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Approach to the Stereoselective Synthesis of (R)- and (S)-4-Methoxydalbergione via Asymmetric Catalytic Hydrogenation

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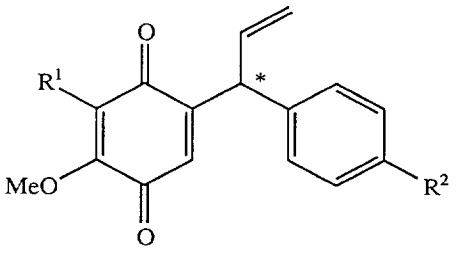
Abstract: Compound 7, a precursor in the synthesis of 4-methoxybalbergione, was prepared from compound 6 with an enantiomeric excess of 17 to 94% by asymmetric catalytic hydrogenation using rhodium or ruthenium chiral complexes. The best hydrogenation results were obtained using [Rh((S,S)-bdpp)(NBD)] ClO_4, and [Rh((R,R)-bdpp)(NBD)] ClO_4, at a hydrogen pressure of 80 bar.

Dalbergiones belong to a small family of quinones found in tropical woods,[1,2] mainly in *Dalbergia* and *Machaerium* species, and are responsible for allergic contact dermatitis (ACD) reactions in patients coming into contact with these plants.[3,4] These optically active quinones have been determined to have an *S* or an *R* absolute configuration, except for 4-methoxydalbergione, which can be found in either form depending on its origin. The *R* product, **1a**, is found in *Dalbergia latifolia* Roxb.,[5] *Dalbergia nigra* Allem.[6] and *Dalbergia retusa* Hemsl.[6] while the *S* isomer, **1b**, is present in *Dalbergia melanoxylon* Guill & Perr.[7] During the course of our studies on the stereoselectivity of ACD reactions,[8,9] we became interested in these molecules as it appeared from the literature that patients sensitized to one enantiomer usually do not react to the other.[10]

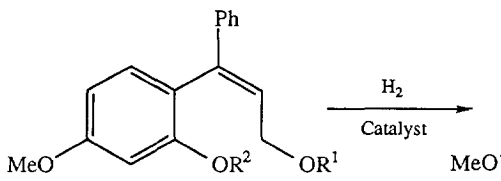


	R^1	R^2	Conf[a]
1a	H	H	*R*
1b	H	H	*S*
2	OMe	H	*R*
3	H	OMe	*S*
4	OMe	OH	*R*
5	H	OH	*S*

[a] Absolute configuration of the natural isomer

In order to obtain enough material, we have been interested in a synthetic access to these molecules. Several racemic syntheses of 4-methoxydalbergione based on Claisen transposition,[11] Pechmann condensation,[12] reduction of 7-methoxycoumarine[13] or regioselective allylation[14] have been reported in the literature. These methods cannot be used to obtain optically active molecules and we have not found any report of attempts to prepare these quinones in an enantiomeric form, probably as a result of the difficult access to such an asymmetric centre.

In the last few years, 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] catalysed by chiral rhodium or ruthenium complexes. We have investigated whether such an approach could give access to optically active quinones of the dalbergione type. A retrosynthetic analysis indicated that these molecules could be prepared from allylic alcohols of type **6** via an asymmetric hydrogenation step.



6a-e 7a-e

	R^1	R^2
a	H	H
b	H	Ac
c	H	Me
d	Ac	Ac
e	Ac	Me

Compounds **6a-e**, whose phenol and alcohol groups were blocked by different protective groups, were prepared and tested for their susceptibility to hydrogenation using several rhodium and ruthenium asymmetric catalysts.[17] Hydrogenations were carried out at 30°C at a hydrogen pressure of 75-80 bars.[18] Reaction times and percentage convertions are listed in table 1.

Table 1: Asymmetric catalytic hydrogenation of compounds **6a-e**.

