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Stereoselective Synthesis of (*R*)- and (*S*)-4-Methoxydalbergione via Asymmetric Catalytic Hydrogenation

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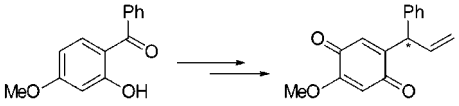
ABSTRACT



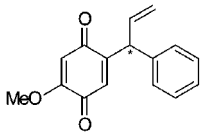
(R)-(+)- and (S)-(-)-4 methoxydalbergione

(*R*)-(+)- and (*S*)-(−)-4-methoxydalbergione were synthesized in seven steps with an enantiomeric excess of up to 95% using an asymmetric catalytic hydrogenation step with [Rh((*S*,*S*)-bdpp)(NBD)]ClO_4 or [Rh((*R*,*R*)-bdpp)(NBD)]ClO_4, respectively, at a hydrogen pressure of 80 bar. This method should give an easy access to the other members of the dalbergione family.

During the course of our studies on the stereospecificity of the reactions involved in allergic contact dermatitis (ACD),[1] we became interested in dalbergiones, as it seemed from the literature that patients sensitized to one enantiomer usually do not react to the other.[2] In the case of α-methylene-γ-butyrolactones, the stereospecificity of the allergic reaction has been explained by the stereoselective addition of nucleophilic protein residues on the lactone[3] and it has been shown that the stereoselectivity of addition parallels enantioselectivity in the allergic reaction.[4]

However, quinones are thought to react with proteins via a 1,4-Michael addition, without creating a new asymmetric center, and the above explanation cannot therefore be applied to these molecules.

Dalbergiones belong to a small family of quinones found in tropical woods[5a−b] mainly in *Dalbergia* and *Machaerium* species.[6] These optically active quinones have been shown to exist uniquely in either the *S* or *R* configuration, except for 4-methoxyalbergione, which can be found in either form, depending on its origin. The *R* product, **1a**, is found in *Dalbergia latifolia* Roxb.,[7] *Dalbergia nigra* Allem.,[8] and *Dalbergia retusa* Hemsl.,[8] while the *S* isomer, **1b**, is present in *Dalbergia melanoxylon* Guill & Perr.[9] and *Dalbergia boroni* Baker (Figure 1).[10]



(R)-(+)- **1a**
(S)-(-)- **1b**

Figure 1. Structures of 4-methoxydalbergiones.

Several racemic syntheses of 4-methoxyalbergione, based on Claisen transposition,[11] Pechmann condensation,[12] reduc-

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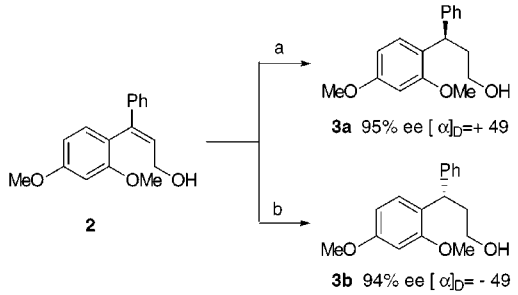
tion of 7-methoxycoumarin,[13] or regioselective allylation,[14] have been reported in the literature. However, these methods cannot be used to produce optically active molecules and we have not found any reports of attempts to prepare these quinones in an enantiomeric form, probably because of the difficult access to such an asymmetric center. We therefore turned our attention to a new synthetic access to these molecules permitting the introduction of an induction step.

In the past few years, methods for the asymmetric hydrogenation of double bonds, using optically active complexes of transition metals, have been extensively developed.[15] This approach has been successfully applied to the preparation of optically active amino acids, via the reduction of acrylic acid derivatives,[15] and to the asymmetric reduction of allylic alcohols,[16] catalyzed by chiral rhodium or ruthenium complexes.

