Note

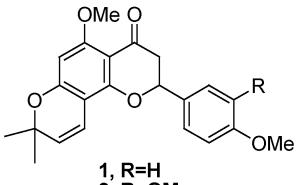
Total Synthesis of (±)-Glyflavanone by a Rigid Quaternary Ammonium Salt

Yu-Ting Fang (方郁婷), Chia-Ning Lin (林嘉寧),
Huan-Ting Wu (吳煥婷) and Yean-Jang Lee* (李衍彰)
Department of Chemistry, National Changhua University of Education, Changhua 50058, Taiwan, R.O.C.

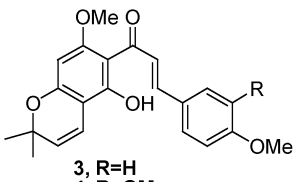
Total synthesis of (±)-glyflavanones and glychalcones was accomplished starting from the known 1-(5-hydroxy-7-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)ethanone (**6**). A new approach to synthesis of flavanones, based on a high yielding *N*-benzylcinchoninium salt catalyzed chromane ring forming enantioselective cyclization process, is described. Also, synthesis of (+)-glyflavanone **1**, the natural enantiomer, was achieved through optical resolution of a key intermediate in racemic synthesis.

Keywords: Enantioselectve; Glyflavanones; *N*-benzylcinchoninium salt.

Studies on the constituents of plants of *Glycosmis citrifolia* (Willd), which are used in traditional herbal medicines in areas of China, show cell growth inhibition of human promyelocytic leukaemic cells (HL-60) and also inhibit macromolecular synthesis.[1] (+)-Glyflavanones and glychalcones were isolated from the leaves of this plant collected in Taiwan by Wu et al. in 1995.[2] The structures of (+)-glyflavanones and glychalcones were elucidated as **1**-**4** by examination of optical rotation, IR, UV, NMR, and high-resolution mass spectra. To date, no (+)-glyflavanones has been synthesized. In addition, phase-transfer catalyzed reaction systems are one of the most useful methodologies in organic syntheses.[3] Recently, Corey et al. reported the development of the chiral quaternary cinchonidium cation as a superior catalyst for enantioselective reactions, including Michael, alkylation, aldol, nitroaldol, and epoxidation reactions.[4] Moreover, due to the medicinal imperatives and the intact structure of interest, the scarcity of (+)-**1** and the clear need for a reliable supply, we undertook the synthesis of one member of this family-(+)-glyflavanone **1**-to confirm the overall structure assignment.



