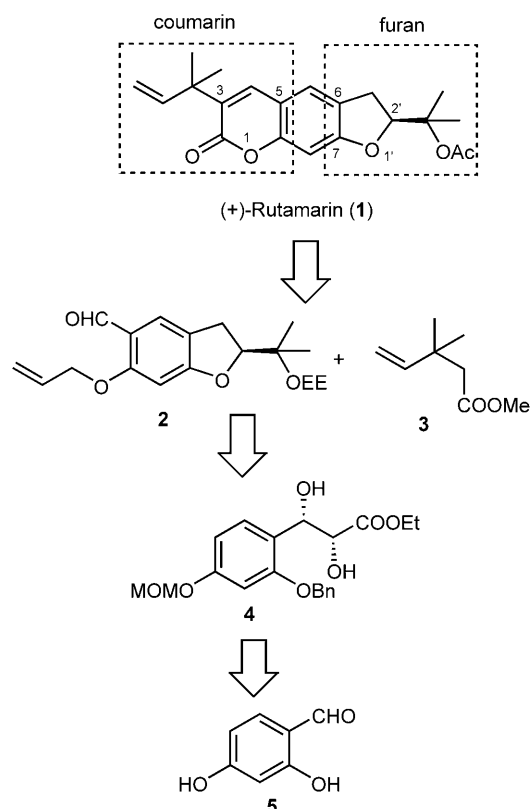
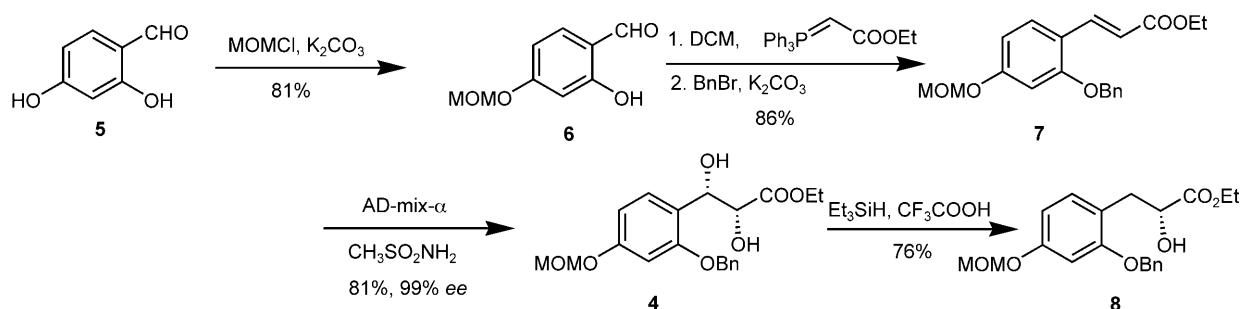


Figure 1. Retrosynthetic analysis of (+)-rutamarin.

