

A FACILE APPROACH TOWARD 8-O-4'-NEOLIGNANS: SYNTHESIS OF *THREO*-7',8'-DIHYDROMACHILIN D THROUGH JACOBSEN EPOXIDATION

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UNA FÁCIL APROXIMACIÓN A LOS NEOLIGNANOS 8-O-4': SÍNTESIS DE *THREO*-7',8'-DIHIDROMACHILIN D A TRAVÉS DE EPOXIDACIÓN DE JACOBSEN

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ABSTRACT

Neolignans are natural phenylpropanoid dimers with C-O-C linkages. Currently, neolignans remain as important synthetic targets due to their reported biological potential against parasites and fungal infections. Thereof, a new approach for the synthesis of the 8-O-4'-neolignan 7',8'-dihydromachilin D based on Jacobsen epoxidation as key step is described here. This stereoselective synthesis proceeded in only 4 steps in 3.9% overall yield. Jacobsen epoxidation was firstly optimized regarding to yield and enantioselectivity employing *trans*-stilbene as model substrate.

Keywords: machilin D, neolignans, Jacobsen epoxidation, synthesis.

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RESUMEN

Los neolignanos son dímeros naturales de los fenilpropanoides con uniones C-O-C. Actualmente, los neolignanos continúan siendo blancos sintéticos importantes debido a su potencial biológico contra parásitos e infecciones fúngicas. Así, se presenta una nueva aproximación a la síntesis de un neolignano 8-O-4' denominado 7',8'-dihydromachilin D, basándose en epoxidación de Jacobsen como paso clave. Esta síntesis estereoselectiva procede en tan solo 4 pasos con un 3,9% de rendimiento global. La epoxidación de Jacobsen fue optimizada previamente respecto a rendimiento y enantioselectividad empleando *trans*-estilbeno como sustrato modelo.

Palabras clave: machilin D, neolignanos, epoxidación de Jacobsen, síntesis.

INTRODUCTION

8-O-4'-type neolignans have been described as secondary metabolites almost exclusive of the Myristicaceae family, and exhibited a plethora of biological properties, including mainly anti-leishmanial (Aveniente *et al.*, 2007), anti-trypanosomal (Nocito *et al.*, 2007), and antifungal (Pinheiro *et al.*, 2004) activities. Virolin (1), surinamensin (2) (Barata *et al.*, 1978), and iryantheral (3) (Bernal and Cuca, 2009) are representative 8-O-4'-neolignan

compounds that have been found in Colombian Myristicaceae plants (Fig. 1). In depth, according to the typical structural features of these compounds, determined enantiomers and/or diastereomers have also been isolated from individual species as specific chemomarkers. At this regard, machilin C (4) and D (5) are diastereomers simultaneously isolated from *Machilus thunbergii* (Shimomura *et al.*, 1987). Machilin C and odoratisol B are enantiomers

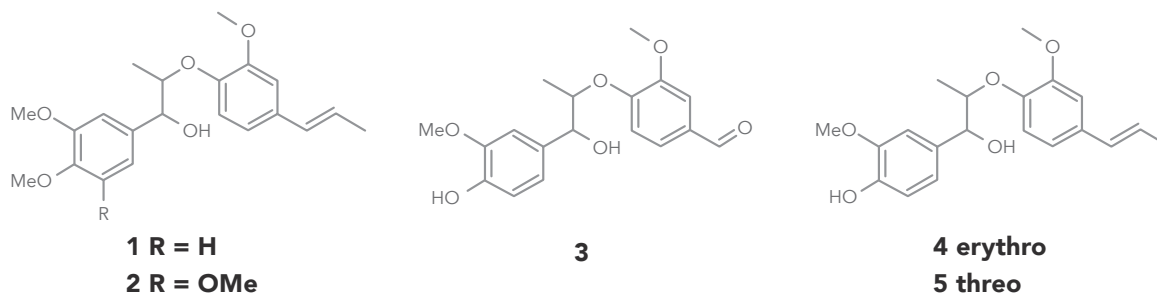


Figure 1. Representative 8-O-4' neolignans.

found in different plant species belonging to the same family (Phan *et al.*, 2006). Similar behavior has been reported to perseal A and B from *Persea obovatifolia* (Tsai *et al.*, 1996) and to perseal A and iryantheral (Bernal and Cuca, 2009).

Structural simplicity of these neolignans convert them in a convenient model study. Compounds 4 and 5 have been found in different plant species belonging to three different plant families as follows: *Machilus odoratissima* (Lauraceae) (Phan *et al.*, 2006), *Machilus thunbergii* (Lauraceae) (Shimomura *et al.*, 1987), *Leucas aspera* (Labiatae) (Sadhu *et al.*, 2003), *Myristica fragrans* (Myristicaceae) (Hada *et al.*, 1988), and *Iryanthera ulei* (Myristicaceae) (Bernal and Cuca, 2009).

The above mentioned properties of the 8-O-4' neolignans have originated great synthetic and biological interests on researchers around the world. Therefore, several methodologies to obtain these neolignans have been reported across different approaches that include propiophenone reduction, aldolic condensation, enantiomeric enrichment of intermediates employing microorganisms, Mitsunobu reaction, or using esters from (S)-lactic acid as starting material by substitution and nucleophilic addition reactions (Sefkow, 2003; Xia *et al.*, 2010a, 2010b; Xia and Wang, 2011; Reddy and Das, 2014). Nevertheless, these methods cannot be extensively scaled due to provide low selectivity (enantioselectivity or diastereoselectivity) and/or involve large number of steps.