1, R=H
2, R=OMe

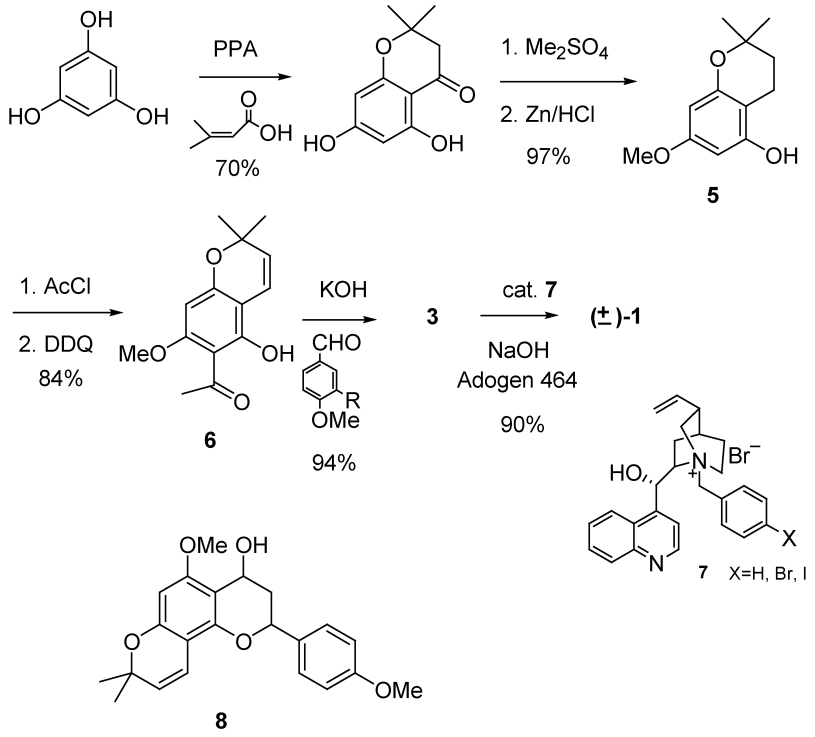


3, R=H
4, R=OMe

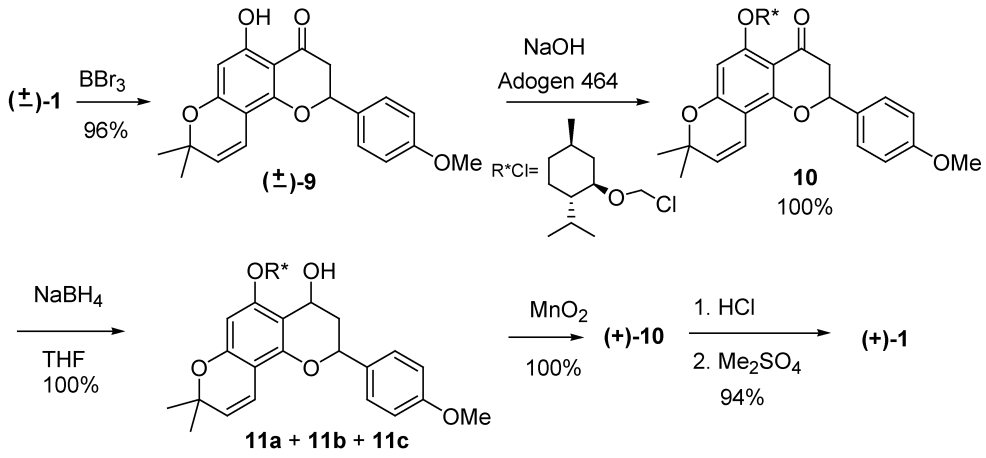
Perhaps the easiest route to optically active **1** would have been to employ the enantioselective cyclization of the glychalcone **3**. Thus, the trans-glychalcone **3** was considered to be an advanced synthetic intermediate for **1**. For the construction of the trans-α,β-unsaturated ketone in **3**, we anticipated that an aldol condensation of **6** and the corresponding benzaldehyde would proceed thermodynamically for the construction of a trans-geometry in **3**. First, we subjected the known[5] 2-hydroxy ketone **6** to aldol reaction with 4-methoxybenzaldehyde to produce the corresponding glychalcone as the trans-geometry **3** in high 94% yield (Scheme I). The *trans*-geometry isomer of **3** was assigned by use of the X-ray crystallographic method.[6] To investigate the scope of the *N*-benzylcinchoninium salt catalyzed enantioselective cyclization process, we examined reactions of various starting materials, including simple chalcones. The results are summarized in Table 1. Flavanones, bearing substituents in the 5,7,4′-positions (entries 1-4), are prepared by use of this method in high yields. 4,6-Dimethoxy-4′-methoxy chalcone also reacts under these conditions to afford the desired product (entries 5-8). However, the enantioselective cyclization of glychalcones, catalyzed by *N*-benzylcinchoninium salts, requires high temperature and leads to generation of only 55% ee glyflavones in > 90% yield (entries 9-12). On the other hand, it is worth noting that NaOH was dissolved in H_2O and Adogen 464 for an efficient route to racemic **1** in Scheme I.

Having established an efficient route to racemic **1** and **2**, we next focused our attention on the synthesis of an optically active **1**. For separation, the reduction of racemic ketone **1** with $NaBH_4$ was smoothly converted to generate the desired diastereomer chromanol **8** in 93% yield. However, attempts to separate diastereomers **8** were unsuccessful. It is worth noting that chromanol **8** underwent the dehy-

Scheme I

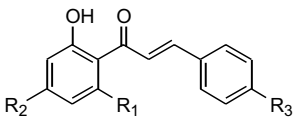


Scheme II



dration reaction at various weak acid conditions as well as standing on chloroform or silica gel. Alternately, when racemic (±)-**1** was treated with BBr_3, the racemic (±)-**9** was produced in excellent yield (96%). Followed by alkylation of the racemic 5-hydroxyflavanone **9** with (-)-chloromethyl menthyl ether, the desired diastereomers **10** were obtained in quantitative yield. However, attempts to separate diastereomers **10** were unsuccessful. Consequently, **10** were further transformed by reduction with $NaBH_4$, and readily separable diastereomers **11a**, **11b**, and **11c** were isolated (Scheme II). The structure of diastereomers, **11a**, **11b**, and **11c**, was assigned by use of COSY (^{1}H-^{1}H) and HSQC (^{1}H-^{13}C) NMR experimental analysis. Both COSY and HSQC spectra of **11a**, **11b**, and **11c** were shown on the supporting material. Subsequently MnO_2 oxidation of **11a** and **11b** produced optically pure **10a** and **10b**, respectively. Finally, enantiomerically pure **10a** or **10b** was eventually converted into (+)-glyflavanone or (-)-glyflavanone using

