Enantioselective Synthesis of (+)-O-Trimethylsappanone B and (+)-O-Trimethylbrazilin†

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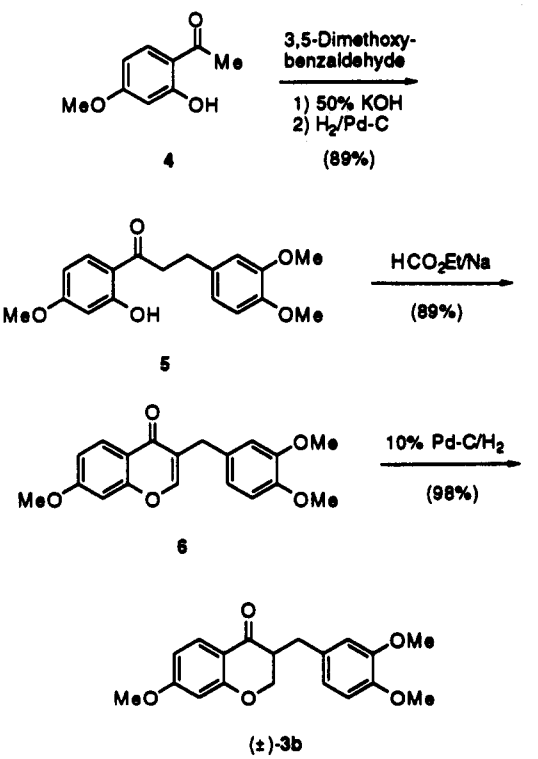
The homoisoflavanoid (+)-O-trimethylbrazilin (**1b**) was prepared in 70% yield and 92% ee by acid-catalyzed rearrangement of O-trimethylsappanol (**8**) prepared by reduction of (*R*)-(−)-O-trimethylsappanone B (**2b**). The key step in the synthesis of (*R*)-(−)-**2b** is the reagent-controlled highly enantioselective hydroxylation (94%) of the sodium enolate of (±)-4-chromanone (**3b**) with the (+)-8,8-dichlorocamphorsulfonyl oxaziridine **7b**.

Brazilin[1] (**1a**) is a tetracyclic homoisoflavanoid isolated from the heartwood of *Caesalpinia* spp.[2] The structure of brazilin (**1a**) was established by chemical and spectroscopic methods as 7,11b-dihydrobenz[*b*]indeno[1,2-*d*]-pyran-3,6a,9,10(6*H*)-tetrol[3] and was confirmed by X-ray analysis of O-trimethylbrazilin (**1b**).[4] Brazilin possesses antibacterial[5] and antiinflammatory activities.[6] Recent studies suggest that brazilin has the potential to improve rheological abnormalities in diabetes, enhancing erythrocyte deformability and reducing blood viscosity which is increased by diabetes.[7] (+)-Sappanone B (**2a**), a new member of the isoflavanoid family, was recently isolated from *Caesalpinia japonica* Sieb and Zucc[8] and *Caesalpinia sappan* L. (leguminosae),[9] a traditional Chinese medicinal plant.[10] The biogenesis of brazilin (**1a**) from sappanone B (**2a**) has been proposed.[9]

Although racemic O-trimethylbrazilin (**1b**) has been the subject of several syntheses,[11] there are no reports on the enantioselective synthesis of (+)-brazilin (**1a**), (+)-sappanone B (**2a**), nor their O-methyl derivatives. Our interest in the asymmetric synthesis of these compounds was stimulated by our earlier, highly successful enantioselective (>95% ee) synthesis of the related homoisoflavanoids (+)- and (−)-5,7-O-dimethyleucomol.[12] It was envisioned that the key chiral tertiary hydroxyl group at C-6a of (+)-O-trimethylbrazilin (**1b**) could be established via the asymmetric enolate oxidation protocol with camphorylsulfonyl oxaziridine derivatives,[13] i.e., asymmetric hydroxylation of the enolate of (±)-3-(3,4-dimethoxybenzyl)-7-methoxy-4-chromanone (**3b**) to (*R*)-(−)-O-trimethylsappanone B (**2b**) (Scheme I).