Entry[a]	Substrate	Catalyst	Reaction time (days)	Conversion	% ee[b]
1	a	[Ru((S)-binap)(OAc)$_2$]	1-3	100	0
2	a	[Rh((S)-binap)(COD)] BF_4	7-10	100	0
3	a	[Rh((R)-binap)(NBD)] BF_4	7-10	100	8
4[c]	a	[Rh(COD)Cl]$_2$+(S)-binap	7-10	100	0
5	a	[Rh(COE)$_2$Cl]$_2$+(S)-binap	7-10	100	0
6[d]	b	[Rh((S,S)-bdpp)(NBD)] ClO_4	8	100	40
7	b	[Rh((S,S)-chiraphos)(NDB)] ClO_4	7	0	-
8	c	[Rh((S,S)-bdpp)(NBD)] ClO_4	7	100	80
9[e]	c	[Rh((S,S)-bdpp)(NBD)] ClO_4	7	100	92
10[e]	c	[Rh((R,R)-bdpp)(NBD)] ClO_4	7	100	94
11	c	[Rh((S,S)-chiraphos)(NDB)] ClO_4	7	100	17
12	d	[Rh((S,S)-bdpp)(NBD)] ClO_4	4	0	-
13	d	[Ru((S)-binap)(OAc)$_2$]	4	0	-
14	e	[Rh((S,S)-bdpp)(NBD)] ClO_4	4	0	-
15	e	[Ru((S)-binap)(OAc)$_2$]	4	0	-

a) Standard conditions: 0.37 mmol of substrate; substrate/ catalyst 100/5; solvant MeOH; P(H_2) = 75-80 bar. b) Determined by ^1H NMR in $CDCl_3$ by adding 0.4 equiv. of tris[3-(trifluoromethyl-hydroxymethylene)-(+)-camphorato], europium (III). c) The catalyst was prepared in situ by mixing [Rh(COD)Cl]$_2$ (0.01 mmol) and (S)-binap (0.02 mmol). d) Solvent: MeOH/CH_2Cl_2 10/2. e) Substrate/ catalyst 100/10.

The first point to emerge is the low susceptibility of these substrates to hydrogenation. Despite a pressure of 75-80 bars and 5 mol% of catalyst, a high rate of conversion was only obtained using reaction times of 3 days for binap-Ru(II) complexes and 7-10 days for rhodium catalysts. When these reaction times are compared with that of 12 h at 30 bar pressure for the reduction of geraniol using binap-Ru(II),[16] it is clear that the high hindrance of the double bound is a disfavorable factor. The second point to emerge is the requirement for a free allylic alcohol function. Thus compounds **6d** and **6e**, in which the hydroxyl function is protected by an acetyl group, were not hydrogenated.

Enantiomeric excess was determined by ^1H NMR on the methoxy (compound **7c**) or acetyl (compound **7b**) signal using tris[3-(trifluoromethyl-hydroxymethylene)-(+)-camphorato], europium (III) as a chiral chemical shift reagent. Prior to the determination, compound **7a** was quantitatively converted into compound **7c** by reaction with MeI, K_2CO_3 in acetone.

Reactions using compound **6a** (entry 1-5), in which both the phenol and alcohol functions are free, yielded reduced compounds with a high conversion level but with no significant enantiomeric excess. Only a slight enantiomeric excess (8% ee) was seen using [Rh((R)-binap)(NBD)] BF_4 (entry 3). To see if the free phenol group was a limiting factor, e.g. competing with the allylic hydroxyl group as a chelating function for the catalyst, we protected the phenol group with an acetyl (compound **6b**) or methyl (compound **6c**) group. When hydrogenated in the presence of 5 mol% of [Rh((S,S)-bdpp)(NBD)] ClO_4, enantiomeric excesses of 40% and 80%, respectively, were seen with **6b** and **6c** (entry 6 and 8). With the same substrates, [Rh((S,S)-chiraphos)(NBD)] ClO_4 gave 0% conversion with compound **6b** and complete conversion with compound **6c,** but with only an enantiomeric excess of 17 %. This confirmed the importance of phenol group protection and the greater efficiency of the methyl group relative to the acetyl group in terms of conversion and asymmetric induction. For compound **6c**, the significant difference in asymmetric induction seen using [Rh((S,S)-bdpp)(NBD)] ClO_4 (entry 8) and [Rh((S,S)-chiraphos)(NBD)] ClO_4 (entry 11), which differ only by one carbone on the diphosphine,[18] is certainly due to differences in the complex geometry.

The use of [Rh((S,S)-bdpp)(NBD)] ClO_4 and [Rh((R,R)-bdpp)(NBD)] ClO_4 (entry 9 and 10) gave access to both enantiomers with enantiomeric excess of 92 and 94% respectively. The absolute configuration has not yet been determined but both compounds are of opposite optical rotation (+ 49 and - 49 respectively) and the major diastereoisomers formed with tris[3-(trifluoromethyl-hydroxymethylene)-(+)-camphorato], europium (III) are of opposite chemical shift. The total synthesis of the 4-methoxydalbergione from **7b** is in progress and will allow to identify the absolute configuration by comparison with the natural quinone.