Table 1. Asymmetric synthesis of flavanones with various *n*-benzylcinchoninium salts

Entry	Chalcones	Conditions	Product/ flavanones	Yield (%)[a]	ee%[b]
		cat. 7a X=H 7b X=Br 7c X=I (10 mol%)			
1	R_1=R_3=H, R_2=OMe	7b, Et_3N, 0 °C		99	31
2	R_1=R_3=H, R_2=OMe	7c, Et_3N, 0 °C		98	33
3	R_1=R_3=H, R_2=OMe	7c, NaOH, 0 °C		99	30
4	R_1=R_3=H, R_2=OMe	7c, Dabco, 0 °C		98	28
5	R_1=R_3=R_2=OMe	7b, Et_3N, 0 °C		18	4
6	R_1=R_3=R_2=OMe	7b, Et_3N, 60 °C		56	8
7	R_1=R_3=R_2=OMe	7c, NaOH, 60 °C		34	5
8	R_1=R_3=R_2=OMe	7c, NaOH, Adogen 464, 60 °C		70	9
9	**3**	7a, Et_3N, 60 °C		90	0
10	**3**	7b, Et_3N, 60 °C		95	13
11	**3**	7c, Et_3N, 60 °C		93	15
12	**3**	7c, NaOH, 60 °C		92	55

[a] Isolated yield; [b] Determined by HPLC analysis using a chiral column.

a deprotection and methylation reaction sequence. The synthesized optically active (+)-**1** had a consistent specific rotation with that of natural (+)-**1** {$[\alpha]_D$ +15 (c 0.06, $CHCl_3$) for synthetic, lit.[2] $[\alpha]_D$ +13.5 (c 0.065, $CHCl_3$) for natural}. In addition, ^1H, ^{13}C NMR, and high-resolution mass spectra of the synthetic product are in agreement with those reported for the naturally derived material.[2] Although ^1H and ^{13}C NMR spectroscopic analysis of these substances showed that they contained the desired glyflavanone ring system, the data were not sufficient to enable unambiguous assignments of the structures. Thus, **1** was subjected to X-ray crystallographic analysis,[6] which provided the structure.

In summary, we have proposed the versatility of the *N*-benzylcinchoninium salt catalyzed chromane ring forming enantioselective cyclization process. We have achieved the total synthesis of (±)-glyflavanones in 7 steps in an overall yield 48% starting with commercially available phloroglucinol dihydrate. In addition, optical resolution of the key intermediates **11a** and **11b** led to the syntheses of natural (+)- and unnatural (-)-glyflavanone. However, the mechanistic issues uncovered in the enantioselective cyclization process as well as the scope and generality of this new synthetic method will be probed in detail in our continuing studies in this area. Further syntheses of (+)-glyflavanones are currently underway to employ this strategy for supplying biological assays.

EXPERIMENTAL SECTION[7]

1-(5-Hydroxy-7-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)ethanone (6)

This compound was prepared as a yellow solid from phloroglucinol dihydrate (Acros) according to the literature[8] (Scheme I). The mp, ^1H and ^{13}C NMR spectra are in agreement with those reported.[9]

1-(5-Hydroxy-7-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)-3-(4-methoxyphenyl)propenone (3)

A mixture of **6** (0.50 g, 2.0 mmol) and 4-methoxybenzaldehyde (0.41 g, 3.0 mmol) in 25 mL ethanol was introduced into 10 mL KOH (1.20 g in H_2O/ethanol 1:1) under a nitrogen atmosphere at 0 °C. The suspension was then stirred and maintained at room temperature for 8 h. A dark brown suspension was neutralized with HCl until pH = 4 and then followed by extraction with CH_2Cl_2 (3 × 100 mL). The organic layer was concentrated and the crude product was subjected to column chromatography (SiO_2, Hexane/EA 10/1) to yield glychalcone **3** (0.69 g, 94%) as a red solid: mp 115-117 °C (lit.[2] mp 112-114 °C); ^1H NMR [$(CD_3)_2CO$] δ 1.41 (s, 6H), 3.84 and 3.98 (s, 6H), 5.55 (d, *J* = 10.0 Hz, 1H), 6.01 (s, 1H), 6.60 (d, *J* = 10.0 Hz, 1H), 6.99 and 7.68 (d, *J* = 8.8 Hz, 4H), 7.95 and 8.10 (d, *J* = 15.4 Hz, 2H); ^{13}C NMR [$(CD_3)_2CO$] δ 28.7, 55.9, 56.7, 79.0, 92.6, 103.6, 106.7, 115.5, 116.7, 125.9, 126.5, 129.1, 131.3,

143.5, 161.4, 162.8, 163.4, 163.9, 193.6; HRMS (EI) calcd for $C_{22}H_{22}O_5$ (M^+) 366.1467, found 366.1461; Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.12; H, 6.05; O, 21.83. Found: C, 72.26; H, 5.89; O, 21.92.