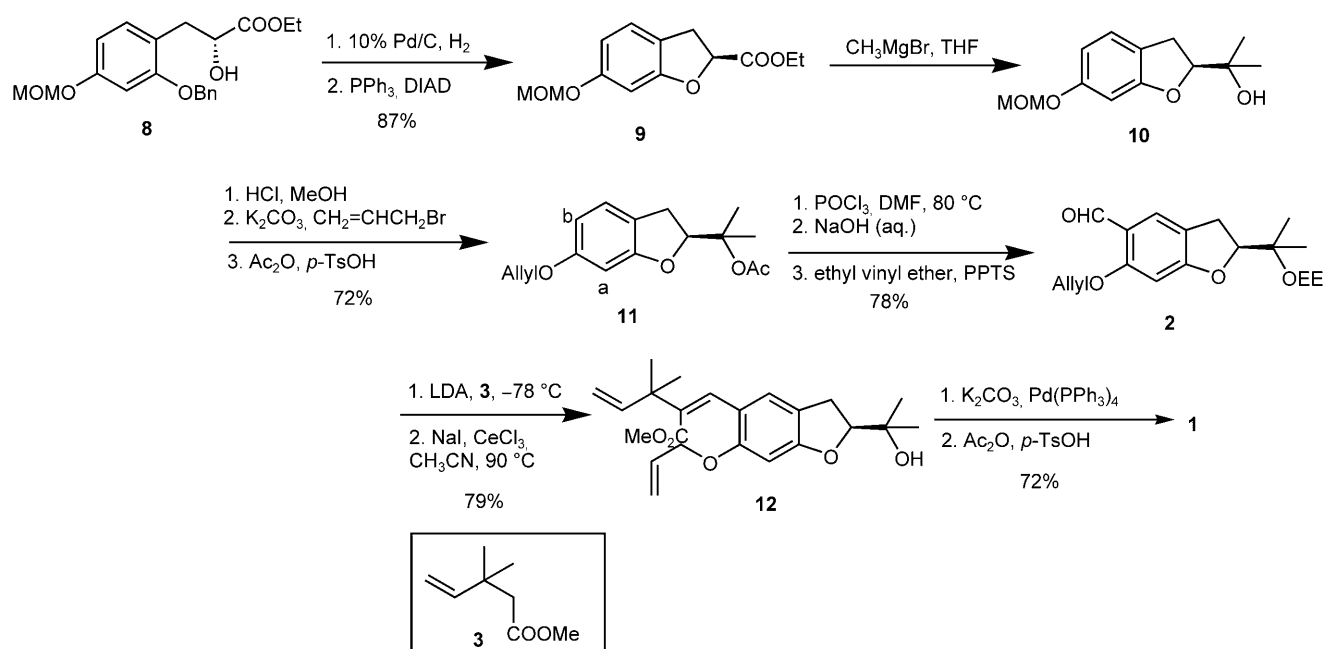
enables us to introduce different side chains at position 3 for the synthesis of analogues to help in the evaluation of structure-activity relationships of the natural product. Second, the highly enantioselective assembly of the chiral center (e.g., C-2') in the dihydrobenzofuran is a challenging task because of the bulky tertiary alcohol moiety. Several methods for establishing the chiral dihydrobenzofuran related to coumarins have been described. Hayashi reported a Pd-catalyzed asymmetric Wacker cyclization.^[8a] However, low yields and *ee* were observed for trisubstituted olefin precursor. Yamaguchi used the Sharpless kinetic resolution to obtain the enantiomer.^[8b] Thirdly, only poor regioselectivity was observed in Snider's

route.^[8c] Enders and co-workers developed an asymmetric organocatalytic strategy to get dihydrobenzofuranols with a high *ee* after necessary recrystallization.^[8d] With the realization of the drawbacks of these methods, we proposed to employ the reliable and highly enantioselective Sharpless dihydroxylation reaction to install the chiral center in **4**, which could be efficiently converted to the furan system through an intramolecular Mitsunobu reaction^[9] and meanwhile building the quaternary carbon.^[10] Compound **4** can be traced back to commercially available 2,4-dihydroxybenzaldehyde **5**.

The total synthesis of (+)-rutamarin (**1**) is shown in Scheme 1 and Scheme 2. Chemoselective protection of the 4-hydroxy group in **5** as the methoxymethyl ether (MOM) was achieved using MOMCl in the presence of K₂CO₃ in 81% yield as a result of the steric effect and the formation of intramolecular H-bonding between the 2-OH and CHO groups (Scheme 1). Horner–Emmons reaction of aldehyde **6** with Wittig reagent Ph₃P=CHCOOEt under reflux in dichloromethane gave rise to the highly *E* selective cinnamic ethyl ester, which was then protected as benzyl ether **7** in 86% yield in a two-step transformation. It was found that the protection form of the 2-hydroxy group was critical for the subsequent Sharpless dihydroxylation reaction. If the protective group was acetoxy or benzoyl, no oxidation reaction of the C=C double bond occurred. The standard Sharpless dihydroxylation reaction using AD-Mix- α was used to oxidize olefin **7** to the key intermediate chiral diol **4** in 81% yield and with an excellent level of enantioselectivity (99% *ee*) based on chiral HPLC analysis. Exposure of the resulting diol **4** to triethylsilane and trifluoroacetic acid led to selective reduction of the benzylic hydroxy group to afford α -hydroxy ester **8** in 76% yield. It should be noted that, before finding the successful route, we also attempted alternative approaches to the asymmetric synthesis of the α -hydroxy ester **8** from the enol oxidation of chiral precursors of camphorsulfonyloxazirindine or Evan's chiral auxiliaries.^[11] However, low enantioselectivity was seen or a longer synthetic sequence was required in the transformations.



Scheme 1. Synthesis of intermediate **8**.



Scheme 2. Synthesis of (+)-rutamarin 1.