We have previously investigated whether such an approach could give access to optically active quinones of the dalbergione type and found that intermediates **3a** and **3b** could be prepared from the allylic alcohol **2** with an enantiomeric excess of up to 95%, via an asymmetric hydrogenation step (Scheme 1).[17] The enantiomeric excess

Scheme 1[a]

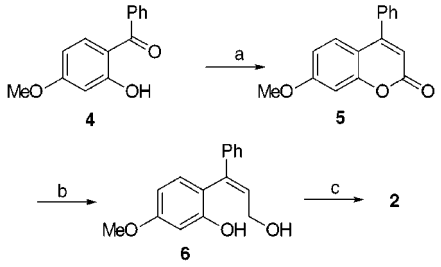


[a] Reagents: (a) H_2, MeOH, [Rh((*S*,*S*)-bdpp)(NBD)]ClO_4; (b) H_2, MeOH, [Rh((*R*,*R*)-bdpp)(NBD)]ClO_4.

was determined by ^{1}H NMR using tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]europium(III), but at that time the absolute configuration could not be determined.

Despite the presence of two rather similar aromatic functions on the allylic alcohol **2**, the large enantiomeric excess obtained opens the way to the synthesis of dalbergione-type molecules. We now report the stereoselective synthesis of (*R*)- and (*S*)-4-methoxyalbergione, thus providing a new access to this family of optically active quinones. 7-Methoxy-4-phenylcoumarin (**5**)[18] was prepared from 2-hydroxy-4-methoxybenzophenone (**4**) and ((ethoxycarbonyl)-methylene)triphenylphosphorane by a Wittig-type reaction in refluxing toluene with a 78% yield (Scheme 2). The

Scheme 2[a]



[a] Reagents, conditions, and yields: (a) $Ph_3P{=}CHCO_2Et$, toluene, reflux, 10 days, 78%; (b) $LiAlH_4$, THF/Et_2O, 0 °C, 97%; (c) MeI, K_2CO_3, acetone, 100%.

coumarin **5** was then reduced at 0 °C using $LiAlH_4$ in a 1/1 mixture of ether and THF to give, in 97% yield, the allylic alcohol **6**.[19] Note that the same reaction carried out in THF alone gave an unseparable mixture of allylic and saturated alcohols. Subsequent treatment of **6** with MeI and K_2CO_3 in refluxing acetone gave the key intermediate **2**.

The induction step was carried out on a 2 mmol scale, using either [Rh((*R*,*R*)-bdpp)(NBD)]ClO_4 or [Rh((*S*,*S*)-bdpp)-(NBD)]ClO_4 as catalyst (substrate/catalyst 10/1) at an hydrogen pressure of 80 bar with a reaction time of 7 days. Thus, hydrogenation of **2** provided selective access to both enantiomers **3a** and **3b** with enantiomeric excess up to 95%.[20]

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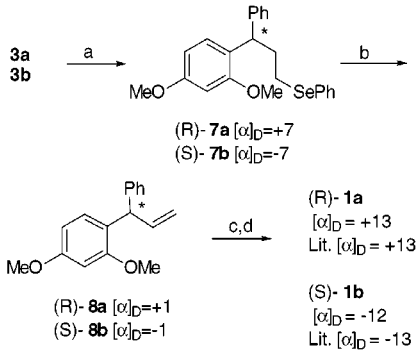
(18) 7-Methoxy-4-phenylcoumarin (**5**): white crystals, mp 105−106 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.86 (s, 3H), 6.15 (s, 1H), 6.40 (dd, 1H, J = 9.0 Hz, J = 2.4 Hz), 6.50 (d, 1H, J = 2.4 Hz), 7.45−7.86 (m, 6H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 55.7, 101.1, 111.7, 112.2, 112.4, 128.3, 128.7, 129.5, 135.5, 155.7, 155.9, 161.0, 161.1, 182.7. Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80. Found: C, 75.94; H, 4.71.