3-(3,4-Dimethoxyphenyl)-1-(5-hydroxy-7-methoxy-2,2-dimethyl-2*H*-chromen-6-yl)propenone (4)

This unsaturated ketone **4** was prepared, using the above procedure, from **6** (0.50 g, 2.0 mmol) and 3,4-dimethoxybenzaldehyde (0.50 g, 3.0 mmol) using base KOH (1.3 g) in ethanol (25 mL) for 8 h. The product was isolated in 96% yield (0.77 g, 1.9 mmol) after flash chromatography (SiO_2, hexane/EA 10/1) as a yellow solid: mp 130-132 °C; ^{1}H NMR [$(CD_3)_2CO$] δ 1.42 (s, 6H), 3.85, 3.89, and 3.99 (s, 9H), 5.55 (d, *J* = 10.0 Hz, 1H), 6.01 (s, 1H), 6.60 (d, *J* = 10.0 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 4H), 7.27 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.30 (d, *J* = 1.9 Hz, 1H), 7.72 and 7.88 (d, *J* = 15.4 Hz, 2H); ^{13}C NMR [$(CD_3)_2CO$] δ 28.7, 56.2, 56.3, 56.7, 79.0, 92.6, 103.6, 106.7, 111.8, 112.7, 116.7, 123.9, 126.1, 126.6, 129.3, 143.9, 150.7, 152.9, 163.4, 163.9, 193.6.

5-Methoxy-2-(4-methoxyphenyl)-8,8-dimethyl-2,3-dihydro-8*H*-pyrano[2,3-*j*]chromen-4-one (1)

Ketone **3** (0.44 g, 1.2 mmol) and freshly prepared benzylcinchoninium salt[10] (0.056 g, 10 mol %) were dissolved in 25 mL of H_2O/CH_2Cl_2 (1:1). To NaOH (0.072 g, 1.8 mmol) in 3 mL of distilled H_2O was added one portion at 0 °C followed by 3 mL of Adogen 464. The reaction mixture was heated to 60 °C (oil bath) under reflux for 2 h. After cooling, the organic and aqueous phase was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phase and organic extracts were dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, cyclohexane/EA 5/1) to give **1** (0.40 g, 90%) as light yellow solid: mp 114-115 °C (lit.[2] mp 112-114 °C); ^{1}H NMR [$(CD_3)_2CO$] δ 1.39 and 1.41 (s, 6H), 2.63 (dd, *J* = 16.4, 3.0 Hz, 1H), 2.97 (dd, *J* = 16.4,12.5 Hz, 1H), 3.81 (s, 3H), 5.44 (dd, *J* = 12.5,3.0 Hz, 1H), 5.55 (d, *J* = 10.0 Hz, 1H), 6.08 (s, 1H), 6.52 (d, *J* = 10.0 Hz, 1H), 6.97 and 7.47 (d, *J* = 8.6 Hz, 4H); ^{13}C NMR [$(CD_3)_2CO$] δ 27.1, 27.4, 44.8, 54.4, 55.0, 77.2, 78.4, 93.2, 102.1, 105.2, 113.5, 115.5, 126.0, 127.4, 131.0, 158.3, 159.0, 159.6, 161.8, 186.9; HRMS (EI) calcd for $C_{22}H_{22}O_5$ (M^+) 366.1467, found 366.1462.

2-(3,4-Dimethoxyphenyl)-5-methoxy-8,8-dimethyl-2,3-dihydro-8*H*-pyrano[2,3-*j*]chromen-4-one (2)

The glyflavanone **2** was prepared, using the previous procedure, from **4** (0.40 g, 1.0 mmol) and benzylcinchoninium salt (0.047 g, 10 mol %) using base NaOH (0.061 g, 1.5 mmol) in 6 mL of H_2O and Adogen 464 (1:1) for 2 h. The product was isolated in 91% yield (0.36 g, 0.91 mmol) after flash chromatography (SiO_2, cyclohexane/EA 5/1) as a light yellow solid: mp 148-150 °C; ^{1}H NMR [$(CD_3)_2CO$] δ 1.39 and 1.41 (s, 6H), 2.64 (dd, *J* = 16.4, 3.1 Hz, 1H), 3.00 (dd, *J* = 16.4,12.5 Hz, 1H), 3.81 and 3.83 (s, 6H), 5.42 (dd, *J* = 12.5,3.1 Hz, 1H), 5.55 (d, *J* = 10.0 Hz, 1H), 6.07 (s, 1H), 6.54 (d, *J* = 10.0 Hz, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 7.06 (dd, *J* = 8.3,1.9 Hz, 1H), 7.16 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR [$(CD_3)_2CO$] δ 28.2, 28.9, 46.7, 56.8, 56.9, 79.1, 80.6, 95.1, 104.0, 107.2, 111.8, 113.2, 117.3, 120.3, 127.9, 133.4, 151.1, 151.2, 160.2, 160.9, 163.7, 188.8.