After deprotection of the benzyl group in **8** by Pd-catalyzed hydrogenation, the stage was set for the construction of the chiral benzodihydrofuran *via* an intramolecular Mitsunobu reaction (Scheme 2). Gratifyingly, treatment of **8** with triphenylphosphine and diisopropyl azodicarboxylate furnished the desired product **9** with clean inversion of stereochemistry in 87% yield. The resulting tertiary alcohol **10** was obtained in high yield by reaction of excess Grignard reagent (MeMgBr) with ester **9**. Notably, this method can allow for the introduction of different side chains using a variety of Grignard reagents, thus providing an opportunity for making analogues of (+)-rutamarin.

With key intermediate **10** in hand, we attempted to construct the final species 3-substituted coumarin moiety (Scheme 2). It was necessary to change the acid-labile MOM protecting group to an allyl ether due to the following acidic reaction conditions. Cleavage of the methoxymethyl ether by concentrated HCl in warm methanol was followed by selective protection of the phenol hydroxy group as the allyl ether alcohol, which was then acylated by Ac₂O to give **11** in 72% overall yield from **9**. The next step was to introduce an aldehyde group for the subsequent aldol condensation reaction. The main concern of the formylation reaction was regioselectivity because it could occur at positions a and b in **11** (Scheme 2). We were delighted to observe that the employment of the Vilsmeier formylation method using POCl₃ in DMF at 80 °C led to the desired product **2** in excellent regioselectivity. No angular product (position a) was detected in the formylation process presumably due to steric

hindrance. Replacement of the acetoxy ester with the 1-ethoxy-1-ethyl (EE) ether **2** was achieved in 78% yield for the 3-step conversion. Treatment of ester **3** with LDA at –78 °C resulted in an enolate, which reacted with aldehyde **2** and then underwent dehydration of the β-hydroxy under the Bartoli's conditions^[12] directly to give *Z*-selective cinnamic methyl ester **12** owing to the steric hindrance of the isoprene unit in 79% yield in two steps. The one-pot process for the assembly of (+)-rutamarin (**1**) was accomplished through Pd(PPh₃)₄-mediated cleavage of the allyl ether, followed by spontaneous lactonization to form the coumarin system and finally acetylation of the tertiary alcohol by acetic anhydride in the presence of catalytic amount of *p*-TsOH in 72% yield in the 3-step transformation. The spectroscopic and analytical data for synthetic (+)-rutamarin were in full agreement with those reported for the natural product isolated from *Ruta graveolens* L.

Conclusions

In summary, we have reported the first asymmetric total synthesis of (+)-rutamarin, a natural product with a variety of interesting biological activities. The strategy developed is distinguished by the highly enantioselective construction of the chiral dihydrobenzofuran framework *via* intramolecular Mitsunobu reaction, while the chiral center is established by Sharpless asymmetric dihydroxylation. The coumarin moiety was efficiently installed by aldol condensation and subsequent intramolecular lactonization in a one-

pot process. The approach enables one to accomplish the total synthesis of the natural product in an overall 12% yield from readily available substances with high enantioselectivity (99% *ee*). Moreover, significantly, the method can be readily adopted for the preparation of the analogues of (+)-rutamarin that could be used to evaluate structure-activity relationships of this natural product in our on-going medicinal chemistry program.

Experimental Section

General

^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian Mercury-VX300 Fourier transform spectrometer. The chemical shifts were reported in δ (ppm) using the $\delta=7.26$ signal of CDCl_3 (^1H NMR) and the $\delta=77.23$ signal of CDCl_3 (^{13}C NMR) as internal standards. The following abbreviations were used to describe the multiplicities: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. LC-ESI-MS was run on a Bruker Esquire 3000 plus spectrometer in MeOH and HR-ESI-MS was run on a Bruker Atex III spectrometer in MeOH, respectively. Optical rotations were determined on a Perkin-Elmer 341 polarimeter at room temperature. The enantiomeric excess was determined by HPLC with a Chiralpak AD-H, OD-H and AS-H column, 25 °C compared with the racemic or conformational isomer.

All commercially available reagents were used without further purification. The solvents used were all AR (a standard grade of analytical reagents) grade and were redistilled under a positive pressure of dry nitrogen atmosphere in the presence of a proper desiccant when necessary. The progress of the reactions was monitored by analytical thin-layer chromatography (TLC) on HSGF₂₅₄ precoated silica gel plates.