(19) 3-(2′-Hydroxy-4′-methoxyphenyl)-3-phenyl-2-propenol (**6**): white crystals, mp 136−137 °C; ^{1}H NMR ($(CD_3)_2CO$, 200 MHz) δ 2.85 (bt, 1H, J = 6.5 Hz), 3.78 (s, 3H), 4.07 (dd, tlike, J = 6.6 Hz), 6.33 (t, J = 6.6 Hz), 6.46−6.53 (m, 2H), 6.88 (d, 1H, J = 8.2 Hz), 7.20−7.29 (m, 5H), 7.92 (s, 1H); ^{13}C NMR ($(CD_3)_2CO$, 50 MHz) δ 55.5, 61.0, 102.5, 106.2, 119.4, 127.5, 127.8, 128.9, 130.9, 132.6, 139.0, 142.8, 156.5, 161.4. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.98; H, 6.29. Found: C, 74.59; H, 6.39.

(20) The enantiomeric excess was determined using ^{1}H NMR by adding 0.4 equiv of tris[3-(trifluoromethylhydroxymethylene)-(+)-camphorato]-europium(III) to 5 mg of **3a** or **3b** in $CDCl_3$ (0.5 mL). **3a**: ee = 95%, $[\alpha]_D$ = +49° (c = 0.82, $CHCl_3$). **3b**: ee = 94%, $[\alpha]_D$ = −49° (c = 0.82, $CHCl_3$).

Alcohols **3a** and **3b** were then transformed into selenoethers[21] **7a** and **7b**, respectively, by reaction with PhSeCN and *n*-Bu_3P in THF[22] with 81% yields (Scheme 3); subsequent treatment of these selenoethers with $NaIO_4$ in a mixture of water and MeOH in the presence of $NaHCO_3$[23] gave a quantitative yield of compounds **8a** and **8b**.[24]

Scheme 3[a]



[a] Reagents, conditions, and yields: (a) PhSeCN, *n*-Bu_3P, THF, 81%; (b) $NaIO_4$, $NaHCO_3$, H_2O/MeOH, 100%; (c) BBr_3, CH_2Cl_2, 0 °C; (d) salcomine, O_2, DMF.

4-Methoxyalbergiones **1a** and **1b** were obtained by selective deprotection of a methoxy group with 1 equiv of BBr_3 in CH_2Cl_2 at 0 °C and oxidation of the crude phenols with salcomine[25] in DMF under oxygen. The sign and absolute value of the optical rotation of the products[26] showed them to be the (+)-(*R*)-4-methoxyalbergione **1a** and the (−)-(*S*)-4-methoxyalbergione **1b** (synthesized in seven steps) and confirmed the enantiomeric excess of about 95%.

Thus, hydrogenation of the intermediate **2** using either [Rh((*S*,*S*)-bdpp)(NBD)]ClO_4 or [Rh((*R*,*R*)-bdpp)(NBD)]ClO_4 gives access, respectively, to the *R* or *S* chiral center, yielding products of similar optical purity, and this method should give an easy access to the other members of the dalbergione family.

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(21) **1-Phenylseleno-3-(2′,4′-dimethoxyphenyl)-3-phenylpropane (7)**: To a solution of alcohol **3a** or **3b** (500 mg, 1.8 mmol) in THF (20 mL) was added PhSeCN (669 mg, 2 equiv, 3.7 mmol) and *n*-Bu_3P (0.92 mL, 2 equiv, 3.7 mmol). The reaction mixture was stirred for 2 h, the solvent removed under reduced pressure, and the crude product purified by column chromatography over silica (hexane 90%, AcOEt 10%) to give 600 mg (1.5 mmol, 81% yield) of the seleno derivative **7a** or **7b**, respectively, as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.34−2.43 (m, 2H), 2.80−2.88 (m, 2H), 3.74 (s, 3H), 3.77 (s, 3H), 4.28 (t, 1H, J = 7.6 Hz), 6.39−6.45 (m, 2H), 7.02 (d, 1H, $J_{5',6'}$ = 9.0 Hz), 7.14−7.25 (m, 8H), 7.40−7.45 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 26.1, 35.6, 43.3, 55.4, 55.5, 98.8, 104.2, 125.2, 126.0, 126.6, 128.2, 128.3, 129.0, 130.6, 132.4, 144.4, 158.1, 159.3. ^{77}Se NMR ($CDCl_3$, 76 MHz): δ 24.0. Anal. Calcd for $C_{23}H_{24}O_2Se$: C, 67.15; H, 5.88. Found: C, 67.21; H, 5.85. **7a**: $[\alpha]_D$ = +7° (c = 0.94, $CHCl_3$). **7b**: $[\alpha]_D$ = −7° (c = 0.94, $CHCl_3$).