5-Methoxy-2-(4-methoxyphenyl)-8,8-dimethyl-2,3-dihydro-8*H*-pyrano[2,3-*j*]chroman-4-ol (8)

In a solution of racemic **1** (0.31 g, 0.85 mmol) in 30 mL THF was cooled down to 0 °C and then followed by addition of $NaBH_4$ (0.080 g, 2.1 mmol). The mixture was stirred and maintained at room temperature for 2 h. After quenching with methanol, the resulting solution was extracted with CH_2Cl_2 (3 × 100 mL). The solvent was removed *in vacuo*, and the residue was subjected to short column chromatography (SiO_2, cyclohexane:EA 10:1) to provide chromanol **8** (0.29 g, 93%) as a yellow solid: mp 138-140 °C; ^{1}H NMR [$(CD_3)_2CO$] δ 1.34 and 1.37 (s, 6H), 2.04 (ddd, *J* = 13.4,11.9,1.8 Hz, 1H), 2.42 (ddd, *J* = 13.4, 7.4, 1.8 Hz, 1H), 3.79 and 3.85 (s, 6H), 4.00 (s, OH), 4.98 (dd, *J* = 11.9, 1.8 Hz, 1H), 5.16 (t, *J* = 7.4 Hz, 1H), 5.44 (d, *J* = 9.9 Hz, 1H), 6.06 (s, 1H), 6.46 (d, *J* = 9.9 Hz, 1H), 6.94 and 7.41 (d, *J* = 8.6 Hz, 4H); ^{13}C NMR [$(CD_3)_2CO$] δ 28.4, 28.6, 40.0, 56.2, 56.7, 64.2, 77.5, 78.3, 94.3, 104.8, 109.4, 115.3, 118.1, 127.5, 129.0, 134.5, 153.0, 155.4, 160.9, 161.1.

5-Hydroxy-2-(4-methoxyphenyl)-8,8-dimethyl-2,3-dihydro-8*H*-pyrano[2,3-*j*]chromen-4-one (9)

Racemic **1** (0.25 g, 0.68 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and cooled down to -23 °C under a nitrogen atmosphere. To the solution was added BBr_3 (1.2 eq. 1 M 0.82 mL) for 5 h at -23 °C; the resulting solution was quenched with MeOH and subjected to flash chromatography (SiO_2, cyclohexane/EA 10/1) to provide the desired phenol **9** (0.23 g, 96%) as a white solid: mp 156-158 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 and 1.44 (s, 6H), 2.78 (dd, *J* = 17.1, 3.2 Hz, 1H), 3.06 (dd, *J* = 17.1, 12.8 Hz, 1H), 3.83 (s, 3H), 5.36 (dd, *J* = 12.8, 3.2 Hz, 1H), 5.45 (d, *J* = 10.0 Hz,

1H), 5.99 (s, 1H), 6.52 (d, J = 10.0 Hz, 1H), 6.95 and 7.38 (d, J = 8.7 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 28.2, 28.4, 43.0, 55.3, 78.0, 78.8, 97.5, 101.9, 102.8, 114.1, 115.5, 126.3, 127.5, 130.4, 156.8, 159.8, 162.1, 163.7, 195.9.

5-[(-)-(1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy-methoxy]-2-(4-methoxyphenyl)-8,8-dimethyl-2,3-dihydro-8*H*-pyrano[2,3-*j*]chromen-4-one (10)