2-Hydroxy-4-(methoxymethoxy)benzaldehyde (6)

To a mixture of 2,4-dihydroxybenzaldehyde **5** (8.28 g, 60 mmol) and K_2CO_3 in acetone (60 mL) was added the MOMCl (4.8 mL, 63 mmol) dropwise. After addition, the reaction mixture was warmed to reflux for 3 h. After removal of the solvent, the resulting mixture was partitioned between EtOAc and water twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography [50:1, petroleum ether (60–90 °C) : EtOAc] provided **6** as a colorless solid; yield: 8.87 g (81%). ^1H NMR (CDCl_3 , 300 MHz): $\delta=11.35$ (s, 1H), 9.71 (s, 1H), 7.42 (d, $J=8.4$ Hz, 1H), 6.63 (dd, $J=2.1, 8.4$ Hz, 1H), 6.58 (d, $J=2.1$ Hz, 1H), 5.20 (s, 2H), 3.46 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): $\delta=194.8, 164.4, 164.2, 135.5, 116.0, 109.2, 103.5, 94.2, 56.6$; ESI-HR-MS: $m/z=205.0480$, calcd. for $\text{C}_9\text{H}_{10}\text{O}_4\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 205.0477; anal. calcd. for $\text{C}_9\text{H}_{10}\text{O}_4$: C 59.34, H 5.53; found: C 59.30, H, 5.57.

(E)-Ethyl 3-[2-(Benzyloxy)-4-(methoxymethoxy)-phenyl]acrylate (7)

A solution of ethyl (triphenylphosphoranylidene)acetate (2.3 g, 6.6 mmol) in CH_2Cl_2 (10 mL) was added to **6** (1.09 g, 6 mmol) in CH_2Cl_2 (20 mL) dropwise. Then the mixture was refluxed overnight and allowed to cool to room temperature. The resulting mixture was partitioned between CH_2Cl_2 and water twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude product was directly used in the next step without further purification.

To a solution of (E)-ethyl 3-[2-hydroxy-4-(methoxymethoxy)phenyl]acrylate and K_2CO_3 (1.24 g, 9 mmol) in anhydrous DMF solution (15 mL) was added benzyl bromide (0.75 mL, 6.6 mmol). The reaction mixture was stirred at room temperature for 4 h and quenched with water. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (50:1, petroleum ether: EtOAc) provided **7** as a colorless oil; yield: 1.76 g (86% for two steps). ^1H NMR (CDCl_3 , 300 MHz): $\delta=8.00$ (d, $J=16.2$ Hz, 1H), 7.47–7.32 (m, 6H), 6.65 (m, 2H), 6.44 (d, $J=16.2$ Hz, 1H), 5.15 (s, 2H), 5.14 (s, 2H), 4.23 (q, $J=7.2$ Hz, 2H), 3.45 (s, 3H), 1.31 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): $\delta=167.7, 160.1, 158.6, 139.6, 136.4, 129.9, 128.6 \times 2, 128.0, 127.2 \times 2, 117.7, 116.6, 108.3, 101.4, 94.2, 70.3, 60.1, 56.1, 14.3$; ESI-HR-MS: $m/z=365.1357$, calcd. for $\text{C}_{20}\text{H}_{22}\text{O}_5\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 365.1365; anal. calcd. for $\text{C}_{20}\text{H}_{22}\text{O}_5$: C 70.16, H 6.48; found: C 70.31, H 6.60.

(2R,3S)-Ethyl 3-[2-(Benzyloxy)-4-(methoxymethoxy)-phenyl]-2,3-dihydroxypropanoate (4)

To a mixed solution (*t*-BuOH/ H_2O , 25 mL/25 mL) of **7** (1.76 g, 5.14 mmol) and methanesulfonamide (513 mg, 5.4 mmol), AD-mix- α (Aldrich-Sigma, 7.56 g, 5.4 mmol) was added by portions over 1 h under an ice bath. Then, the reaction mixture was allowed to warm to room temperature and stirred for 3 d. After quenching with saturated NaHSO_3 aqueous solution, the resulting mixture was extracted by EtOAc for three times. The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (3:1, petroleum ether: EtOAc) provided **4** as a colorless solid; yield: 1.57 g (81%). ^1H NMR (CDCl_3 , 300 MHz): $\delta=7.45$ –7.34 (m, 6H), 6.67 (m, 2H), 5.38 (d, $J=7.5$ Hz, 1H), 5.13 (s, 2H), 5.04 (d, $J=3.3$ Hz, 2H), 4.47 (dd, $J=2.4, 6.6$ Hz, 1H), 4.20 (m, 2H), 3.45 (s, 3H), 1.21 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): $\delta=173.2, 157.9, 155.8, 136.6, 128.5 \times 2, 127.9, 127.8, 127.0 \times 2, 122.2, 107.6, 100.8, 94.4, 73.4, 69.9, 69.8, 61.7, 55.9, 14.1$; ESI-HR-MS: $m/z=375.1427$, calcd. for $\text{C}_{20}\text{H}_{23}\text{O}_7$ [$\text{M}-\text{H}$] $^+$: 375.1444; anal. calcd. for $\text{C}_{20}\text{H}_{24}\text{O}_7$: C 63.82, H 6.43; found: C 64.15, H 6.39; $[\alpha]_{\text{D}}^{20}$: 0.0 (*c* 0.90, CHCl_3). The enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (hexane: 2-propanol 70:30), 25 °C, $\lambda=254$ nm, 1.0 mL min $^{-1}$, *ee* value: 99%, major enantiomer $t_{2R,3S}=17.47$ min, minor enantiomer $t_{2S,3R}=13.26$ min.