The racemic 4-chromanone **3b** was prepared following a highly efficient procedure developed by us for the synthesis of 5,7-O-dimethyleucomol.[12] Heating 2-hydroxy-4-methoxyacetophenone (**4**) with 3,4-dimethoxybenzaldehyde in methanol using 50% aqueous KOH followed by hydrogenation over 10% palladium on activated carbon gave 2′-hydroxy-4′,3,4-trimethoxydihydrochalcone (**5**) in 89% overall yield. Treatment of **5** in ethyl formate with



sodium sand at 0 °C afforded chromone **6** which was subjected without purification to palladium-catalyzed hydrogenation to give racemic 3-(3,4-dimethoxybenzyl)-7-methoxy-4-chromanone (**3b**) in 89% overall yield.

† This paper is dedicated to Professor Antonino Fava on the occasion of his 70th birthday.

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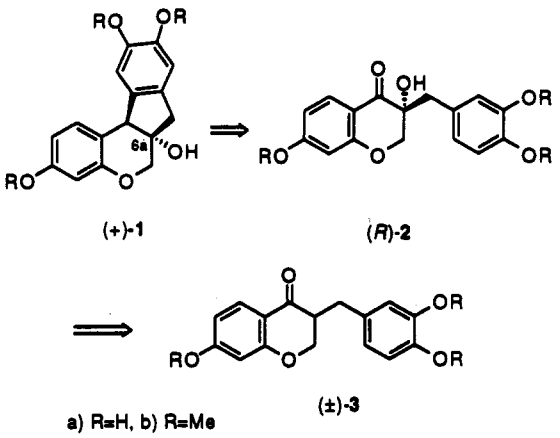
Scheme I



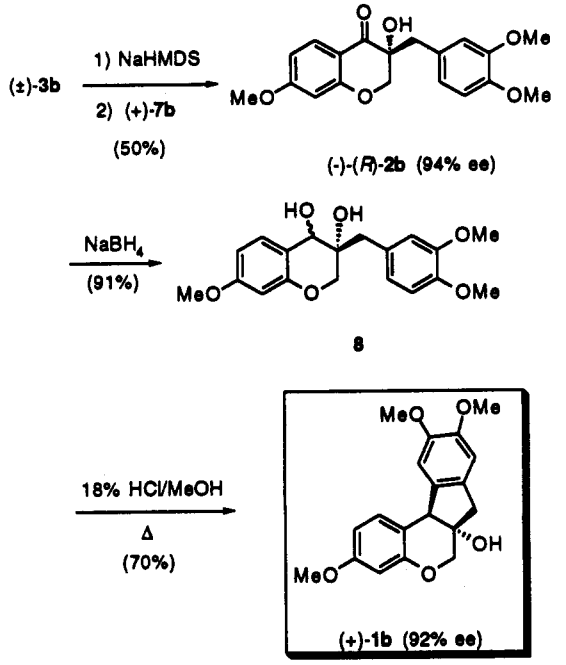
Earlier studies on the asymmetric hydroxylation of the enolates of 2-substituted 1-tetralones and 4-chromanone with camphorylsulfonyl oxaziridine derivatives demonstrated that stereoselectivity is highly dependent not only on the reaction conditions (temperature, counterion, etc.), but the substitution pattern of the enolate.[13] For example the 8,8-dimethoxycamphorylsulfonyl oxaziridine **7a** afforded the best stereoselectivities with enolates of 2-substituted tetralones bearing an 8-methoxy group.[14] For those enolates lacking this substituent, the 8,8-dichlorocamphorylsulfonyl oxaziridine **7b** was the reagent of choice.[15] The absolute stereochemistry of the product is controlled by the configuration on the oxaziridine ring.

