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Total synthesis of (±)-camphorataimides and (±)-himanimides by $NaBH_4/Ni(OAc)_2$ or Zn/AcOH stereoselective reduction

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Abstract

Maleic anhydride **1** of *Antrodia camphorate*, which can be isolated from Chinese herbal medicine, is achieved in which the longest linear sequence is only five steps, in 40% overall yield from commercially available succinic anhydride. The crucial antrodimides **3** and **2** can be readily transformed by the chemoselective reduction with Zn/AcOH and $NaBH_4/Ni(OAc)_2 \cdot 4H_2O$ to afford the naturally occurring camphorataimides, **4** and **5**, in high yields as well, respectively. This synthetic strategy can also be modified to give access to a variety of different maleic acid derivatives, himanimides **6**–**8**.
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Keywords: Antrodia camphorate; Himanimides; $NaBH_4/Ni(OAc)_2$; Zn/AcOH; Stereoselective reduction

1. Introduction

As part of our research aims to uncover from natural products new compounds with improved biological activities, including antioxidant, anti-human immunodeficiency virus (HIV), and tumor growth inhibition activities, we attended to the coumarin and benzofuran family. Recently, several structurally interesting compounds with substituted maleic anhydride and maleimide moieties have been isolated as bioactive natural products.[1] Studies on the constituents of the mycelium of *Antrodia camphorate* (Polyporaceae, Aphyllophorales),[1b] which is used as a traditional Chinese medicine, showed them to contain a number of pharmacological interests.[2] Maleic anhydride **1**, maleimide **2** and **3** together with succinic acids **4** and **5** were isolated from the chloroform-soluble fraction of the mycelium of *A. camphorate* and repeatedly chromatographed on silica gel with *n*-hexane/acetone and $CHCl_3$/MeOH. In addition, maleimides **2** and **3** showed appreciable cytotoxic activity against Lewis lung carcinoma cell lines. Recently, during the syntheses of the phytotoxins, carpacin[3] and ailanthoidol,[4] we became aware of the facile conversion of *p*-alkoxyphenyl bromide to aryl stannanes and the proceeding Stille[5] coupling of bromomaleic acid derivatives with stannanes to substituted maleiate skeleton. Therefore, **1**–**3** are ideal synthetic target for the application of these reactions. Although **1**–**3** have been synthesized by Argade[6a] and Stewart,[6b] they were achieved with very time-consuming and complicated synthetic approaches. To date, no **4** and **5** have been synthesized and deficiently examined the biological activity of the molecules, we undertook the first total synthesis of (±)-camphorataimides, **4** and **5**, the structural novelty of this family (Fig. 1).

Perhaps the easiest route to **1** would have been to sequentially couple the known dibromomaleic anhydride **10**, *i*-BuMgBr, and the known[7] bromo(prenyloxy)benzene. In previous projects[8] we have achieved such coupling by treating a mixture of two aryl bromides with a bis(trialkyltin) in the presence of a palladium catalyst. The reaction proceeds via in situ conversion of one aryl bromide to the corresponding stannane followed by coupling of the latter with the other aryl bromide.[8a] In addition, although Stewart et al. have achieved cross-coupling by the Negishi and Suzuki reactions, we would still like to investigate the versatility of Stille cross-

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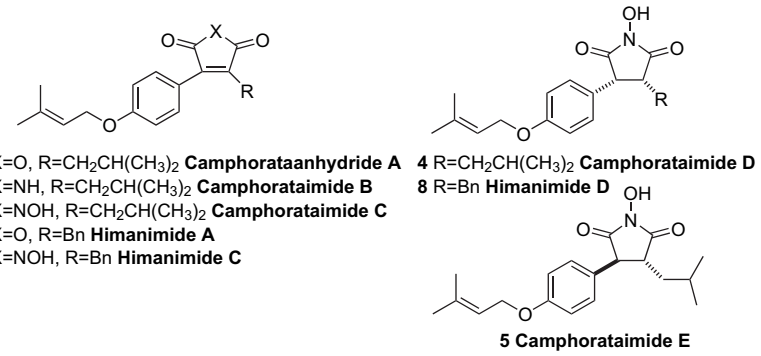


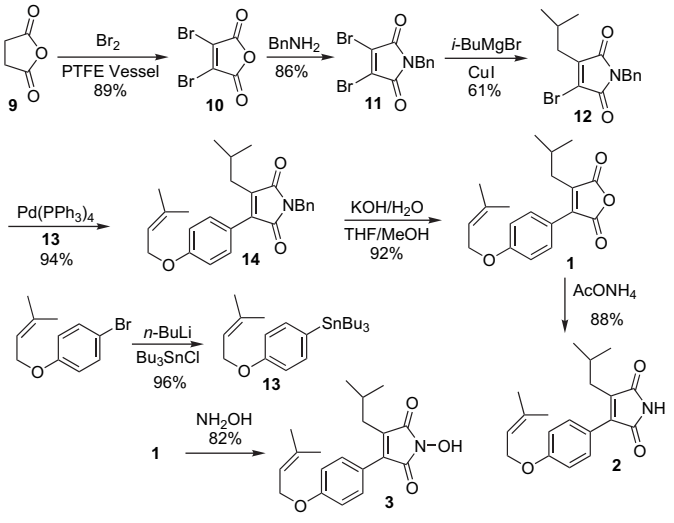
Figure 1. Maleic anhydride and maleimide natural products of *Antrodia camphorate* and himanimide.

coupling reactions to provide **1**, hence synthesizing the target (±)-camphorataimides **4** and **5**. Herein, we report the first synthesis of the naturally occurring (±)-*cis*-camphorataimide D and applied the Stille reaction and stereoselective reduction with Zn/AcOH to achieve (±)-*cis*-himanimide D.