Considering the above mentioned limitations to the common synthetic methods of 8-O-4' neolignans, the use of a chiral epoxide as key structural intermediate is proposed here. The new strategy is based on the ring opening of the epoxide previously obtained by Jacobsen epoxidation from a simple and cheap phenylpropene compound-type as starting material. Herein, we report a new approach to the enantioselective synthesis of an 8-O-4' neolignan derivative.

MATERIALS AND METHODS

General

¹H-NMR and ¹³C-NMR spectra were recorded on a Bruker Avance 400 spectrometer. IR spectra were recorded on a Prestige-21 Shimadzu spectrometer in film on NaCl window. UV spectra were obtained in a Thermoscientific Evolution 300. HRMS were obtained on a LC-MS-IT-TOF Shimadzu system under direct injection. HPLC separations and quantification were accomplished on a HPLC-UV-DAD Merck-Hitachi system. Yields to epoxidation of *trans*-stilbene were determined by RP-HPLC using a Phenomenex Ultracarb C30 column (150 x 4.6 mm i.d., 5 µm). Enantiomeric excesses were determined by NP-HPLC using a Chiralcel OD-H column (250 x 4.6 mm i.d.). Optical rotation was measured on a Polartronic E Schmidt + Haensch polarimeter equipped with a sodium lamp (589 nm) and 1.00 mL cuvette. HPLC grade solvents were employed to HPLC separations. Flash column chromatography was performed on silica gel (230-400 mesh) and TLC on silica gel HF₂₅₄ plates. Organic solvents were distilled and dried according standard procedures before use. All reagents were acquired from Hopkin & Williams Ltd., Acros Organics and Sigma-Aldrich.

Synthesis of (E)-1-(benzyloxy)-2-methoxy-4-(prop-1-en-1-yl)benzene (7)

To well stirred solution of KOH (21.6 mmol) in ethanol (60 mL) was added dropwise isoeugenol (14.7 mmol). Benzyl bromide (20.2 mmol) was then slowly added with vigorous stirring and heated to reflux for 4 h under nitrogen atmosphere. The reaction mixture was filtered, concentrated in vacuo, and extracted with isopropyl acetate (AcO*i*Pr; 3x15 mL). The combined organic layers were washed with water (4x20 mL). The extract was dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. Flash column chromatography of the residue

gave the compound **7**. White amorphous solid. IR (film/cm⁻¹): 3024, 2932, 2855, 1601, 1582, 1510, 1458, 1414, 1379, 1260, 1225, 1136, 1028, 962, 854, 783, 737, 696. ¹H-NMR (400 MHz, CDCl₃): 1.89 (1H, *dd*, 1.4/6.6 Hz, H-3'), 3.93 (3H, *s*, OCH₃), 5.17 (2H, *s*, OCH₂Ph), 6.13 (1H, *qd*, 6.6/15.6 Hz, H-2'), 6.36 (1H, *dd*, 1.4/15.6 Hz, H-1'), 7.55-6.75 (*m*, Ar-H). ¹³C-NMR (100 MHz, CDCl₃): 18.3 (C-3'), 55.9 (OCH₃), 71.1 (OCH₂Ph), 109.2 (C-3), 114.2 (C-6), 118.5 (C-5), 124.0 (C-2'), 127.2, 127.7, 128.5, 130.6 (C-1'), 131.7 (C-4), 137.2, 147.3 (C-1), 149.7 (C-2).

Epoxidation of *trans*-stilbene (**11**)

Epoxidation reaction was performed according to literature (Jacobsen *et al.*, 1991; Zhang and Jacobson, 1991). In brief, a solution of commercial household bleach (Clorox®, 20 mL) was diluted with 0.05 M Na₂HPO₄ (30 mL aprox.) up to pH of 11.3. This solution (3 mL) was cooled at 4°C (ice-water mixture) and then added to a stirred solution of *trans*-stilbene (**11**, 0.55 mmol) in dichloromethane (1 mL) with (*R,R*)-Jacobsen catalyst (0.022 mmol). Additive or oxidant (0.044 mmol) was then added. The mixture was vigorously stirred and its progress was monitored by TLC during 6-24 h depends on the additive and oxidant employed. After completion, dichloromethane (15 mL) was added and organic layer separated and washed with water (4×10 mL). Solvent was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was submitted to flash column chromatography on silica gel to afford **12** (*trans*-2,3-diphenyloxirane) (Imuta and Ziffer, 1979). IR (film/cm⁻¹): 3088, 3061, 3032, 2984, 1602, 1495, 1452, 1102, 1071, 1026, 860, 744, 696, 613, 509. NMR signals are presented in Table 2.

Determination of the yield to the epoxidation of *trans*-stilbene by RP-HPLC

A stock solution of the *trans*-stilbene epoxide previously isolated and characterized was prepared in methanol. Adequate dilutions of the stock were

prepared to give a series of standard solutions in the range of 0.03 to 0.45 mM. Each standard solution was independently injected on the RP-HPLC system under optimized chromatographic conditions and peak area was then measured at 228 nm (maximum absorption wavelength). Calibration curve was built as peak area versus *trans*-stilbene epoxide concentration (*r*² = 0.9988).

Each dried and crude reaction product was dissolved in dichloromethane and appropriately diluted. Then those were injected on RP-HPLC system and peak area measured. In order to determine the mass of pure product **12**, peak area was interpolated into the calibration curve. Based on the obtained mass, reaction yield was calculated.