(+)-7

a) X=OMe
b) X=Cl

On the basis of these considerations and the fact that (*R*)-(−)-*O*-trimethylsappanone B (**2b**) is required for rearrangement to (+)-*O*-trimethylbrazilin (**1b**), oxaziridine (+)-**7b** was chosen for introduction of the hydroxy group into (±)-**3b**. Thus, treatment of (±)-**3b** with 1.5 equiv of NaHMDS at −78 °C followed by addition of 1.5 equiv of (+)-**7b** afforded **2b** in 50% yield following isolation by preparative TLC. Comparison with reported values revealed that the enantiomeric purity of (+)-**2b** was 94% and that it had the (*R*)-configuration.[16]

Reduction of (*R*)-(−)-**2b** with $NaBH_4$ in ethanol gave better than 95% *cis*-trimethylsappanol (**8**) in 91% yield as determined by integration of C-5 chromone proton at δ 7.22.[8] One-pot treatment of the crude diol mixture with 18% HCl and refluxing for 2 h finished (+)-*o*-trimethylbrazilin (**1b**) in 71% yield.[16] The enantiomeric purity of synthetic (+)-**1b** was 92% ee based on comparison of its optical rotation with literature values,[16] indicating that rearrangement of **8** to **1b** occurs without epimerization at the chiral centers.



Attempts to demethylate (+)-*O*-trimethylbrazilin (**1b**) to (+)-brazilin (**1a**) with boron tribromide proved unsuccessful resulting in a complex mixture of products from which no identifiable materials could be isolated.

Experimental Section

Details concerning the recording of spectra, the analytical instruments used, the determination of melting points, elemental analyses and the purification of solvents (freshly distilled) have been previously reported.[14] Enolate oxidations were performed in flame-dried flasks equipped with rubber septa. All reactions were performed under an argon atmosphere. Sodium bis(trimethylsilylamide) (NHMDS), 1.0 M solution in THF, was purchased from Aldrich Chemical Co. Camphorylsulfonyl oxaziridines (+)-**7a**[14] and (+)-**7b**[15] were prepared as previously described. 2′-Hydroxy-4′-methoxyacetophenone was purchased from Aldrich.

2′-Hydroxy-4,3,4′-trimethoxydihydrochalcone (5). To a mixture of 3.32 g (20 mmol) of 2′-hydroxy-4′-methoxyacetophenone (**4**) and 3.32 g (20 mmol) of 3,4-dimethoxybenzaldehyde in 40 mL of CH_3OH and 20 mL of H_2O was added 20 g of solid KOH. The resulting solution was refluxed for 15 min and cooled in an ice–water bath, and the reaction mixture acidified with 40 mL of concd HCl. The solution was diluted with 200 mL of H_2O and stored in the refrigerator overnight. The precipitated yellow solid was collected by suction filtration and dried to give 5.60 g (89%) of crude 2′-hydroxy-4,3,4′-trimethoxychalcone of sufficient purity for the next step: mp 153–155 °C (lit.[18] mp 156 °C); IR (KBr) 3420 (OH), 1635 (ArC=O), 1564 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.88 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 6.50–7.95 (m, 8 H), 13.56 (s, 1 H, OH).

In a Parr hydrogen flask was placed a solution of 2.51 g (8 mmol) 2′-hydroxy-4,3,4′-trimethoxychalcone in 30 mL of ethyl acetate to which was added 1.5 g of 10% Pd/C catalyst. The mixture was hydrogenated for 45 min at 14–21 psi of H_2. The catalyst was removed by filtration and the solution evaporated to dryness to give 2.5 g (89% from **4**) of 2′-hydroxy-4,3,4′-trimethoxydihydrochalcone (**5**): mp 77–79 °C (lit.[19] mp 78–79

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°C), IR (KBr) 3447 (OH), 1636 (ArC=O), 1571 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 3.05 (t, J = 8.3 Hz, 2 H, CH_2), 3.25 (t, J = 8.3 Hz, 2 H, CH_2), 3.87 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 6.40–7.70 (m, 6 H), 12.86 (s, 1 H, OH).