(R)-Ethyl 3-[2-(Benzyloxy)-4-(methoxymethoxy)phenyl]-2-hydroxypropanoate (8)

To a solution of **4** (1.5 g 4 mmol) in anhydrous CH_2Cl_2 (40 mL) under argon, triethylsilane (1.96 mL, 12 mmol) and trifluoroacetic acid (3 mL, 40 mmol) were added in sequence under ice bath conditions. The reaction mixture was stirred for about 1 h with TLC monitoring at 0°C and quenched with saturated aqueous NaHCO_3 solution carefully. After that, the resulting mixture was extracted by EtOAc for three times. The combined organic layers were washed with water, brine, dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (10:1, petroleum ether: EtOAc) provided **8** as a colorless oil; yield: 1.09 g (76%). ^1H NMR (CDCl_3 , 300 MHz): δ = 7.43–7.32 (m, 5H), 7.08 (d, J = 8.1 Hz, 1H), 6.66 (s, 1H), 6.61 (dd, J = 2.1, 8.1 Hz, 1H), 5.14 (s, 2H), 5.07 (s, 2H), 4.45 (m, 1H), 4.10 (m, 2H), 3.47 (s, 3H), 3.20 (dd, J = 4.2, 13.5 Hz, 1H), 2.91 (m, 1H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ = 174.8, 157.7, 157.6, 136.9, 132.1, 128.8 $\times$ 2, 128.1, 127.3 $\times$ 2, 118.9, 107.8, 101.5, 94.7, 70.8, 70.2, 61.6, 56.2, 35.7, 14.3; ESI-HR-MS: m/z = 383.1472, calcd. for $\text{C}_{20}\text{H}_{24}\text{O}_6\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 383.1471; anal. calcd. for $\text{C}_{20}\text{H}_{26}\text{O}_4$: C 66.65, H 6.71; found: C 66.79, H 6.80; $[\alpha]_{\text{D}}^{20}$: –6.7 (c 0.90, CHCl_3).

(S)-Ethyl 6-(Methoxymethoxy)-2,3-dihydrobenzofuran-2-carboxylate (9)

A mixture of **8** (1.08 g, 3 mmol), 10% Pd/C (0.5 g) in EtOAc (15 mL) was stirred under an atmosphere of H_2 overnight. After that, the mixture was filtered through a fritted funnel and the filtrate was concentrated under vacuum. The product was directly used in the next step without purification.

To a solution of (R)-ethyl 3-[4-(methoxymethoxy)phenyl]-2-hydroxypropanoate and triphenylphosphine (865 mg, 3.3 mmol) in anhydrous THF was added diisopropyl azodicarboxylate (0.7 mL, 3.6 mmol) under ice bath conditions. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. After evaporating the superfluous solution, the resulting mixture was partitioned between EtOAc and water twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (50:1, petroleum ether: EtOAc) afforded **9** as a colorless oil; yield: 0.66 g (87% for two steps). ^1H NMR (CDCl_3 , 300 MHz): δ = 7.02 (d, J = 8.1 Hz, 1H), 6.62 (d, J = 2.1 Hz, 1H), 6.55 (dd, J = 2.1, 8.1 Hz, 1H), 5.18 (dd, J = 6.9, 10.5 Hz, 1H), 5.10 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 3.51–3.45 (m, 1H), 3.44 (s, 3H), 3.27 (dd, J = 6.9, 15.3 Hz, 1H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ = 171.3, 160.3, 158.1, 124.8, 118.1, 109.1, 99.1, 94.7, 79.9, 61.7, 56.0, 33.4, 14.3; ESI-HR-MS: m/z = 275.0907, calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_5\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 275.0895; anal. calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_5$: C 61.90, H 6.39; found: C 62.13, H 6.42; $[\alpha]_{\text{D}}^{20}$: –42.7 (c 1.80, CHCl_3).