2. Results and discussion

In the beginning of our synthesis, although **10** has been synthesized by several groups,[9] it was achieved with very time-consuming and complicated synthetic approaches. To overcome these technical difficulties, we report our studies on the synthesis of **10** from the commercially available succinic anhydride with Br_2 in a PTFE-vessel reactor in very good yield (89%). In the case of **10** and 4-bromo(prenyloxy)benzene, however, the palladium-catalyzed reaction with $(Me_3Sn)_2$ to give **1** was unsuccessful. The major product was biphenyl, the product from the homocoupling of 4-bromo(prenyloxy)benzene.

With the aim of developing a successful route to **1**, an alternative method of construction was examined (Scheme 1). Coupling of dibromide **11** with the commercially available isobutyl magnesium bromide proceeded in dioxane by Pd(0)-catalysis to give the desired **12** in very poor 12% yield. The isolated yield might be low because Grignard reagent and

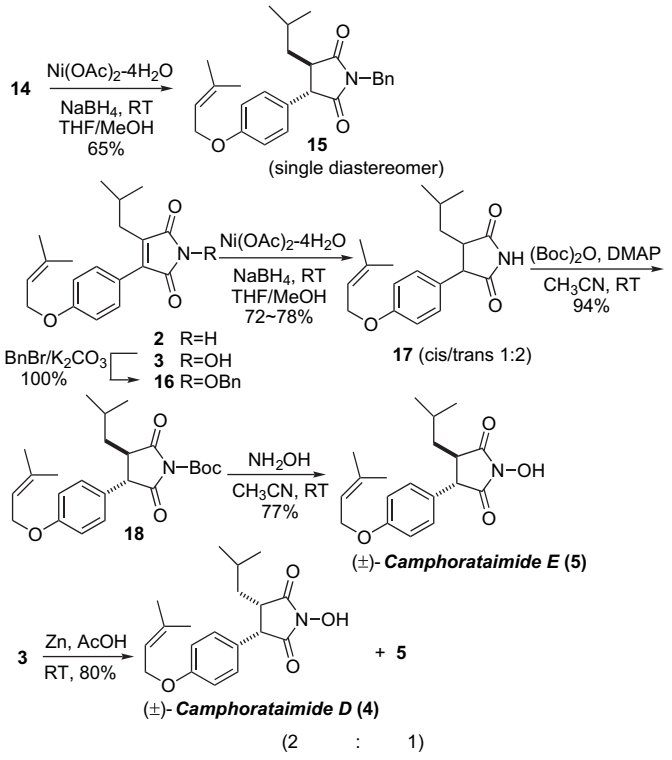


Scheme 1.

pyrroledione **11** appeared a competitive reactant in the 1,2-addition of carbonyl group. Fortunately, the expected **12** can be afforded with CuI instead of Pd-catalyst in moderate 61% yield. Similarly, bromomaleimide **12** and the corresponding stannane **13** could also undergo the palladium-catalyzed cross-coupling to give the key product **14** in an excellent yield (94%). The resultant benzyl maleimide **14** was then transformed into the target compound **1** under reflux in $KOH/H_2O/THF/MeOH$. Finally, the anhydride **1** was readily converted by heating at 85 °C in $AcONH_4$ or $NH_2OH\cdot HCl$/pyridine to afford the natural products, maleimides **2** and **3**, respectively. ^1H and ^{13}C NMR spectra of the synthetic products are in agreement with those reported for the naturally derived materials.[1]

A further insight into the nature of $NaBH_4$ with metallic salts,[10] it was envisioned that a chemoselective reduction of **3** could prove legible for the formation of the thermodynamically more stable (±)-*trans*-camphorataimide E (**5**). With the crucial intermediate **14** in hand, the chemoselective reduction was smoothly testified with $NaBH_4/Ni(OAc)_2\cdot 4H_2O$ in mixed solvent (THF/MeOH 1:1) to provide the expected (±)-*trans*-succinimide **15** only in good yield 65%. Unfortunately, the resultant **15** wasn't then transformed into the corresponding anhydride under reflux in $KOH/H_2O/THF/MeOH$. Subsequently, the task turned to extend the original system with a functioning prototype so that the variety of substrates was evaluated by 1,4-reduction with the Luche's reagent. For instance, compound **2** was employed by the Luche's method to give the desired *cis*/*trans*-**17** (1:2 ratio) in high yield 78%. It is worth noting that the stereoselectivity preferentially provided the trans-isomer with the Luche's reagent, but the mechanistic issues uncovered in the stereoselective process as well as the scope and generality of this area will be probed in detail in our continuing studies. In addition, the N–O bond of **3** and **16** was first broken to provide **2**, and then efficiently reduced to afford the precedent **17** in high yield. Fortunately, and to our greater satisfaction, we succeeded in obtaining (±)-*trans*-isomer **18** only from **17**, which epimerized the C-3 position to give the thermodynamically more stable trans diastereomer as the major product in an excellent 94% yield, suitable for further transformation to achieve the desired **5** (Scheme 2).