Determination of the enantiomeric excess for *trans*-stilbene epoxide (**12**) by HPLC

Purified products from epoxidation reaction were dissolved in hexane and submitted to chiral separation on HPLC under previously optimized conditions. Peak areas were measured and employed to calculate the enantiomeric excess.

Synthesis of 2-(4-(benzyloxy)-3-methoxyphenyl)-3-methyloxirane (**8**)

Epoxidation of **7** was accomplished using the same methodology that the above described to **11** although purification was efficiently completed on neutral alumina. Compound **8** was obtained as amorphous yellowish solid. [α]_D²⁰ = -11.3° (c. 0.004; CH₂Cl₂). IR (film/cm⁻¹): 2963, 2928, 1591, 1514, 1458, 1414, 1379, 1314, 1265, 1227, 1159, 1136, 1024, 843, 808, 741, 689. ¹H-NMR (400 MHz, CDCl₃): 1.46 (3H, *d*, 5.2 Hz, H-3'), 3.05 (1H, *dq*, 2.0/5.2 Hz, H-2'), 3.55 (1H, *d*, 2.0 Hz, H-1'), 3.91 (3H, *s*, OCH₃), 5.17 (2H, *s*, OCH₂Ph), 6.77-6.90 (*m*, Ar-H), 7.27-7.50 (*m*). ¹³C-NMR (100 MHz, CDCl₃): 17.7 (C-3'), 55.8 (OCH₃), 58.7 (C-2'), 59.4 (C-1'), 71.0 (OCH₂Ph), 108.5 (C-3), 113.9 (C-6), 118.2 (C-5), 127.1, 127.7, 128.4, 130.8 (C-4), 137.0,

147.9 (C-1), 149.8 (C-2). HRESIMS: 293.0705 [M+Na]⁺ and 271.0848 [M+H]⁺. Calculated for C₁₇H₁₈NaO₃: 293.0732 and for C₁₇H₁₉O₃: 271.0872.

Synthesis of (E)-1-(4-(benzyloxy)-3-methoxyphenyl)-2-(2-methoxy-4-(prop-1-en-1-yl)phenoxy)propan-1-ol (9)

Isoeugenol (**6**, 0.74 mmol) and KOH (1.3 mmol) were mixed in ethanol (3 mL) during 30 min. Subsequently, epoxide **8** (0.20 mmol) dissolved in ethanol (1 mL) was dropwise added and the mixture was then heated to reflux for 3 h. Progress of the reaction was monitored by TLC. Reaction was quenched with cold water (10 mL) and followed by extraction with ethyl ether (3×15 mL). Organic layer was washed with 0.2 N NaOH (3×10 mL) and water (3×10 mL). Finally, it was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was submitted to flash column chromatography to afford **9**. Yellowish oil. [α]_D²⁰ = -10.0° (c. 0.002; MeOH). IR (film/cm⁻¹): 3450, 2932, 1599, 1510, 1458, 1416, 1379, 1261, 1225, 1134, 1028, 856, 812, 741. ¹H-NMR (400 MHz, CDCl₃): 1.24 (3H, *d*, 6.4 Hz, H-3), 1.87 (3H, *dd*, 1.5/6.6 Hz, H-3'''), 3.90 (3H, *s*), 3.92 (3H, *s*), 4.09 (1H, *m*, H-2), 4.89 (1H, *d*, 4.5 Hz, H-1), 5.16 (2H, *s*), 6.11 (1H, *qd*, 6.6/15.7 Hz, H-2'''), 6.31 (1H, *dd*, 1.5/15.7 Hz, H-1'''), 6.69-7.06 (*m*, Ar-H), 7.30-7.50 (*m*, Ar-H). ¹³C-NMR (100 MHz, CDCl₃): 17.7 (C-3), 18.3 (C-3'''), 55.9 (OCH₃), 56.0 (OCH₃), 70.6 (C-1), 71.0 (OCH₂Ph), 86.9 (C-2), 109.3 (C-2'), 110.6 (C-3''), 113.6 (C-5), 118.1 (C-5''), 118.7 (C-6), 119.6 (C-6''), 124.5 (C-2'''), 127.3, 127.8, 128.5, 130.5 (C-1'''), 131.3 (C-1'), 132.8 (C-4''), 137.1, 146.8 (C-1''), 147.9 (C-4'), 149.7 (C-3'), 150.5 (C-2''). HRESIMS: 457.1965 [M+Na]⁺. Calculated for C₂₇H₃₀NaO₅: 457.1991.

Synthesis of (E)-1-(4-(hydroxy)-3-methoxyphenyl)-2-(2-methoxy-4-(prop-1-en-1-yl)phenoxy)propan-1-ol (10)

Compound **9** (0.020 mmol) was dissolved in methanol (3 mL) and mixed with Pd/C catalyst (10%).