Phenol **9** (0.21 g, 0.59 mmol) was dissolved in 30 mL of distilled CH_2Cl_2. NaOH (0.036 g, 0.89 mmol) in 0.50 mL of distilled water was added in one portion at 0 °C (ice bath) followed by 0.50 mL of Adogen 464. The reaction mixture was allowed to stir for 30 min at room temperature and was then cooled to 0 °C. (-)-Chloromethy menthyl ether (0.13 g, 0.66 mmol) was then added dropwise over 0.5 h until reaction was complete. The organic and aqueous phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase and organic extracts were dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. Purification by flash column chromatography (SiO_2, cyclohexane/EA 10/1) afforded the desired ketone **10** (0.31 g, 100%) as a white solid: mp 116-118 °C; ^{1}H NMR [$(CD_3)_2CO$] δ 0.55 and 0.62 (d, J = 6.6 Hz, 6H), 0.81 and 0.89 (d, J = 7.2 Hz, 12H), 0.89-1.27 (m, 6H), 1.34-1.40 (m, 4H), 1.37, 1.39, 1.40 and 1.42 (s, 12H), 1.60-1.62 (m, 4H), 2.01-2.05 (m, 4H), 2.65 (dd, J = 16.3, 3.1 Hz, 2H), 2.93 (dd, J = 12.5, 4.2, 2H), 3.51 (m, 2H), 3.80 (s, 6H), 5.29 (dd, J = 7.2, 2.4 Hz, 2H), 5.35-5.48 (m, 6H), 5.57 (d, J = 10.0 Hz, 2H), 6.25 (s, 2H), 6.53 (d, J = 10.0 Hz, 2H), 6.97 and 7.47 (d, J = 9.0 Hz, 8H); ^{13}C NMR ($CDCl_3$) δ 15.4, 15.5, 21.0, 22.3, 22.9, 25.2, 25.3, 27.7, 28.1, 28.2, 28.5, 31.4, 34.4, 40.8, 45.6, 48.1, 55.3, 77.9, 78.0, 78.6, 90.9, 91.0, 97.2, 103.5, 106.1, 114.0, 116.1, 126.6, 127.5, 131.0, 158.5, 159.6, 159.7, 189.2.

5-[(-)-(1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy-methoxy]-2-(4-methoxyphenyl)-8,8-dimethyl-2,3-dihydro-8*H*-pyrano[2,3-*j*]chroman-4-ol (11)

These diastereomers **11** were prepared, using the above procedure, from **10** (0.20 g, 0.38 mmol) and $NaBH_4$ (0.036 g, 0.96 mmol) in THF (25 mL) for 4 h. The benzyl alcohols were separated by column chromatography (SiO_2, cyclohexane, cyclohexane/EA 10/1) to afford **11a**, **11b**, and **11c** in 40, 44, 16% yield (0.080, 0.088, 0.032 g), respectively.

11a: $[\alpha]_D$ = -74.5° [acetone; c 0.8]; ^{1}H NMR [$(CD_3)_2CO$] δ 0.62-1.02 (m, 2H), 0.66 and 0.85 (d, J = 7.2 Hz, 6H), 0.88 (d, J = 6.6 Hz, 3H), 1.21-1.27 (m, 1H), 1.33 and 1.38 (s, 6H), 1.34-1.42 (m, 2H), 1.59-1.65 (m, 2H), 2.02-2.08 (m, 1H), 2.17-2.20 (m, 2H), 2.42 (ddd, J = 9.6, 7.8, 2.4 Hz, 1H), 3.56 (ddd, J = 15.0, 10.8, 4.2 Hz, 1H), 3.79 (s, 3H), 4.04 (d, J = 2.4 Hz, 1H), 4.98 (dd, J = 12.0, 1.2 Hz, 1H), 5.18 (ddd, J = 9.0, 7.8, 2.4 Hz, 1H), 5.32 (d, J = 7.2 Hz, 1H), 5.46 (d, J = 9.6 Hz, 1H), 5.47 (d, J = 7.2 Hz, 1H), 6.26 (s, 1H), 6.47 (d, J = 9.6 Hz, 1H), 6.95 and 7.41 (d, J = 8.4 Hz, 4H); ^{13}C NMR [$(CD_3)_2CO$] δ 16.1, 21.4, 22.6, 23.6, 26.0, 27.4, 28.3, 32.1, 35.0, 39.3, 41.8, 49.0, 55.5, 63.7, 76.6, 77.6, 78.8, 92.1, 96.5, 104.7, 109.2, 114.5, 117.4, 127.2, 128.3, 133.8, 152.2, 154.4, 157.9, 160.4.