(S)-2-[6-(Allyloxy)-2,3-dihydrobenzofuran-2-yl]propan-2-yl Acetate (11)

To a solution of **9** (630 mg, 2.5 mmol) in anhydrous THF (20 mL) under argon was added slowly a solution of methylmagnesium bromide (2.5 mL, 3M in THF) under ice bath conditions. The reaction mixture was stirred for about 1 h

with TLC monitoring at 0°C and quenched with saturated aqueous NH_4Cl solution. The resulting mixture was partitioned between EtOAc and water twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The *ee* value of the crude product **10** was found to be 97%. The enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (hexane:2-propanol 95:5), 25°C, λ = 254 nm, 0.6 mL min $^{-1}$, major enantiomer t_{S} = 16.45 min, minor enantiomer t_{R} = 18.68 min.

Crude (S)-2-[6-(methoxymethoxy)-2,3-dihydrobenzofuran-2-yl]propan-2-ol **10** was dissolved in MeOH (25 mL) with concentrated HCl (0.2 mL) added. Then, the mixture was allowed to warm to 45°C with stirring for 1 h. After evaporation of the superfluous solution, the resulting mixture was partitioned between EtOAc and water twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The product was directly used in the next step without purification.

To a solution of 2-(2-hydroxypropan-2-yl)-2,3-dihydrobenzofuran-6-ol and K_2CO_3 (414 mg, 3 mmol) in anhydrous DMF solution (5 mL) was added allyl bromide (0.26 mL, 3 mmol). The reaction mixture was stirred at room temperature overnight and quenched with water. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. Then, the crude product was dissolved in acetic anhydride (2 mL) with a catalytic amount of *p*-toluenesulfonic acid (21 mg, 0.12 mmol). The mixture was stirred for 1 h at room temperature and water was added followed by additional stirring for 0.5 h. The aqueous layer was extracted with Et_2O twice. The combined organic layer was washed with saturated NaHCO_3 , brine, dried over Na_2SO_4 and concentrated under vacuum. Purification by column chromatography (70:1, petroleum ether: EtOAc) afforded **11** as a colorless oil; yield: 500 mg (72% from **9**). ^1H NMR (CDCl_3 , 300 MHz): δ = 6.93 (d, J = 8.7 Hz, 1H), 6.34 (m, 2H), 5.99–5.92 (m, 1H), 5.33 (dd, J = 1.5, 17.1 Hz, 1H), 5.21–5.17 (m, 1H), 4.90 (t, J = 8.7 Hz, 1H), 4.41 (dd, J = 1.5, 3.9 Hz, 2H), 3.10–2.92 (m, 2H), 1.92 (s, 3H), 1.48 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (CDCl_3 , 75 MHz): δ = 170.4, 161.0, 159.3, 133.4, 124.7, 118.6, 117.6, 106.9, 96.8, 87.6, 82.7, 69.1, 30.2, 22.5, 21.9, 21.0; ESI-HR-MS: m/z = 299.1239, calcd. for $\text{C}_{16}\text{H}_{20}\text{O}_4\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 299.1259; $[\alpha]_{\text{D}}^{20}$: +43.2 (c 0.60, CHCl_3); anal. calcd. for $\text{C}_{16}\text{H}_{20}\text{O}_4$: C 69.54, H 7.30; found: C 69.71, H 7.56.

(S)-6-(Allyloxy)-2-[2-(1-ethoxyethoxy)propan-2-yl]-2,3-dihydrobenzofuran-5-carbaldehyde (2)

To a solution of **11** (442 mg, 1.6 mmol) in anhydrous DMF, phosphoryl trichloride (0.3 mL, 3.2 mmol) was added dropwisely at room temperature. The reaction mixture was stirred at 80°C for 1 h and then allowed to cool to room temperature. After quenching with water, the resulting mixture was extracted by Et_2O twice. The combined organic layer was washed with saturated NaHCO_3 , brine, dried over Na_2SO_4 and concentrated under vacuum. The product was directly used in the next step without purification.