This mixture was submitted to reaction with hydrogen overnight at room temperature. The crude was filtered and concentrated in vacuo. Flash column chromatography of the residue gave **10**. Colorless oil. ¹H-NMR (400 MHz, CDCl₃): 0.91 (3H, *t*, 7.3 Hz, H-3'''), 1.00 (3H, *d*, 6.3 Hz, H-3), 1.58 (2H, *m*, H-2'''), 2.49 (2H, *t*, 7.5 Hz, H-1'''), 3.89 (6H, *bs*, 2 × OCH₃), 4.06 (1H, *m*, H-1), 4.39 (1H, *d*, 8.3 Hz, H-2), 5.63 (1H, *s*, OH), 6.52 (1H, *bd*, 7.5 Hz, H-5''), 6.58 (1H, *d*, 8.0 Hz, H-6'), 6.70 (1H, *bs*, H-3''), 6.84 (1H, *bd*, 8.3, H-6'), 6.89 (1H, *d*, 8.1 Hz, H-5'), 6.94 (1H, *bs*, H-2'). ¹³C-NMR (100 MHz, CDCl₃): 13.8 (C-3'''), 17.9 (C-3), 24.6 (C-2'''), 37.8 (C-1'''), 55.7 (OCH₃), 56.0 (OCH₃), 71.6 (C-1), 91.3 (C-2), 109.2 (C-2'), 112.0 (C-3''), 114.1 (C-5'), 118.9 (C-6''), 120.5 (C-5''), 120.8 (C-6'), 131.1 (C-1'), 137.9 (C-4''), 145.6 (C-4'), 146.0 (C-1''), 146.8 (C-3'), 150.3 (C-2''). HRESIMS: 369.1642 [M+Na]⁺. Calculated for C₂₀H₂₆NaO₅: 369.1678.

RESULTS AND DISCUSSION

General synthetic strategy

Neolignans are a great group of secondary plant metabolites related to shikimic acid pathway. In depth, neolignans are the product of the oxidative coupling of two phenylpropanoid units (formed by C-O-C' linkages). Compounds **4** and **5** (Fig. 1) are 8-O-4' neolignans in which the two phenylpropanoid units are the same, allowing establishing them as derived from isoeugenol. The compound 7',8'-dihydromachilin D (**10**), a derivative of **5**, was selected as model target here. The synthetic route to **10** is illustrated in Fig. 2. The present approach was based on ring opening of an epoxide as key intermediate. In order to accomplish an asymmetric synthesis, chiral epoxide was required. In the first step, commercial available isoeugenol was protected by benzylation. Second step was based on formation of a chiral epoxide by employing Jacobsen's catalyst. At this level, *trans*-stilbene (**11**) can be employed as simple

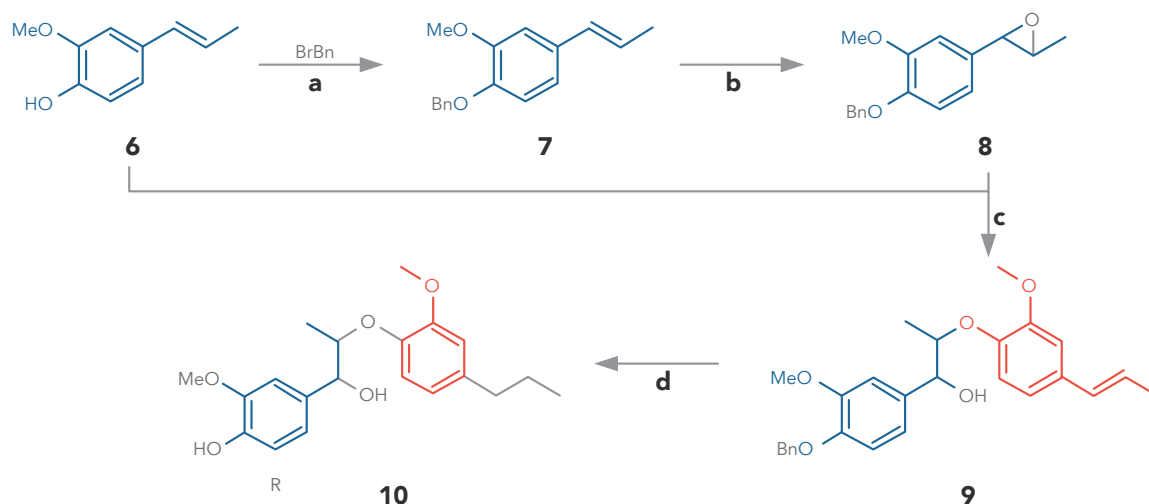


Figure 2. Synthetic route to 7',8'-dihydromachilin D. a) KOH/EtOH, reflux; b) (*R,R*)-Jacobsen's catalyst/ CH_2Cl_2 and NaClO, 4°C; c) KOH/EtOH, reflux; d) H_2 and Pd/C, r.t., overnight.

trans- model substrate to accomplish the optimization of the catalytic reaction conditions. Ring opening epoxide by isoeugenolate salt was the next step in the proposed route. Finally, reductive hydrogenolysis reaction was carried out to achieve **10**. Herein, isoeugenol (**6**) was selected as starting material according to its commercial availability and low cost.

Benzoylation of **6**

The first step in the synthesis of the 8-*O*-4' neolignan was the protection of the hydroxyl group into the structure of isoeugenol **6** (Fig. 2). Compound **6** was submitted to benzoylation by nucleophilic substitution of benzyl bromide under three previously reported conditions (Table 1). In spite of potassium carbonate have been reported as common use base in benzoylation (Gu *et al.*, 2000; Barrero *et al.*, 1998; Buchi *et al.*, 1967), it was not able to accomplish successfully the reaction on **6** (entry 1, Table 1). The addition of molecular sieve together with temperature increasing was not efficient either. Since base strength was not sufficient to deprotonate the

phenolic hydroxyl group, more drastic conditions were required (entry 3, Table 1; Pond and Beers, 1897). Potassium hydroxide in ethanol was then used obtaining acceptable yield percentage.