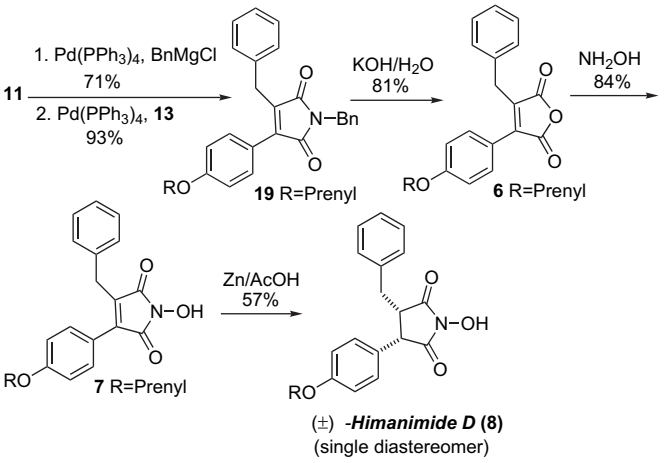
With the aim of developing a successful route to (±)-*cis*-**4**, an alternative method of construction, which was recently



Scheme 2.

investigated by Comins et al.,[11] was examined. As predicted, chemoselective reduction of **3** with Zn/AcOH afforded the desired (±)-*cis*-camphorataimide D (**4**) and the unexpected (±)-*trans*-**5** in high yield 80% (*cis*/*trans* 2:1). Although the mechanism of obtaining the trans-isomer of herein is still unknown, it is likely similar to catalytic hydrogenation to produce the major cis-isomer, which is unstable under basic and thermodynamic conditions, thus converting to trans-isomer. The ^{1}H and ^{13}C NMR spectra of the synthetic products are in agreement with those reported for the naturally derived materials.[1]

It is worth noting that our synthetic strategy can be employed in the syntheses of himanimides **6**–**8** (Scheme 3). Coupling of the dibromomaleimide **11** with sequent BnMgCl and stannane **13** proceeded in dioxane by Pd(0)-catalysis to obtain the predictable **19** in 66% yield over two steps. Similarly, it involved removal of the benzyl-protected group with KOH/H_2O followed by heating at 85 °C in $NH_2OH{\cdot}HCl$/pyridine to afford the natural products, maleic anhydride **6** and maleimide **7**, respectively. Finally, **7** can readily transform by the stereoselective reduction with Zn dust in acetic acid to achieve the single diastereomer (±)-*cis*-himanimide (**8**) in moderate 57% yield. In contrast, **8** was determined to be cis-isomer from the coupling constant between H-3 and H-4 (4.0 and 8.0 Hz for trans and cis, respectively). In addition, the appreciable NOE was observed between H-3 and H-4 in the NOESY spectrum of **4**, while no NOE was observed in that of **5**. The other ^{1}H and ^{13}C NMR spectra of the synthetic products are in agreement with those reported for the naturally derived materials.[12]



Scheme 3.

3. Conclusion

In summary, a concise route to maleic anhydride **1**, maleimide **2** and **3** has been achieved in which the longest linear sequence is only five or six steps from commercially available materials in overall 40%, 36%, and 33% yield, respectively. This synthesis is high yielding and easily modified to give access to a variety of different (±)-*cis*-maleimide analogs using Zn/AcOH stereoselective reduction, and (±)-*trans*-isomers by $NaBH_4/Ni(OAc)_2{\cdot}4H_2O$ as well. In addition, it demonstrated the usefulness of the Stille coupling and Zn/AcOH stereoselective reduction for substituted maleimide synthesis of (±)-*cis*-himanimide D. The preparation of these compounds is currently underway and their biological activities will be investigated to evaluate the efficacy of these compounds as anti-tumor agents.

4. Experimental

4.1. General

Melting points were determined on a Mel Temp II melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured with a Bruker-200, Bruker-300, or Varian-600 spectrometer. Chemical shifts are reported in parts per million (δ, ppm) using $CHCl_3$ (δ_H 7.26) as an internal standard. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) were determined on a JEOL JMS-HX 110 mass spectrometer from National Chung-Tsing University, Taichung. Elemental analyses were performed on a Heracus CHN-OS Rapid spectrometer in the Taichung Instrumentation Center, National Science Council, Taiwan. Solvents were freshly distilled prior to use from phosphorus pentoxide or CaH_2. THF was distilled from sodium diphenyl ketyl. All reactions were carried out under nitrogen atmosphere unless otherwise stated. Silica gel (silica gel 60, 230–400 mesh, Merck) was used for chromatography. Organic extracts were dried over anhydrous $MgSO_4$.

4.1.1. 2,3-Dibromomaleic anhydride (**10**)

A mixture of succinic anhydride (1.01 g, 10.1 mmol), and bromine (3.70 g, 23.1 mmol) was stirred in a small autoclave (PTFE-lined vessel)[13] at 210 °C (sand bath) for 3 h (*Caution*: Don't run over 2.00 g each time or raise temperature rapidly, otherwise, it might appear explosion.). After cooling down to room temperature, the mixture was dissolved in ethyl ether. The solvent was then removed and the residue was purified by chromatography (SiO_2, 1:4 hexane/diethyl ether) to give 2,3-dibromomaleic anhydride (2.30 g, 89%) as a white solid, mp 116–117 °C (lit.[9g] mp 113–114 °C). ^{13}C NMR ($CDCl_3$) δ 125.0, 163.0. Anal. Calcd for $C_4O_3Br_2$: C, 18.78; O, 18.76. Found: C, 18.96; O, 18.90.

4.1.2. N-Benzyl-3,4-dibromomaleimide (**11**)

This compound was prepared as a white solid from anhydride **10** according to the procedure of Viaud-Massuard.[9g] To a solution of **10** (4.62 g, 18.0 mmol) in acetic acid (20.0 mL) was added benzylamine (2.0 mL, 18.0 mmol) dropwise at room temperature. The mixture was stirred for 10 min and then heated at reflux for 2 h. After cooling down to room temperature, the mixture was extracted with EtOAc (3×30.0 mL). The solvent was then removed and the residue was purified by chromatography (SiO_2, 3:1 hexane/CH_2Cl_2) to give **11** (5.32 g, 86%) as a white solid, mp 112–113 °C (lit.[14] mp 117–117.5 °C). ^1H NMR ($CDCl_3$) δ 4.75 (s, 2H), 7.31–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 43.1, 128.2, 128.7, 128.8, 129.4, 135.1, 163.5. Anal. Calcd for $C_{11}H_7O_2NBr_2$: C, 38.30; H, 2.05; N, 4.06; O, 9.28. Found: C, 38.59; H, 1.74; N, 4.22; O, 9.23.