The crude product from above was hydrolyzed in a solution of 5N NaOH (1 mL), MeOH (1 mL) and THF (2 mL) at room temperature overnight. After neutralizing the su-

perfluorous base with 2N HCl, the mixture was partitioned between EtOAc and water twice, dried over Na₂SO₄, and evaporated under vacuum. Without further purification, the residue was directly dissolved in anhydrous CH₂Cl₂ with a catalytic amount of pyridinium *p*-toluenesulfonate (10 mg, 0.03 mmol). Ethyl vinyl ether (0.19 mL, 2 mmol) was added to the mixture and the reaction was stirred for 4 h. The resulting mixture was participated between CH₂Cl₂ and water twice. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. Purification by column chromatography (20:1, petroleum ether: EtOAc) afforded **2** as a colorless oil; yield: 420 mg (78% for three steps). ¹H NMR (CDCl₃, 300 MHz): δ = 10.27 (s, 1H), 7.61 (s, 1H), 6.33 (s, 1H), 6.06–5.96 (m, 1H), 5.40 (dd, *J* = 1.5, 17.1 Hz, 1H), 5.28 (dd, *J* = 1.5, 10.5 Hz, 1H), 4.97 (t, *J* = 8.4 Hz, 1H), 4.74–4.66 (m, 1H), 4.55 (dd, *J* = 1.5, 3.9 Hz, 2H), 3.51–3.39 (m, 2H), 3.16–3.06 (m, 2H), 1.29–0.76 (m, 12H); ¹³C NMR (CDCl₃, 75 MHz): δ = 188.2, 167.0 (166.9), 163.3, 132.4, 124.5 (124.5), 120.5, 120.4, 119.0, 118.1, 94.5 (94.2, 94.2, 94.1), 91.0 (90.9), 76.6 (76.4), 69.4, 58.7 (58.5), 29.5 (29.3), 24.0, 22.8 (22.6), 21.7 (21.7, 21.3, 21.2), 15.6 (15.5); ESI-HR-MS: *m/z* = 357.1684, calcd. for C₁₉H₂₆O₅Na [M+Na]⁺: 357.1678; anal. calcd. for C₁₉H₂₆O₅: C 68.24, H 7.84; found: C 68.44, H 7.94.

(S,Z)-Methyl 2-[[6-(Allyloxy)-2-(2-hydroxypropan-2-yl)-2,3-dihydrobenzofuran-5-yl]ethylene]-3,3-dimethylpent-4-enoate (12**)**

Anhydrous THF (2 mL) and diisopropylamine (0.24 mL, 1.7 mmol) were placed in a flask under argon in an ice bath. *n*-Butyllithium (0.65 mL, 2.2M in hexane) was added dropwise over 5 min. The reaction mixture was stirred for additional 10 min to complete LDA formation and cooled to –78 °C with an dry ice-acetone bath. The 3,3-dimethylpentanoic methyl ester (200 mg, 1.44 mmol) in 2 mL of THF was then added to the LDA solution over a period of 5 min and then the mixture was stirred for another 90 min to afford the lithium ester enolate. To this solution maintained at –78 °C, **2** (400 mg, 1.2 mmol) in 2 mL of THF was added during 5 min. After stirring for 2 h, the reaction mixture was quenched by adding 1 mL of saturated NH₄Cl solution, followed by water and EtOAc. The aqueous layer was extract with EtOAc twice. The combined organic layer was washed with water, brine, dried over Na₂SO₄ and concentrated under vacuum. Without further purification, the residue was dissolved in 12 mL of CH₃CN with cerium chloride heptahydrate (670 mg, 1.8 mmol) and sodium iodide (270 mg, 1.8 mmol). The resulting mixture was stirred for 4 h at refluxing temperature. After quenching with saturated NaHSO₃ solution, the resulting mixture was extracted by Et₂O twice. The combined organic layer was washed with saturated NaHCO₃, brine, dried over Na₂SO₄ and concentrated under vacuum. Purification by column chromatography (10:1, petroleum ether: EtOAc) afforded **12** as a colorless oil; yield: 230 mg (78.8% for two steps). ¹H NMR (CDCl₃, 300 MHz): δ = 6.96 (s, 1H), 6.78 (s, 1H), 6.31 (s, 1H), 6.00–5.91 (m, 2H), 5.40 (d, *J* = 16.8 Hz, 1H), 5.23 (d, *J* = 10.8 Hz, 1H), 5.08 (d, *J* = 17.1 Hz, 1H), 5.03 (d, *J* = 9.6 Hz, 1H), 4.57 (t, *J* = 9 Hz, 1H), 4.42 (d, *J* = 3.3 Hz, 2H), 3.57 (s, 3H), 3.00 (d, *J* = 8.7 Hz, 2H), 1.30 (s, 6H), 1.24 (s, 3H), 1.16 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz): δ = 171.2,

160.6, 156.7, 145.9, 139.8, 133.2, 124.8, 123.8, 118.6, 118.2, 116.8, 111.9, 94.8, 90.5, 71.8, 69.1, 51.5, 41.5, 30.1, 26.7 × 2, 26.0, 24.1; ESI-HR-MS: *m/z* = 409.2008, calcd. for C₂₅H₃₀O₅Na [M+Na]⁺: 409.1991; anal. calcd. for C₂₅H₃₀O₅: C 71.48, H 7.82; found: C 71.59, H 7.88; [α]_D²⁰: +35.4 (*c* 0.35, CHCl₃).