Epoxidation of *trans*-stilbene

The selected epoxidation process in the present research corresponded to that known as Jacobsen epoxidation, which consist in reaction of an olefin with a terminal oxidant in presence of a chiral [Mn(salen)] complex (Jacobsen *et al.*, 1991; Zhang and Jacobsen, 1991). Several terminal oxidants and additives have been used to improve the yields and/

Table 1. Benzoylation of **7** under different reaction conditions.

Entry	Reagent	Solvent	Yield (%)
1	K_2CO_3	Acetone	17.3
2	K_2CO_3 + MS 4Å	Toluene	18.1
3	KOH	Ethanol	80.0

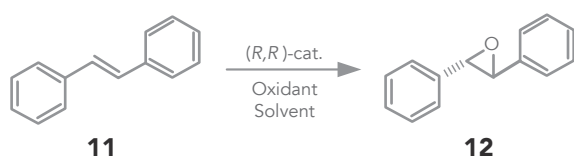


Figure 3. Epoxidation reaction of *trans*-stilbene.

or enantioselectivities (Skarzewski *et al.*, 1995; Bahramian *et al.*, 2006; Zhang *et al.*, 1990; Zheng *et al.*; 2004; Clarke *et al.*, 2005; Liao and List, 2009). There are a great number of reports about application of Jacobsen epoxidation to broad range of *cis* substrates, but poor results to *trans* substrates respect to enantioselectivities and yields have been found (McGarrigle and Gilheany, 2005). So, it was mandatory to find optimized reaction conditions for the epoxidation of the compound **6**. To accomplish it, *trans*-stilbene (**11**) was used as a simple *trans* model substrate. The general epoxidation reaction to the compound **11** is shown in Fig. 3. Relative configuration of the isolated product **12** was defined as *trans* by comparing its NMR assignments with those previously reported to *cis* and *trans* products (Table 2).

Due to low yields were observed in preliminary assays of the Jacobsen epoxidation to **11**, quantification of **12** was carried out by external standard

HPLC procedure. Optimal separation conditions were achieved under acetonitrile-water gradient for a representative reaction mixture (Fig. 4). The corresponding calibration curve is shown in Fig. 5. Diastereomeric ratio was also determined to the reaction crude products by $^1\text{H-NMR}$. The signals were compared with those previously reported (Imuta and Ziffer, 1979) and let us to establish a *trans/cis* ratio major than 95%. In order to determine the enantiomeric excesses (ee) of the obtained epoxide **12**, chromatographic conditions were optimized employing a chiral column and a racemic mixture. This racemate was obtained by epoxidation reaction with $[\text{Mn}(\text{salen})\text{Cl}]$ complex instead of chiral Jacobsen complex. A representative HPLC profile for ee determination is shown in Fig. 6.

Table 3 shows the different conditions attempted in the epoxidation of **11**. It can be seen that yields were moderate (up to 68%), whereas the ee's were low in all cases (up to 20% ee). In entries 1 and 10 (Table 3), only Jacobsen catalyst and an oxidant (H_2O_2 and NaOCl , respectively) were used. However, ineffectiveness of hydrogen peroxide as terminal oxidant in the epoxidation of **11** was found. Some additives were then employed in this reaction according to their highly frequent uses in this catalytic reaction (Skarzewski *et al.*, 1995; Bahramian *et al.*, 2006; Zhang *et al.*, 1990; Zheng *et al.*; 2004; Clarke *et al.*, 2005). The addition of ammonium acetate or imidazole (entries 2-6, Table 3) decreased the yields, accompanied by decreasing of enantioselectivity. The use of pyridine as additive (entries 7-9, Table 3) gave yields around 50%, although ee was closed to 10%. The yield was slightly increased when pyridine excess was employed (entry 8, Table 3).

Imidazole have also been used as additive in Jacobsen epoxidation due to its *trans* effect on the $\text{Mn}(\text{salen})$ complex that bring to $\text{Mn}=\text{O}$ bond enlargement and reactivity is then increased. Nevertheless, coordination of imidazole to manganese

Table 2. Configuration assignment of **12** by NMR.

Position	<i>trans</i> -epoxide*		<i>cis</i> -epoxide*		Isolated product	
	δ_{C}	δ_{H}	δ_{C}	δ_{H}	δ_{C}	δ_{H}
Ca	62.9	3.84 (s)	59.9	4.34 (s)	62.8	3.87 (s)
1	137.2		134.5		137.1	
2,6	125.6		126.9		125.5	
3,5	128.6		127.9		128.5	
4	128.4		127.5		128.3	

* From literature (Imuta and Ziffer, 1979).