4.1.3. N-Benzyl-3-bromo-4-isobutylmaleimide (**12**)

A solution of benzyldibromomaleimide **11** (1.04 g, 3.0 mmol) and CuI (0.02 g, 0.1 mmol) in anhydrous THF (30.0 mL) was cooled down to 0 °C under N_2 pressure for 20 min. The commercially available Grignard reagent (isobutyl magnesium bromide; 2 M, 2.2 mL) was added dropwise at 0 °C, and allowed to warm to room temperature. After stirring for 8 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl (1.2 mL) and added $MgSO_4$ for the removal of water. The resulting solution was filtered and the filtrate evaporated. The product was isolated by flash column chromatography (SiO_2, 9:1 cyclohexane/CH_2Cl_2) to give **12** (0.59 g, 61%) as an oil. ^1H NMR ($CDCl_3$) δ 0.95 (d, J=7.2 Hz, 6H), 2.08 (sep, J=7.2 Hz, 1H), 2.35 (d, J=7.2 Hz, 2H), 4.69 (s, 2H), 7.27–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 22.6, 27.8, 34.1, 42.2, 125.5, 127.9, 128.4, 128.6, 135.8, 145.1, 165.1, 168.9; HRMS (EI) calcd for $C_{15}H_{16}O_2NBr$ (M^+) 321.0368, found 321.0363.

4.1.4. 4-[(3-Methyl-2-butenyloxy)phenyl]bromide

This compound was prepared as a colorless oil from 4-bromophenol according to the procedure of Bernard.[7] To a mixture of 4-bromophenol (10.0 g, 57.8 mmol), KI (0.58 g, 3.5 mmol), and K_2CO_3 (19.94 g, 144.5 mmol) in acetone (100.0 mL) was added 3-methyl-2-butenyl bromide (11.20 g, 75.1 mmol) at room temperature, and then refluxed at 80 °C for 12 h. After cooling, the solution was evaporated in vacuo and the brown solid was subjected to flash chromatography (SiO_2, 5:1 hexane/diethyl ether) to obtain the known[7] 4-[(3-methyl-2-butenyloxy)phenyl]bromide (13.88 g, 57.8 mmol) in 100% yield. ^1H NMR ($CDCl_3$) δ 1.73 (s, 3H), 1.79 (s, 6H), 4.47 (d, J=6.6 Hz, 2H), 5.46 (br t, J=6.6 Hz, 1H), 6.78 (d, J=9.0 Hz, 2H), 7.35 (d, J=9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 18.2, 25.8, 65.0, 112.7, 116.5, 119.3, 132.2, 138.5, 157.9.

4.1.5. 4-[(3-Methyl-2-butenyloxy)phenyl]tributylstannane (**13**)

The stannane **13** was prepared, using the previous procedure,[8f] from 4-[(3-methyl-2-butenyloxy)phenyl]bromide. A solution of 4-[(3-methyl-2-butenyloxy)phenyl]bromide (1.02 g, 4.2 mmol) in 60.0 mL of dry THF was placed in a dry, two-necked, 100-mL, round-bottomed flask under a nitrogen atmosphere with a small magnetic stir bar. The flask was then immersed in an acetone/dry ice bath. *n*-Butyllithium solution (2.9 mL, 1.6 M in hexanes, 4.6 mmol) was introduced slowly (1 drop/2 s) during which time the solution changed color from pale yellow to dark orange. After the solution was stirred for 15 min at −78 °C, the reaction was treated at this temperature with neat tributyltin chloride (1.51 g, 4.6 mmol). The dry ice bath was removed and the solution was allowed to reach room temperature. The reaction was quenched with 0.5 mL of H_2O and the solution concentrated in vacuo. After removal of the solvent, the residue was purified by chromatography (SiO_2, 3:1 hexane/CH_2Cl_2) to give **13** (1.82 g, 4.0 mmol) in 96% yield as colorless oil. ^1H NMR ($CDCl_3$) δ 0.84–1.05 (m, 15H), 1.27–1.69 (m, 12H), 1.73 (s, 3H), 1.79 (s, 3H), 4.50 (d, J=6.6 Hz, 2H), 5.50 (br t, J=6.6 Hz, 1H), 6.91 (d, J=8.3 Hz, 2H), 7.35 (d, J=8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 9.6, 13.7, 18.1, 25.8, 27.4, 29.1, 64.4, 114.6, 119.8, 129.4, 137.4, 138.0, 159.0; HRMS (EI) calcd for $C_{23}H_{40}OSn$ (M^+) 452.2101, found 452.2107.