11b: $[\alpha]_D$ = -114° [acetone; c 0.8]; ^{1}H NMR [$(CD_3)_2CO$] δ 0.63 and 0.81 (d, J = 7.2 Hz, 6H), 0.64-1.02 (m, 2H), 0.89 (d, J = 6.6 Hz, 3H), 1.19-1.26 (m, 1H), 1.34 and 1.35 (s, 6H), 1.32-1.39 (m, 2H), 1.59-1.65 (m, 2H), 2.02-2.12 (m, 2H), 2.17-2.20 (m, 1H), 2.42 (ddd, J = 9.0, 7.2, 1.2 Hz, 1H), 3.56 (ddd, J = 15.0, 10.8, 4.2 Hz, 1H), 3.79 (s, 3H), 4.03 (d, J = 2.4 Hz, 1H), 4.97 (dd, J = 12.0, 1.2 Hz, 1H), 5.17 (ddd, J = 9.6, 7.2, 2.4 Hz, 1H), 5.35 (d, J = 7.2 Hz, 1H), 5.46 (d, J = 9.6 Hz, 1H), 5.44 (d, J = 7.2 Hz, 1H), 6.24 (s, 1H), 6.48 (d, J = 9.6 Hz, 1H), 6.94 and 7.41 (d, J = 8.4 Hz, 4H); ^{13}C NMR [$(CD_3)_2CO$] δ 16.0, 21.3, 22.6, 23.6, 26.0, 27.4, 27.8, 27.9, 32.2, 35.0, 39.3, 41.8, 48.9, 55.5, 63.6, 76.7, 77.6, 78.8, 91.8, 96.4, 104.7, 109.2, 114.5, 117.5, 127.2, 128.3, 133.8, 152.2, 154.3, 157.8, 160.3.

11c: $[\alpha]_D$ = -105° [acetone; c 0.3]; ^{1}H NMR [$(CD_3)_2CO$] δ 0.58 and 0.80 (d, J = 6.6 Hz, 6H), 0.81-1.02 (m, 2H), 0.89 (d, J = 7.2 Hz, 3H), 1.18-1.23 (m, 1H), 1.34 and 1.37 (s, 6H), 1.34-1.40 (m, 2H), 1.58-1.65 (m, 2H), 1.89-1.94 (m, 1H), 2.10-2.13 (m, 2H), 2.20-2.23 (m, 1H), 3.53 (ddd, J = 15.0, 10.8, 4.2 Hz, 1H), 3.80 (s, 3H), 4.94 (ddd, J = 9.0, 7.2, 4.2 Hz, 1H), 5.18 (dd, J = 12.0, 1.2 Hz, 1H), 5.31 and 5.35 (d, J = 7.2 Hz, 1H), 5.46 (d, J = 10.2 Hz, 1H), 6.21 (s, 1H), 6.51 (d, J = 10.2 Hz, 1H), 6.96 and 7.41 (d, J = 9.0 Hz, 4H); ^{13}C NMR [$(CD_3)_2CO$] δ 15.9, 21.3, 22.6, 23.6, 25.9, 27.5, 28.2, 32.1, 35.1, 38.8, 41.7, 48.9, 55.5, 59.1, 73.7, 76.6, 78.3, 91.5, 95.9, 104.4, 107.8, 114.6, 117.5, 126.8, 128.4, 134.3, 151.8, 154.8, 157.7, 160.3.

5-[(-)-(1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxy-methoxy]-2-(4-methoxyphenyl)-8,8-dimethyl-2,3-dihydro-8*H*-pyrano[2,3-*j*]chromen-4-one (10a)

To a solution of benzyl alcohol **11a** (0.080 g, 0.15 mmol) in 10 mL of ether and EA (1:1) was added MnO_2 (0.033 g, 0.38 mmol) at room temperature and stirred for 1 h. To the suspension was added the other portion of MnO_2

(0.033 g, 0.38 mmol) and then it was allowed to stir 1 h. After filtering with celite, the filtrate was subjected to column chromatography (SiO_2, cyclohexane/EA 5/1) to produce optically pure ketone **10a** (0.080 g, 100%) as a white solid: mp 115-117 °C; $[\alpha]_D$ = -64.2° [acetone; c 0.8].

5-[(-)-(1R,2S,5R)-2-isopropyl-5-methylcyclohexyloxymethoxy]-2-(4-methoxyphenyl)-8,8-dimethyl-2,3-dihydro-8*H*-pyrano[2,3-*j*]chromen-4-one (10b)

This optically pure **10b** was prepared, using the above procedure, from **11b** (0.088 g, 0.17 mmol) and MnO_2 (0.074 g, 0.84 mmol) in ether/EA (10 mL) for 2 h. Column chromatography (SiO_2, cyclohexane/EA 5/1) provided optically pure ketone **10b** (0.089 g, 100%) as a white solid: mp 115-116 °C; $[\alpha]_D$ = -54.5° [acetone; c 0.8].