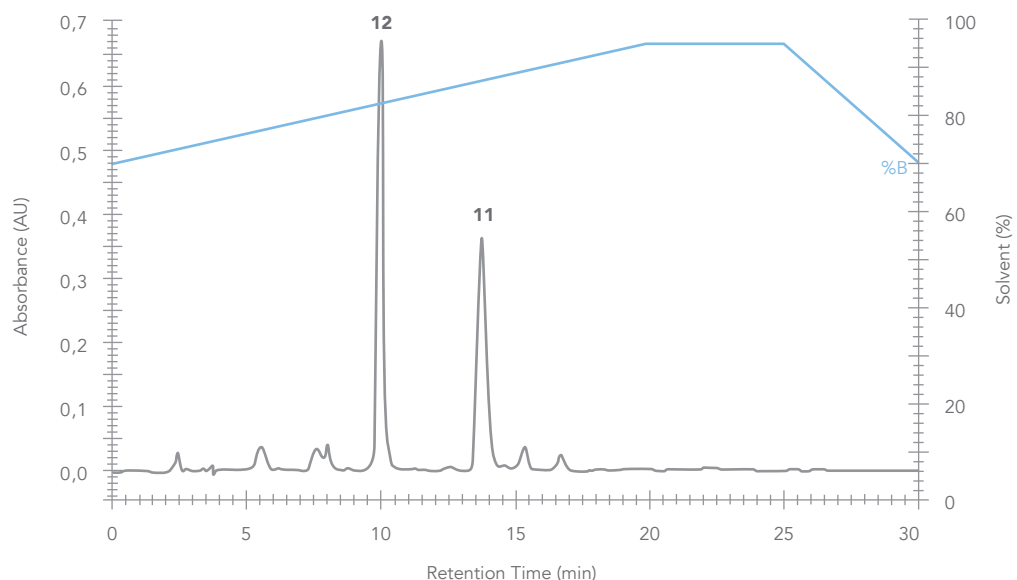


Figure 4. RP-HPLC profile for crude reaction mixture from epoxidation of **11**. Phenomenex Ultracarb ODS C30 column (150 x 4.6 mm i.d., 5 μ m); gradient elution with MeCN-water mixture (blue line).

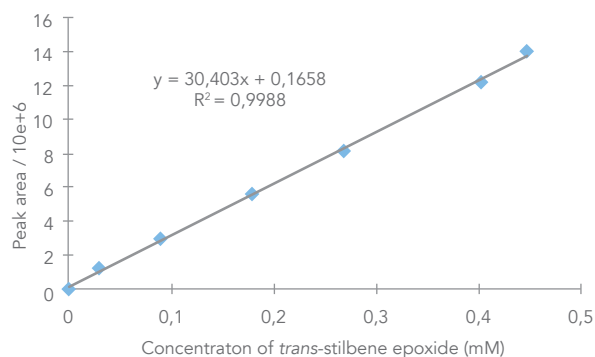


Figure 5. Calibration curve for the quantification of **12** by RP-HPLC.

entails conformational changes in the catalyst which can be attributed as responsible of steric hindrance that causes the poor observed results (Khavrutskii *et al.*, 2004). Pyridine should act in similar way to imidazole (pyridine is σ -donor and π -acceptor ligand (Miessler and Tarr, 2004)). The present results let to consider a differential reaction mechanism in Jacobsen epoxidation according to olefin configuration.

The performance of Jacobsen epoxidation to compound **11** (Table 3) can be explained according to observations of Katsuki and collaborators (McGarigle and Gilheany, 2005; and references cited herein). Moreover, different proposed conformations of [Mn(salen)] complexes play an important role in the enantioselectivity (McGarigle and Gilheany, 2005) and even have been studied by means of theoretical calculations (Cavallo and Jacobsen, 2003; Khavrutskii *et al.*, 2004). These conformations let us attribute the obtained ee's to the poor asymmetric induction established by the Jacobsen-catalyst for *trans*-substrate. However, favorable conformation to epoxidation of **11** could be achieved by chemical interaction of the catalyst with particular additives.

Ionic liquids have been reported as versatile solvents and excellent co-catalysts in organic as well as transition metal catalyzed reactions (Zhao *et al.*, 2002; Baudequin *et al.*, 2003; Welton, 2004; Song *et al.*, 2005; Durand *et al.*, 2007; Pârvulescu and Hardacre,

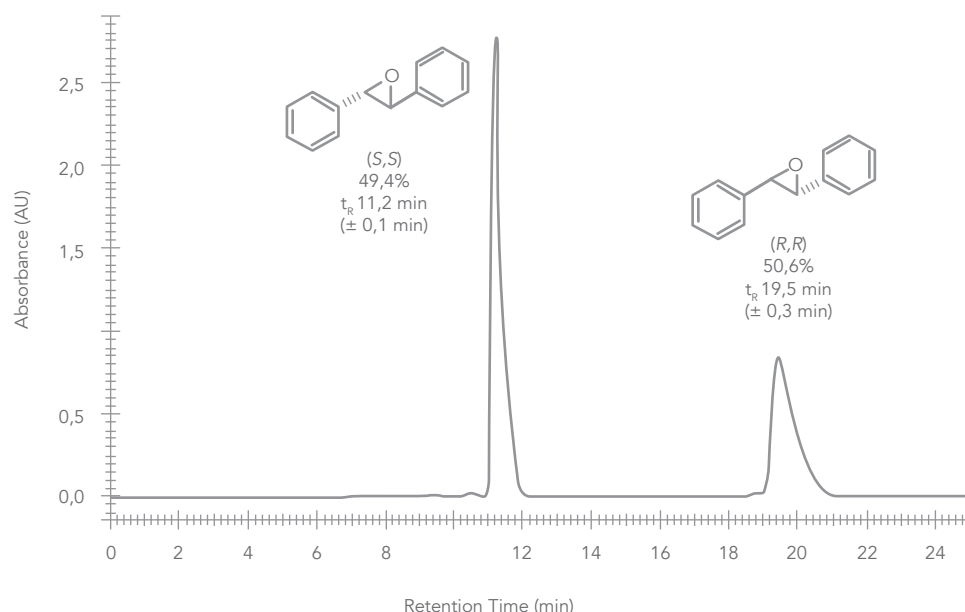


Figure 6. Chiral HPLC profile for the racemate of **12**. Chiralcel OD-H column (250 x 4.6 mm d.i.); isocratic elution with n-Hexane-IPA (9:1). Assignments were based on literature (Chang and Sharpless, 1996).