4.1.6. N-Benzyl-3-isobutyl-4-[4-(3-methyl-2-butenyloxy)-phenyl]maleimide (**14**)

Bromide **12** (0.52 g, 1.6 mmol), tetrakis(triphenylphosphine)palladium(0) (0.18 g, 10 mol %), and stannane **13** (0.73 g, 1.6 mmol) were introduced into a sealable tube containing anhydrous dioxane (10.0 mL), and the reaction mixture degassed. The tube was sealed and heated for 5 h at 145 °C, after cooling, and the solution was filtered and evaporated in vacuo. The filtrate residue was subjected to flash chromatography (SiO_2, 1:3 CH_2Cl_2/diethyl ether) to provide the desired **14** (0.61 g, 94%) as a light green-yellow oil. ^1H NMR ($CDCl_3$) δ 0.89 (d, J=7.2 Hz, 6H), 1.87 (s, 3H), 1.88 (s, 3H), 2.07 (sep, J=7.2 Hz, 1H), 2.51 (d, J=7.2 Hz, 2H), 4.55 (d, J=6.6 Hz, 2H), 4.72 (s, 2H), 5.49 (br t, J=6.6 Hz, 1H), 6.96 (d, J=9.0 Hz, 2H), 7.49 (d, J=9.0 Hz, 2H), 7.24–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.2, 22.7, 25.8, 28.1, 32.9, 41.7, 64.8, 114.7, 119.2, 121.4, 127.7, 128.4, 128.6, 130.9, 136.7, 137.7, 138.1, 138.6, 159.9, 171.1, 171.9; HRMS (EI) calcd for $C_{26}H_{29}O_3N$ (M^+) 403.2147, found 403.2149.

*4.1.7. 3-Isobutyl-4-[4-(3-methyl-2-butenyloxy)phenyl]furan-2,5-dione (**1**)*

A mixture of benzyl maleimide **14** (0.45 g, 1.1 mmol) in THF/MeOH (50.0/50.0 mL), water (50.0 mL), and KOH (0.43 g) was refluxed for 3 h. After it was poured into water, acidified with 1 N HCl, and then extracted with EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$ and brine, and then dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (SiO_2, 7:3 EtOAc/cyclohexane) to provide **1** (0.32 g, 92%) as an oil. ^{1}H NMR ($CDCl_3$) δ 0.94 (d, J=7.2 Hz, 6H), 1.77 (s, 3H), 1.82 (s, 3H), 2.13 (sep, J=7.2 Hz, 1H), 2.60 (d, J=7.2 Hz, 2H), 4.55 (d, J=6.6 Hz, 2H), 5.50 (br t, J=6.6 Hz, 1H), 7.02 (d, J=9.0 Hz, 2H), 7.62 (d, J=9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 18.2, 22.7, 25.8, 27.9, 33.6, 65.0, 115.1, 118.9, 119.9, 131.1, 139.0, 139.8, 140.2, 160.9, 165.4, 166.4; HRMS (EI) calcd for $C_{19}H_{22}O_4$ (M^+) 314.1518, found 314.1513.

*4.1.8. 3-Isobutyl-4-[4-(3-methyl-2-butenyloxy)phenyl]-1H-pyrrol-2,5-dione (**2**)*

A solution of furandione **1** (0.22 g, 0.7 mmol) and ammonium acetate (0.32 g, 4.2 mmol) in acetic acid (20.0 mL) was heated at reflux for 24 h. After cooling, the solvent was removed in vacuo and the resulting solid was subjected to column chromatography (SiO_2, 1:1 diethyl ether/CH_2Cl_2) to obtain **2** (0.19 g, 88%) as a white solid, mp 104.5–105 °C (lit.[1] mp 110–111 °C). ^{1}H NMR ($CDCl_3$) δ 0.90 (d, J=7.2 Hz, 6H), 1.76 (s, 3H), 1.81 (s, 3H), 2.06 (sep, J=7.2 Hz, 1H), 2.51 (d, J=7.2 Hz, 2H), 4.56 (d, J=6.9 Hz, 2H), 5.50 (br t, J=6.9 Hz, 1H), 6.99 (d, J=6.9 Hz, 2H), 7.51 (d, J=6.9 Hz, 2H), 7.69 (br s, NH); ^{13}C NMR ($CDCl_3$) δ 18.2, 22.7, 25.8, 28.1, 32.8, 64.9, 114.8, 119.2, 121.1, 130.9, 138.6, 138.7, 139.1, 160.0, 171.3, 171.9; HRMS (EI) calcd for $C_{19}H_{23}NO_3$ (M^+) 313.1678, found 313.1676.

*4.1.9. 1-Hydroxy-3-isobutyl-4-[4-(3-methyl-2-butenyloxy)-phenyl]-1H-pyrrol-2,5-dione (**3**)*

A mixture of furandione **1** (0.19 g, 0.6 mmol) and hydroxylamine hydrochloride (0.10 g, 1.4 mmol) in pyridine (10.0 mL) was heated at reflux for 2 h. After cooling, the solvent was removed in vacuo and the resulting solid was subjected to column chromatography (SiO_2, 1:10 EtOAc/cyclohexane) to obtain **3** (0.16 g, 82%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.89 (d, J=7.2 Hz, 6H), 1.76 (s, 3H), 1.81 (s, 3H), 2.04 (sep, J=7.2 Hz, 1H), 2.51 (d, J=7.2 Hz, 2H), 4.56 (d, J=6.6 Hz, 2H), 5.49 (br t, J=6.6 Hz, 1H), 6.98 (d, J=8.7 Hz, 2H), 7.51 (d, J=8.7 Hz, 2H), 8.53 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.2, 22.7, 25.8, 28.1, 33.0, 64.9, 114.9, 119.0, 120.7, 131.0, 135.8, 135.9, 138.9, 160.2, 168.2, 168.9; HRMS (EI) calcd for $C_{19}H_{23}NO_4$ (M^+) 329.1627, found 329.1619.