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(24) **3-(2′,4′-Dimethoxyphenyl)-3-phenyl-1-propene (8)**: colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.74 (s, 3H), 3.80 (s, 3H), 4.89 (ddd, dt like, 1H, J = 1.6 Hz, J = 1.6 Hz, J = 17.0 Hz), 5.07 (ddd, dt like, 1H, J = 6.6 Hz, J = 1.6 Hz, J = 1.6 Hz), 5.17 (ddd, dt like, 1H, J = 1.6 Hz, J = 1.6 Hz, J = 10 Hz), 6.37 (ddd, 1H, J = 6.6 Hz, J = 10.0 Hz, J = 17 Hz), 6.43−6.48 (m, 2H), 7.01 (d, 1H, J = 9.0 Hz), 7.16−7.25 (m, 5H).^{13}C NMR ($CDCl_3$, 50 MHz): δ 47.3, 55.4, 55.6, 99.0, 104.2, 115.8, 124.4, 126.0, 128.2, 128.7, 129.8, 140.8, 143.6, 158.0, 159.6. Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.20; H, 7.26. **8a**: $[\alpha]_D$ = +1° (c = 1.0, $CHCl_3$). **8b**: $[\alpha]_D$ = −1° (c = 1.0, $CHCl_3$).

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(26) **4-Methoxydalbergione 1**: To a solution of **8a** or **8b** (100 mg, 0.39 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added a solution of BBr_3 in CH_2Cl_2 (0.4 mL, 1 equiv, 0.40 mmol). The reaction mixture was stirred for 1 h, hydrolyzed using a saturated solution of $NaHCO_3$ (1 mL), and filtered on Celite; then CH_2Cl_2 (10 mL) was added. The organic layer was washed with water (2 × 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. To the crude quinol in distilled DMF (3 mL) under an atmosphere of O_2 was added a suspension of salcomine (13 mg, 0.039 mmol) in DMF (2 mL). The reaction mixture was stirred for 4 h and concentrated under reduced pressure. The crude quinone was purified by chromatography over silica using degassed solvents (hexane 80%, AcOEt 20%), then crystallized in cyclohexane to give 62 mg (0.24 mmol, 61% yield) of dalbergione **1a** or **1b** as yellow crystals. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.81 (s, 3H), 4.93 (ddd, dt like, 1H, J = 1.7 Hz, J = 1.7 Hz, H = 6.8 Hz), 5.00 (ddd, dt like, J = 1.7 Hz, J = 1.7 Hz, J = 17.0 Hz), 5.27 (ddd, dt like, 1H, J = 1.7 Hz, J = 1.7 Hz, J = 10.0 Hz), 5.91 (s, 1H), 6.10 (ddd, 1H, J = 6.8 Hz, J = 10.0 Hz, J = 17.0 Hz), 6.48 (s, 1H), 7.18−7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 47.1, 55.3, 107.0, 118.2, 127.2, 128.6, 128.8, 131.6, 137.3, 139.4, 151.1, 158.6, 182.4, 186.3. (*R*)-4-Methoxydalbergione **1a**: mp 115−116 °C (lit.[8] mp 114−116 °C), $[\alpha]_D$ = +13° (c = 1.3, $CHCl_3$, lit.[8] $[\alpha]_D$ = +13°). (*S*)-4-methoxydalbergione **1b**: mp 116−117 °C (lit.[10] mp 118−119 °C), $[\alpha]_D$ = −12° (c = 1.3, $CHCl_3$, lit.[10] $[\alpha]_D$ = −13°).