2007), including Jacobsen epoxidation (Song and Roh, 2000; Kumar, 2007; Pinto *et al.*, 2008; Tang *et al.*, 2008). In general, the use of ionic liquids as solvent (entries 11-17, Table 3) showed low yields (up to 29.5%) and very low enantioselectivities too (up to 15% ee). Combined use of ionic liquids with organic solvent brought to acceptable yield (entry 14, Table 3) but enantioselectivity was decreased. For his part, [OPIC][BF₄] (entry 11, Table 3) demonstrated to be able to increase the enantioselectivity of the reaction when compared with the most of the entries in Table 3, although it was smaller than that obtained with conventional method without additives (entry 10, Table 3). Increase in yield was achieved by pyridine addition on [OPIC][BF₄] medium (entry 12, Table 3). Other ionic liquids were employed without favorable results (entries 15-17, Table 3). In spite of results, *cis*-olefin epoxidation in ionic liquids has been reported as only comparable with that in organic solvents as far as conversion and enantioselectivity is concerned.

Epoxidation of **7**

Compound **7** was submitted to epoxidation reaction employing the conditions that provided highest yield and ee for **11** (4 mol% Jacobsen catalyst and NaOCl as oxidant without additives, entry 10, Table 3). The epoxide **8** was stereoselectively obtained in *trans* conformation and moderate yield (Table 4). This could be expected according to above described findings for **11**. However, the present result is relevant due to employed olefin have *trans*-configuration. Besides, the substituent groups on **7** can limit the interaction among C=C and metallic center in the active species, [Mn=O(salen)]. Moreover, oxygen atoms in the substituent groups of **7** can involve negative effects on catalytic performance by interaction with the highly oxophilic manganese atom. Diastereomeric ratio was determined such as it was done for the compound **12** (Fig. 7). This determination was accomplished by measuring of the integrals of the ¹H-NMR signals at 1.46 and 1.13 ppm, which

Table 3. Jacobsen epoxidation of **11** under different reaction conditions^a.

Entry	Solvent	Oxidant ^b	Additive ^c	Time(h)	Yield ^d (%)	ee ^e (%)
1	CH ₂ Cl ₂	H ₂ O ₂	--	>6	--	--
2	CH ₂ Cl ₂	NaOCl	NH ₄ AcO	24	36.0	16.2
3	CH ₂ Cl ₂	H ₂ O ₂	NH ₄ AcO	24	15.2	n.d.
4	CH ₂ Cl ₂	NaOCl	Imidazole	7	19.0	3.8
5	CH ₂ Cl ₂	H ₂ O ₂	Imidazole	7	9.8	n.d.
6	CH ₂ Cl ₂	H ₂ O ₂ ^f	Imidazole	24	4.5	n.d.
7	CH ₂ Cl ₂	NaOCl	Pyridine	4	50.3	9.7
8	CH ₂ Cl ₂	NaOCl	Pyridine ^g	2	59.0	9.8
9	CH ₂ Cl ₂	H ₂ O ₂	Pyridine ^g	6	2.1	n.d.
10	CH ₂ Cl ₂	NaOCl	--	6	67.9	19.8
11	[OPIC][BF ₄]	NaOCl	--	24	16.1	15.4
12	[OPIC][BF ₄]	NaOCl	Pyridine ^g	6	29.5	9.2
13	[OPIC][BF ₄]	H ₂ O ₂ ^f	--	24	10.8	n.d.
14	[BMIM][BF ₄]-CH ₂ Cl ₂	NaOCl	--	6	48.3	4.2
15	[BMIM][PF ₆]	NaOCl	Pyridine ^g	6	9.6	n.d.
16	[EMIM][[(CF ₃ SO ₂) ₂ N]	NaOCl	Pyridine ^g	6	19.5	3.2
17	[EMIM][SO ₄ Et]	NaOCl	Pyridine ^g	6	15.4	0.2
18	CH ₃ CN-(CH ₃) ₂ CO	NaOCl	(CH ₃) ₄ NCl	24	5.5	n.d.

^a 4 mol % of (R,R)-catalyst; ^b 2 eq of NaOCl or 3 eq of H₂O₂; ^c 2 eq; ^d quantification by RP-HPLC; ^e determined by chiral HPLC; ^f 10 eq; ^g 5 eq.

can be attributed to H atom from the methyl group in phenyl oxiranes (Tian *et al.*, 2002). On the other hand, the product **8** resulted to be decomposed on silica gel, so that neutral alumina was required to purification process (Table 4). One recycling process of the catalyst was also attempted finding comparable yield and stereoselectivity (entry 3, Table 4).

The obtained product **8** was established as a *trans*-epoxide according to the coupling constant between H-1 and H-2 (*J* = 2 Hz) and comparing it with literature (Solladié-Cavallo *et al.*, 2000). Although enantiomeric excess cannot be determined, optical rotation was evident. Therefore, some asymmetric induction was achieved.