*4.1.10. (±)-trans-1-Benzyl-3-isobutyl-4-[4-(3-methyl-2-butenyloxy)phenyl]pyrrolidine-2,5-dione (**15**)*

A solution of **14** (0.16 g, 0.4 mmol) in THF (5.0 mL) was introduced into the pre-dissolved solution of $Ni(OAc)_2\cdot 4H_2O$ (0.10 g, 0.4 mmol) in MeOH (5.0 mL) and stirred for 30 min at room temperature. To the resulting mixture was added one portion of $NaBH_4$ (29 mg, 0.8 mmol) and stirred for 30 min, followed by the other portion of $NaBH_4$ (29 mg, 0.8 mmol) at room temperature. The suspension was allowed to stir for 4 h and then quenched with saturated aqueous NH_4Cl, which was extracted with CH_2Cl_2 (3×20.0 mL). After the removal of solvent, the yellow residue was subjected to column chromatography (SiO_2, 10:1:0.005 hexane/diethyl ether/AcOH) to provide **15** (0.10 g, 65%) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.73 (d, J=6.0 Hz, 3H), 0.81 (d, J=6.0 Hz, 3H), 1.49–1.73 (m, 1H), 1.49–1.73 (m, 1H), 1.73 (s, 3H), 1.79 (s, 3H), 1.84 (sep, J=6.0 Hz, 1H), 2.91 (td, J=5.4, 4.8 Hz, 1H), 3.55 (d, J=4.8 Hz, 1H), 4.48 (d, J=6.9 Hz, 2H), 4.70 (ABq, J=14.4 Hz, 2H), 5.47 (br t, J=6.9 Hz, 1H), 6.86 (d, J=8.7 Hz, 2H), 7.03 (d, J=8.7 Hz, 2H), 7.27–7.39 (m, 5H); ^{13}C NMR [$(CD_3)_2CO$] δ 17.4, 20.8, 22.6, 25.0, 25.3, 40.3, 42.0, 46.9, 52.3, 64.5, 114.8, 120.2, 127.5, 128.0, 128.5, 129.2, 129.9, 136.7, 136.8, 158.4, 176.8, 178.5; MS (EI) *m/z* 405 (M^+, 4), 337 (16), 281 (100), 203 (27), 133 (99), 91 (56), 69 (27); HRMS (EI) calcd for $C_{26}H_{31}NO_3$ (M^+) 405.2304, found 405.2300.

*4.1.11. N-Benzyloxy-3-isobutyl-4-[4-(3-methylbutenyloxy)-phenyl]-1H-pyrrol-2,5-dione (**16**)*

To a mixture of **3** (0.15 g, 0.5 mmol) and K_2CO_3 (0.19 g, 1.4 mmol) in acetone (5.0 mL) was added BnBr (60.0 μL, 0.5 mmol) at room temperature, and then refluxed at 65 °C for 12 h. After cooling, the solution was evaporated in vacuo, and the brown solid was subjected to flash chromatography (SiO_2, 1:15 EtOAc/hexane) to give **16** (0.19 g, 0.5 mmol) in 100% yield. ^{1}H NMR ($CDCl_3$) δ 0.88 (d, J=7.2 Hz, 6H), 1.75 (s, 3H), 1.81 (s, 3H), 2.00 (sep, J=7.2 Hz, 1H), 2.47 (d, J=7.2 Hz, 2H), 4.55 (d, J=6.6 Hz, 2H), 5.15 (s, 2H), 5.49 (br t, J=6.6 Hz, 1H), 6.97 (d, J=8.7 Hz, 2H), 7.48 (d, J=8.7 Hz, 2H), 7.36–7.53 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.2, 22.6, 25.8, 28.0, 32.9, 64.8, 79.5, 114.8, 119.1, 120.8, 128.5, 129.2, 129.8, 130.9, 134.0, 135.4, 135.7, 138.7, 160.1, 167.0, 167.7; HRMS (EI) calcd for $C_{26}H_{29}NO_4$ (M^+) 419.2097, found 419.2099.

*4.1.12. (±)-trans-3-Isobutyl-4-[4-(3-methylbutenyloxy)-phenyl]pyrrolidine-2,5-dione (**17**)*

A solution of **2** (0.25 g, 0.8 mmol) in THF (8.0 mL) was introduced into the pre-dissolved solution of $Ni(OAc)_2\cdot 4H_2O$ (0.20 g, 0.8 mmol) in MeOH (8.0 mL) and stirred for 30 min at ambient temperature. To the resulting mixture was added one portion of $NaBH_4$ (58 mg, 1.6 mmol) and stirred for 30 min, followed by the other portion of $NaBH_4$ (58 mg, 1.6 mmol) at ambient temperature. The suspension was allowed to stir for 4 h and then quenched with saturated aqueous NH_4Cl, which was extracted with CH_2Cl_2 (3×20.0 mL). After the removal of solvent, the yellow residue was subjected to column chromatography (SiO_2, 1:3 EtOAc/cyclohexane) to provide **17** (0.19 g, 78%, *cis*/*trans* 1:2) as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.73 (d, J=6.3 Hz, 3H), 0.91 (d, J=6.3 Hz, 3H), 1.53–1.89 (m, 1H), 1.53–1.89 (m, 1H), 1.74 (s, 3H), 1.77 (s, 3H), 1.86 (sep, J=6.3 Hz, 1H), 2.98 (td, J=5.4, 4.8 Hz, 1H), 3.60 (d, J=4.8 Hz, 1H), 4.49 (d, J=6.9 Hz, 2H), 5.49 (br t, J=6.9 Hz, 1H), 6.90 (d, J=8.7 Hz, 2H), 7.12 (d, J=8.7 Hz, 2H), 8.86 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.2, 21.3, 23.0,

25.5, 25.8, 40.5, 48.2, 53.7, 64.7, 115.3, 119.4, 128.5, 128.7, 138.4, 158.5, 178.1, 179.9; HRMS (EI) calcd for $C_{19}H_{25}NO_3$ (M^+) 315.1834, found 315.1837.