(+)-5-Methoxy-2-(4-methoxyphenyl)-8,8-dimethyl-2,3-dihydro-8*H*-pyrano[2,3-*j*]chromen-4-one (1)

A solution of **10a** (0.050 g, 0.096 mmol) in 5 mL CH_2Cl_2 was treated with diluted HCl (0.1 mL conc. HCl in 1 mL CH_2Cl_2) at 0 °C for 10 min. The resulting solution was subjected to column chromatography (SiO_2, cyclohexane/EA 4/1) to give phenol **9** (0.034 g, 0.096 mmol), which is then transformed to the methylation reaction. To a mixture of phenol **9** and K_2CO_3 (0.066 g, 0.48 mmol) in 5 mL acetone was heated to reflux at 70 °C (oil bath), followed by addition of Me_2SO_4 (0.024 g, 0.19 mmol) and maintained for 2 h. After cooling, the resulting suspension was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase and organic extracts were dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The residue was subjected to flash column chromatography (SiO_2, cyclohexane/EA 5/1) to give (+)-**1** (0.033 g, 94%) as a light yellow solid: mp 114-115 °C; $[\alpha]_D$ = +18.5° [acetone; c 0.33].

(-)-5-Methoxy-2-(4-methoxyphenyl)-8,8-dimethyl-2,3-dihydro-8*H*-pyrano[2,3-*j*]chromen-4-one (1)

From **10b** (0.064 g, 0.12 mmol), according to the previous procedure, (-)-**1** (0.041 g, 92%) was achieved in high yield as a light yellow solid; mp 114-115 °C; $[\alpha]_D$ = -18.3° [acetone; c 0.4].

ACKNOWLEDGEMENTS

We thank the National Science Council of the Republic of China for financial support (Research Grant NSC 90-2113-M-018-008 and NSC 91-2113-M018-003). We also acknowledge with appreciation the NSC-supported High Resolution Mass and 500 MHz NMR spectrometry facility (Department of Chemistry, National Chung Tsing University) for providing high-resolution Mass and 2-D NMR spectra.

Supporting Information Available

Spectroscopic characterization and copies of ^1H and ^{13}C NMR spectra of the compounds described in the text, and tables giving all of the crystallographic details and the structure refinement information for **1** and **3**, and including COSY (^1H-^1H) and HSQC (^1H-^{13}C) of **11a**, **11b**, and **11c** are available free of charge via the Internet at http://www.ccs.sinica.edu.tw/publish33.asp.

Received November 21, 2006.

REFERENCES

1. Chou, T. C.; Tzeng, C. C.; Wu, T. S.; Watanabe, K. A.; Su, T. L. *Phytotherapy Res*. **1989**, *3*, 237.
2. Wu, T. S.; Chang, F. C.; Wu, P. L. *Phytochemistry* **1995**, *39*, 1453-1457.
3. For recent books on PTC, see: (a) *Phase-Transfer Catalysis. Mechanism and Syntheses*; Halpern, M. E., Ed.; American Chemical Society: Washington, D C, 1997. (b) *Handbook of Phase Transfer Catalysis*; Sasson Y.; Neumann R., Eds.; Blackie A. & M. 1997. (c) Liu, K. T.; Kuo, M. Y. *J. Chin. Chem. Soc*. **1981**, *28*, 209-211. (d) Wang, X. Y.; Wang, Y. L.; Wang, C .L.; Li, J. P.; Wang, H.; Zhang, Z. Y. *J. Chin. Chem. Soc*. **1999**, *46*, 971-974.
4. Corey, E. J.; Zhang, F. Y. *Org. Lett.* **1999**, *1*, 1287-1290; and references cited therein.
5. Manandhar, M. D.; Hussaini, F. A.; Kapil, R. S.; Sloeb, A. *Phytochemistry* **1985**, *24*, 199-200.
6. The X-ray data for **1**, **3** are deposited at CCDC as numbers 219655 and 219654, respectively.
7. For general experimental procedures, see (a) Lee, J. M.; Tseng, T. H.; Lee, Y. J. *Synthesis* **2001**, *15*, 2247-2254. (b) Tseng, T. H.; Tsheng, Y. M.; Lee, Y. J.; Hsu, H. L. *J. Chin. Chem. Soc.* **2000**, *47*, 1165-1169. (c) Lee, Y. J.; Wu, T. D. *J. Chin. Chem. Soc*. **2001**, *48*, 201-206.
8. Vijayalakshmi, C. S.; Subramanian, M.; Rajendra Prasad, K. J. *Indian J. Chem.* **1990**, *29B*, 661-663.
9. (a) Barton, D. H. R.; Donnelly, D. M. X.; Finet, J. P.; Guiry, P. J. *Tetrahedron Lett.* **1990**, *31*, 7449-7452. (b) Ahluwalia, V. K.; Arora, K. K. *Tetrahedron* **1981**, *37*, 1437-1440.
10. Arai, S.; Tsuge, H.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 7563-7566.