(+)-Rutamarin (1**)**

To a stirred solution of **12** (347 mg, 0.9 mmol) in MeOH was added catalytic amounts of tetrakis(triphenylphosphine)palladium (20 mg, 0.018 mmol) under argon at room temperature. The slightly yellow solution was stirred for 5 min, and K₂CO₃ (373 mg, 2.7 mmol) was added with replacement of argon once again. The reaction mixture was stirred for 3 h and then quenched when open to fresh air. The resulting mixture was partitioned between CH₂Cl₂ and water twice. The combined organic layers were washed with brine, dried over Na₂SO₄ and concentrated under vacuum. Then, the crude product was dissolved in acetic anhydride (2 mL) with catalytic amount of *p*-toluenesulfonic acid (8 mg, 0.045 mmol). The mixture was stirred for 1 h at room temperature and water was added followed by additional stirring for 0.5 h. The aqueous layer was extracted with Et₂O twice. The combined organic layer was washed with saturated NaHCO₃, brine, dried over Na₂SO₄ and concentrated under vacuum. Purification by column chromatography (20:1, petroleum ether: EtOAc) afforded **1** as a colorless solid; yield: 500 mg (72% for two steps). ¹H NMR (CDCl₃, 300 MHz): δ = 7.44 (s, 1H), 7.17 (s, 1H), 6.63 (s, 1H), 6.11 (dd, *J* = 10.5, 18.0 Hz, 1H), 5.05–5.00 (m, 3H), 3.22–3.13 (m, 2H), 1.94 (s, 3H), 1.51 (s, 3H), 1.47 (s, 3H), 1.41 (s, 6H); ¹³C NMR (CDCl₃, 75 MHz): δ = 170.3, 162.5, 160.2, 154.7, 145.6, 138.2, 130.8, 124.0, 123.2, 113.1, 112.1, 97.1, 88.4, 82.2, 40.3, 29.7, 26.2 × 2, 22.4, 22.0, 21.1; ESI-HR-MS: *m/z* = 357.1710, calcd. for C₂₁H₂₅O₅ [M+H]⁺: 357.1702; anal. calcd. for C₂₁H₂₅O₅: C 70.77, H 6.79; found: C 70.90, H 6.91; [α]_D²⁰: +24.6 (*c* 0.35, CHCl₃). The enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (hexane:2-propanol 70:30), 25 °C, λ = 210 nm, 1.0 mL min^{–1}, *ee* value: 99%, major enantiomer *t*_R = 6.92 min, minor enantiomer *t*_R = 11.65 min.

GLUT4 Membrane Translocation Assay

The CHO-K1/GLUT4 cells were grown in a 96-well plate at a density of 10,000 cells/well before compound incubation. Compound **2** and rutamarin were dissolved in DMSO and stored at –20 °C. Before experiment, the compounds were diluted in the F-12 culture medium for cell incubation. An equal concentration of DMSO was used as the vehicle control. The cells were starved and pre-incubated with compounds for 8 h, and then were stimulated with insulin (80 nM) for 5 min. Immediately after stimulation, the cells were fixed with 3.7% formaldehyde. The plasma membrane-bound GLUT4 was determined by immunocytochemistry. Briefly, the fixed cells were incubated with anti-c-myc primary antibody and subsequently the Cy5-conjugated secondary antibody. The whole procedure was detergent-free, so only membrane GLUT4 could be stained. Membrane-associated GLUT4 was quantified by calculating the intensity of Cy5 fluorescence. Similarly, the total GLUT4 was evaluated through calculating the intensity of GFP fluorescence. The

relative membrane translocation ratio was therefore determined by evaluating the fluorescence ratio of membrane/total GLUT4. Data from the IN Cell Analyzer 1000 were analyzed by using the IN Cell Analyzer workstation version 3.2. Paired Student's *t* test was performed to determine the statistical significance, and unless otherwise indicated, *n* = 6. A *P* value < 0.05 was thought to be statistically significant.

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