4.1.13. (±)-cis-3-Isobutyl-4-[4-(3-methylbutenyloxy)-phenyl]pyrrolidine-2,5-dione (**17**)

^{1}H NMR ($CDCl_3$) δ 0.67 (d, J=6.3 Hz, 3H), 0.81 (d, J=6.3 Hz, 3H), 1.47−1.52 (m, 1H), 1.47−1.52 (m, 1H), 1.74 (s, 3H), 1.79 (s, 3H), 1.79 (sep, J=6.3 Hz, 1H), 3.13 (dt, J=9.0, 5.4 Hz, 1H), 4.11 (d, J=9.0 Hz, 1H), 4.49 (d, J=6.6 Hz, 2H), 5.48 (br t, J=6.6 Hz, 1H), 6.88 (d, J=8.7 Hz, 2H), 7.02 (d, J=8.7 Hz, 2H), 9.04 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.1, 21.7, 22.5, 25.3, 25.8, 35.2, 44.1, 51.4, 64.8, 115.0, 119.4, 125.8, 130.0, 138.3, 158.4, 178.6, 180.4; MS (EI) *m/z* 315 (M^+, 1), 247 (26), 191 (100), 176 (14), 133 (84), 69 (30); HRMS (EI) calcd for $C_{19}H_{25}NO_3$ (M^+) 315.1834, found 315.1833.

4.1.14. (±)-trans-1-(tert-Butoxycarbonyl)-3-isobutyl-4-[4-(3-methyl-2-butenyloxy)phenyl]pyrrolidine-2,5-dione (**18**)

To a mixture of **17** (0.19 g, 0.6 mmol) and DMAP (7.3 mg, 0.06 mmol) in CH_3CN was added Boc_2O (0.14 g, 0.7 mmol) dropwise at 0 °C. Stirring continued at 0 °C for 30 min and at room temperature for 1 h. Evaporation and chromatography (SiO_2, 1:9 EtOAc/hexane) gave **18** (0.23 g, 94%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.74 (d, J=6.3 Hz, 3H), 0.90 (d, J=6.3 Hz, 3H), 1.48−1.65 (m, 1H), 1.58 (s, 9H), 1.74 (s, 3H), 1.77 (s, 3H), 1.80−1.91 (m, 1H), 1.80−1.91 (m, 1H), 2.99 (m, 1H), 3.60 (d, J=6.0 Hz, 1H), 4.50 (d, J=6.6 Hz, 2H), 5.48 (br t, J=6.6 Hz, 1H), 6.91 (d, J=8.7 Hz, 2H), 7.13 (d, J=8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 18.2, 21.4, 22.9, 25.5, 25.8, 27.7, 40.4, 47.0, 52.9, 64.8, 86.2, 115.3, 119.4, 127.9, 128.9, 138.4, 146.5, 158.6, 173.3, 175.2; HRMS (EI) calcd for $C_{24}H_{23}NO_5$ (M^+) 415.2359, found 415.2360.

4.1.15. (±)-trans-1-Hydroxy-3-isobutyl-4-[4-(3-methyl-2-butenyloxy)phenyl]pyrrolidine-2,5-dione (**5**)

To a solution of **18** (0.17 g, 0.4 mmol) in CH_3CN was added an excess (50 wt %) aqueous solution of NH_2OH (0.2 mL, 3.4 mmol) at ambient temperature. The mixture was allowed to stir for 1 h, and followed by removal of the solvent in vacuo and the resulting solid was subjected to column chromatography (SiO_2, 6:1 CH_2Cl_2/EtOAc) to obtain **5** (0.10 g, 77%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.69 (d, J=6.0 Hz, 3H), 0.89 (d, J=6.0 Hz, 3H), 1.51 (m, 1H), 1.73 (s, 3H), 1.79 (s, 3H), 1.72−1.84 (m, 1H), 1.72−1.84 (m, 1H), 2.87 (m, 1H), 3.52 (d, J=4.2 Hz, 1H), 4.47 (d, J=6.6 Hz, 2H), 5.47 (br t, J=6.6 Hz, 1H), 6.87 (d, J=8.4 Hz, 2H), 7.08 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 18.2, 21.3, 23.0, 25.3, 25.8, 40.3, 44.6, 49.8, 64.7, 115.3, 119.3, 128.0, 128.9, 138.4, 158.6, 173.4, 175.1; HRMS (EI) calcd for $C_{19}H_{25}NO_4$ (M^+) 331.1784, found 331.1792.

4.1.16. (±)-cis-1-Hydroxy-3-isobutyl-4-[4-(3-methyl-2-butenyloxy)phenyl]pyrrolidine-2,5-dione (**4**)

To a solution of **3** (0.13 g, 0.4 mmol) in 5.0 mL of acetic acid was added Zn dust (3.9 mmol) in one portion. The mixture was stirred at room temperature for 2 h, quenched by addition of water (2.0 mL), and extracted with CH_2Cl_2 (3×5.0 mL). After removal of the solvent, the residue was subjected to column chromatography (SiO_2, 1:2 EtOAc/cyclohexane) to provide **5** (0.035 g, 27%) and **4** (0.070 g, 53%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.67 (d, J=6.0 Hz, 3H), 0.81 (d, J=6.0 Hz, 3H), 1.03 (m, 1H), 1.44−1.48 (m, 1H), 1.44−1.48 (m, 1H), 1.73 (s, 3H), 1.79 (s, 3H), 3.09 (m, 1H), 4.08 (d, J=8.4 Hz, 1H), 4.48 (d, J=6.6 Hz, 2H), 5.47 (br t, J=6.6 Hz, 1H), 6.85 (d, J=8.4 Hz, 2H), 6.97 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 18.2, 21.7, 22.4, 25.2, 25.8, 35.3, 40.2, 47.4, 64.8, 115.0, 119.3, 125.3, 130.2, 138.3, 158.6, 174.1, 175.5; HRMS (EI) calcd for $C_{19}H_{25}NO_4$ (M^+) 331.1784, found 331.1791.