3-(3,4-Dimethoxybenzyl)-7-methoxy-4-chromanone (3b). (*Caution: hot sodium sand is dangerous.*) Sodium metal (2 g, 86 mmol) in 10 mL of toluene was refluxed until all of the sodium had melted at which time the condenser was replaced by a rubber septum. The hot flask was shaken (wear gloves!) until fine sodium sand was obtained. The solvent was carefully removed by syringe. The reaction flask was attached to a bubbler for venting of H_2 gas and cooled in an ice–water bath, and 2 g (6.3 mmol) of **5** in 40 mL of ethyl formate was slowly added via a syringe. The resultant mixture was stirred overnight at room temperature, cooled at 0 °C, and cautiously quenched by addition of 30 mL of water. The reaction mixture was acidified by addition of 10 mL of concd HCl and the solid product collected by filtration and air-dried to give 1.84 g (89%) of 3-(3,4-dimethoxybenzyl)-7-methoxy-4-chromone (**6**): mp 96–98 °C (lit.[20] mp 98 °C), IR (KBr) 1637 (C=O), 1609 cm^{-1}, ^1H-NMR ($CDCl_3$) δ 3.75 (s, 2 H, CH_2Ar), 3.83 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 6.82–8.20 (m, 7 H).

In a Parr hydrogen bottle was placed a solution of 1.0 g (3.1 mmol) of **6** in 50 mL of ethyl acetate followed by 1.0 g of 10% Pd/C catalyst. The mixture was hydrogenated for 4 h at 25 psi of H_2. After removing the catalyst the solution was evaporated to give 1.0 g (98%) of (±)-**3b**: mp 91–93 °C (lit.[21] mp 92–93 °C); IR (KBr) 1670 (C=O), 1622 cm^{-1}, ^1H-NMR ($CDCl_3$) δ 2.60–2.85 (m, 2 H), 3.20 (m, 1 H), 3.84 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.15–4.42 (m, 2 H), 6.82–8.20 (m, 6 H).

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(*R*)-(−)-O-Trimethylsappanone B (2b). (±)-**3b** (65.6 mg, 0.2 mmol) in 3 mL of dry THF was cooled to −78 °C. Added via syringe was 0.3 mL (0.3 mmol) of NaHMDS, and the solution was stirred for 30 min at which time 89 mg (0.3 mmol) of the (+)-8,8-dichlorocamphorylsulfonyl oxaziridine **7b** in 2 mL of THF was added dropwise and the mixture was stirred for 30 min. The reaction mixture was quenched at −78 °C by 1.0 mL of saturated $KHCO_3$, 10 mL of H_2O was added, and the mixture was extracted with ethyl acetate (3 × 10 mL). Drying and removal of the solvent followed by preparative TLC (5% ether in CH_2Cl_2) gave 34 mg (50%) of **2b** as an oil: $[\alpha]^{20}_D$, −30.2° (*c* 1.68, $CHCl_3$), 94% ee, ([lit.[16] $[\alpha]^{20}_D$ −32.1° (*c* 1.00, $CHCl_3$)]; IR (KBr) 3416 (OH), 1620 (C=O), 1588 cm^{-1}, ^1H-NMR ($CDCl_3$) δ 2.87 (s, 2 H), 3.80 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.06 (d, J = 11.2 Hz, 1 H), 4.24 (d, J = 11.2 Hz, 1 H), 6.45 (d, J = 2.2 Hz, 1 H), 6.63–6.85 (m, 4 H), 7.79 (d, J = 8.8 Hz, 1 H).

(+)-O-Trimethylbrazilin (1b). To 90 mg (0.26 mmol) of (*R*)-(−)-**2b** in 20 mL of ethanol was added 90 mg (24 mmol) of $NaBH_4$ at 0 °C. The solution was warmed to rt and stirred for 2 h at which time 0.5 mL of concd HCl was added. After refluxing the reaction solution for 2 h, the solvent was removed in vacuo and the crude product purified by preparative TLC (1:5 acetone/benzene) to give 60.5 mg (71%) of (+)-**1b**: mp 138–139 °C, $[\alpha]_D$ +117.2° (*c* 1.08, $CHCl_3$), 92% ee [lit.[2c] mp 136–137 °C, $[\alpha]_D$ +127.4° (*c* 0.51, $CHCl_3$)]; IR (KBr) 3430 (OH), 1595 cm^{-1}, ^1H-NMR ($CDCl_3$) δ 3.08 (AB q, J = 16.2 Hz, 2 H), 3.80 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.80–4.12 (m, 4 H), 6.48–7.38 (m, 5 H).

The intermediate diol **8** was isolated (82 mg, 91%) after neutralization of the reaction mixture with 18% HCl and extraction with ethyl acetate. It had spectral properties identical with reported values.[8]

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