In conclusion, despite the presence of two rather similar aromatic functions on the allylic alcohol **6**, it is possible to produce compound **7**, a precursor for the synthesis of 4-methoxydalbergione, with an 94% enantiomeric excess. This therefore opens the way to the synthesis of other molecules of this familly.

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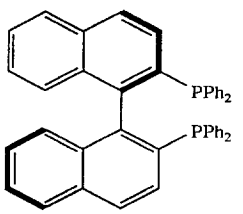
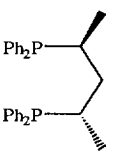
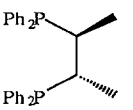
17. Catalyst precursors and catalysts were prepared according to the literature.
18. In a typical experiment, catalytic hydrogenations were carried out as follow: [Rh((P*P)(nbd)] ClO_4 (0.02 mmol) and the substrate (0.4 mmol) were dissolved under argon in methanol (12 mL). The mixture was transferred via a steel capillary into a 50 mL stainless steel autoclave, degassed three times with H_2 (20 bar) and pressurized to 75-80 bar. The reaction was followed by ^1H NMR. After completion of the reaction, the product was recovered by evaporating the solvent under reduced pressure and purified by chromatography.
19. Structures of diphosphines and abbreviations used:



(R)-binap



(S,S)-bdpp



(S,S)-chiraphos

COD: 1,6-cyclooctadiene; NBD: norbornadiene; COE: cyclooctene.

20. All compounds were fully characterized and gave satifactory microanalysis. Compound **6c**: White solid, mp 65°C. ^1H NMR ($CDCl_3$) δ 1.67 (t, J=6.2 Hz, 1H, OH), 3.72 (s, 3H, CH_3O), 3.85 (s, 3H, CH_3O), 4.06 (dd, tlike, J=6.0, J=6.2 Hz, 2H, $C\underline{H}_2OH$), 6.39 (t, J=7.0 Hz, 1H, H_2), 6.53 (m, 2H, $H_{3'}$, $H_{5'}$), 6.95 (d, J=7.2 Hz, 1H, $H_{6'}$), 7.25 (m, 5H, C_6H_5).
^{13}C NMR ($CDCl_3$) δ 55.5, 55.8, 61.2, 99.1, 104.9, 120.4, 126.8, 131.9, 140.0, 141.6, 158.0, 160.6. Anal. calcd for $C_{17}H_{20}O_3$: C, 75.53; H, 6.71. Found: C, 75.70; H, 6.80.
Compound **7c** prepared using [Rh((S,S)-bdpp)(NBD)] ClO_4: ^1H ($CDCl_3$) δ 1.67 (bs, 1H, OH), 2.14 (dddd, J=4.6, J= 5.5, J=10.0, J=13.7 Hz, 1H), 2.37 (dddd, J=5.4, J=5.7, J=9.1, J=13.7 Hz, 1H), 3.56 (ddd, J=4.6, J=5.4, J=10.6 Hz, 1H, C$\underline{H}$OH), 3.79 (ddd, J=5.5, J=9.1, J=10.6Hz, 1H, C$\underline{H}$OH), 3.78 (s, 3H, CH_3O), 3.80 (s, 3H, CH_3O), 4.50 (dd, J=5.7, J=10.0 Hz, 1H), 6.41-6.47 (m, 2H, H_2,H_3), 7.02-7.28 (m, 6H, H_1, C_6H_5). ^{13}C NMR ($CDCl_3$) δ 37.9, 38.9, 55.3, 55.6, 61.2, 98.0, 104.7, 125.5, 125.9, 128.1, 128.3, 128.5, 145.0, 158.0, 169.3.Anal. calcd for: $C_{17}H_{18}O_3$: C, 74.97; H, 7.40. Found: C, 74.83; H, 7.47. $[\alpha]_D$ = +49 (c = 0.82, $CHCl_3$). Compound **7c** prepared using [Rh((R,R)-bdpp)(NBD)] ClO_4: $[\alpha]_D$ = - 49 (c = 0.68, $CHCl_3$)
21. To 5 mg of compound **7c** in $CDCl_3$ (0.5 mL) was added an increasing amount of tris[3-(trifluoromethyl-hydroxymethylene)-(+)-camphorato], europium (III). The optimal separation was obtained using 0.4 equiv. of the chiral chemical shift reagent.

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