4.1.17. N-Benzyl-3-benzyl-4-[4-(3-methyl-2-butenyloxy)-phenyl]maleimide (**19**)

This compound was prepared as a colorless oil from **11** according to the procedure of Kelly.[8f] ^{1}H NMR ($CDCl_3$) δ 1.74 (s, 3H), 1.80 (s, 3H), 3.95 (s, 2H), 4.53 (d, J=6.6 Hz, 2H), 4.72 (s, 2H), 5.48 (br t, J=6.6 Hz, 1H), 6.94 (d, J=9.0 Hz, 2H), 7.53 (d, J=9.0 Hz, 2H), 7.14−7.41 (m, 5H), 7.14−7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.2, 25.8, 29.9, 41.8, 64.8, 114.8, 119.1, 121.0, 126.7, 127.7, 128.4, 128.5, 128.6, 128.8, 131.1, 135.9, 136.5, 137.3, 138.2, 138.7, 160.2, 171.0, 171.6; HRMS (EI) calcd for $C_{29}H_{27}NO_3$ (M^+) 437.1991, found 437.1997.

4.1.18. 3-Benzyl-4-[4-(3-methyl-2-butenyloxy)phenyl]furan-2,5-dione (**6**)

A mixture of benzyl maleimide **19** (0.21 g, 0.5 mmol) in THF/MeOH (20.0 mL/20.0 mL), water (20.0 mL), and KOH (0.23 g) was refluxed for 3 h. After it was poured into water, acidified with 1 N HCl, and then extracted with EtOAc, the organic phase was washed with saturated aqueous $NaHCO_3$ and brine and then was dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography (SiO_2, 1:1 CH_2Cl_2/hexane) to provide **6** (0.14 g, 81%) as an oil. ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3H), 1.81 (s, 3H), 4.03 (s, 2H), 4.57 (d, J=6.9 Hz, 2H), 5.48 (br t, J=6.9 Hz, 1H), 6.99 (d, J=9.0 Hz, 2H), 7.63 (d, J=9.0 Hz, 2H), 7.21 (d, J=7.4 Hz, 2H), 7.25−7.35 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 18.2, 25.8, 30.5, 65.0, 115.2, 118.8, 119.5, 127.3, 128.3, 129.1, 131.3, 135.7, 137.4, 139.0, 140.6, 161.3, 165.3, 166.2; HRMS (EI) calcd for $C_{22}H_{20}O_4$ (M^+) 348.1362, found 348.1366.

4.1.19. 1-Hyroxy-3-benzyl-4-[4-(3-methyl-2-butenyloxy)-phenyl]-1H-pyrrol-2,5-dione (**7**)

A mixture of furandione **6** (0.16 g, 0.5 mmol) and hydroxylamine hydrochloride (0.13 g, 1.8 mmol) in pyridine (10.0 mL) was heated at reflux for 2 h. After cooling, the solvent was removed in vacuo and the resulting solid was subjected to column chromatography (SiO_2, 1:3 EtOAc/hexane) to obtain **7** (0.14 g, 84%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.75 (s, 3H), 1.80 (s, 3H), 3.94 (s, 2H), 4.54 (d, J=6.6 Hz, 2H), 5.48 (br t, J=6.6 Hz, 1H), 6.96 (d, J=9.0 Hz, 2H), 7.54 (d, J=9.0 Hz, 2H), 7.16−7.30 (m, 5H), 8.15 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.2, 25.8, 29.9, 64.9, 115.0, 119.0, 120.3, 126.9, 128.3, 128.9, 131.1, 133.5, 136.2, 136.7, 138.8, 160.6, 167.9,

168.5; HRMS (EI) calcd for $C_{22}H_{21}NO_4$ (M^+) 363.1471, found 363.1469.

*4.1.20. (±)-cis-1-Hydroxy-3-benzyl-4-[4-(3-methyl-2-butenyloxy)phenyl]pyrrolidine-2,5-dione (**8**)*

To a solution of **7** (0.079 g, 0.2 mmol) in 4.0 mL of acetic acid was added Zn dust (1.6 mmol) in one portion. The mixture was stirred at room temperature for 2 h, quenched by addition of water (1.0 mL), and extracted with CH_2Cl_2 (3×5.0 mL). After removal of the solvent, the residue was subjected to column chromatography (SiO_2, 1:2 EtOAc/cyclohexane) to provide the single diastereomer **8** (0.045 g, 57%) as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.59 (s, 3H), 1.62 (s, 3H), 2.43 (dd, J=15.0, 10.5 Hz, 1H), 3.18 (dd, J=15.0, 4.5 Hz, 1H), 3.48 (m, 1H), 4.02 (d, J=8.7 Hz, 1H), 4.47 (d, J=6.9 Hz, 2H), 5.47 (br t, J=6.9 Hz, 1H), 6.70–6.76 (br s, 2H), 6.84 (br s, 4H), 7.08–7.21 (br s, 3H); ^{13}C NMR ($CDCl_3$) δ 18.2, 25.8, 31.6, 43.7, 47.0, 64.8, 114.9, 119.3, 124.8, 126.4, 128.2, 128.4, 130.3, 137.4, 138.4, 158.7, 173.4, 174.1; HRMS (EI) calcd for $C_{22}H_{23}NO_4$ (M^+) 365.1627, found 365.1626.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.02.077.

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