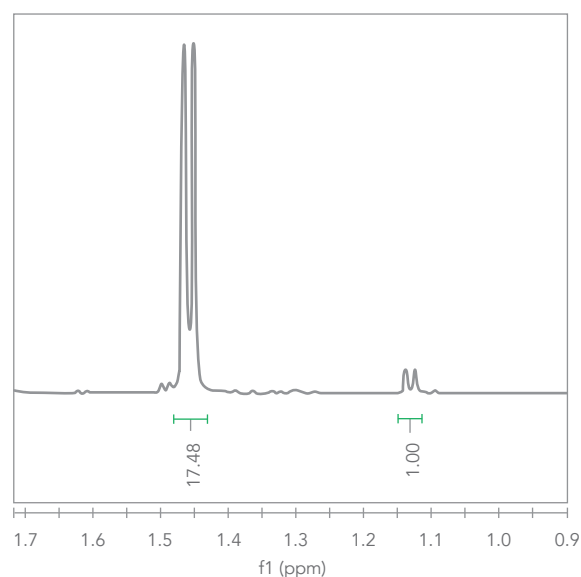


Figure 7. Diastereomeric ratio determination to epoxidation of **7** by ^1H -NMR signals of its methyl group.

Ring opening epoxide

The nucleophilic attack on the epoxide **8** was attempted under several reaction conditions (Table 5). Two major products were identified as originated from nucleophilic substitution reactions, both obtained in very different yields and conversions. An undesired product could be afforded by side radical reactions. Salen complexes (Jacobsen, 2000; Pastor and Yus, 2005; Gupta and Sutar, 2008) and bismuth

salts (Ollevier and Lavie-Compin, 2004) have been employed in ring opening epoxides by aromatic amines. Therefore, Jacobsen catalyst and bismuth nitrate (entry 7 and 9, respectively; Table 5) were tested in ring opening epoxide. Nevertheless, no significant improve were detected respect to entry 1 (Table 5). The use of previously prepared isoeugenol sodium salt (entries 2 and 3, Table 5) not showed the formation of **9**. Acetonitrile was attempted as solvent (entry 4, Table 5) but selectivity of the reaction was completely changed obtaining thus other than the desired product. In contrast, the use of acetonitrile as medium including a weak base (entry 10, Table 5) exhibited a very different performance (neolignan was found in very low yield). Poor results were observed when reaction was carried out at reflux temperature. Thereof, room temperature was also tested (entries 5-9, Table 5). However, significant yields were not exhibited or a great number of side products were observed. Neolignan **9** was only obtained by alcoholic potassium hydroxide under reflux (entry 1, Table 5) although only 23% yield was reached. A common ionic liquid was also tested (entry 8, Table 5) due to his known powerful solvation properties and uses in nucleophilic substitution reactions (Wasserscheid and Welton, 2008; Jorapur and Chi, 2006; Wheeler *et al.*, 2001), but reaction selectivity was turned toward another product.

Reductive hydrogenolysis of **9**

In order to accomplish the proposed synthetic strategy, reductive hydrogenolysis process was attempted. The adopted methodology was based on typical hydrogenolysis reports employing hydrogen and palladium/carbon catalyst (Xia *et al.*, 2010; Llàcer *et al.*, 2006). The compound **10** was obtained in low yield. Not greater than atmospheric pressure of hydrogen was used here, but the catalytic process resulted in debenzilation companied with hydrogenation of the double bond in the second

Table 4. Jacobsen epoxidation of **7**

Entry	Stationary phase	Yield (%)	<i>trans</i> : <i>cis</i> ratio ^a
1	Silica gel	11.9	--
2	Neutral alumina	43.5	94.5:1
3 ^b	Neutral alumina	40.3	95.6:1

^aDiastereomeric ratio determined by integration of ^1H -NMR signals of the methyl groups; ^bdouble addition of substrate and oxidant (one only catalyst load).

Table 5. Ring opening epoxide **8** under different reaction conditions.

Entry	Reagents	Solvent	Condition	Product formation*
1	Isoeugenol + KOH	EtOH	Reflux	9
2	Sodium Isoeugenolate	1,3-dioxolane	Reflux	--
3	Sodium Isoeugenolate	MeCN	Reflux	--
4	Isoeugenol + KOH	MeCN	Reflux	S _a
5	Isoeugenol + KOH	EtOH	r.t.	9
6	Isoeugenol + Et ₃ N	MeCN	r.t.	9
7	Isoeugenol + Jacobsen cat.	TBME	r.t.	9 + S _a
8	Isoeugenol + KOH	EtOH+[BMIM][BF ₄]	r.t.	S _b
9	Isoeugenol + Bi(NO ₃) ₃	Et ₂ O	r.t.	9
10	Isoeugenol + Na ₂ CO ₃	MeCN	Reflux	9

* S_a and S_b represent main products other than **9** according to TLC.

phenylpropene unit introduced. Therefore, the isolated product corresponded to the hydrogenated derivative of machilin D. Compound **10** can be characterized as *threo*-isomer due to coupling constant between H-1 and H-2 of 8.0 Hz and confirmed with chemical shift for C-3 at 17.9 ppm (Herrera *et al.*, 1984). Nevertheless, *erythro*-conformation would be expected from a *trans*-epoxide if reaction conditions had been those to SN2 reaction. The *threo*-conformation suggested a SN1 mechanism in this reaction and let us to propose the loss of the *erythro*-isomer across the purification step.

In conclusion, we have developed an inexpensive and diastereoselective approach to obtain 7',8'-dihydromachilin D in only four steps in 3.9% overall yield for the first time. An enantiomerically enriched epoxide from Jacobsen epoxidation was

used as key intermediate. The present methodology can be extended to any other natural and not natural 8-O-4' neolignan by replacing the phenylpropene at the first step and/or at the ring opening epoxide step.

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