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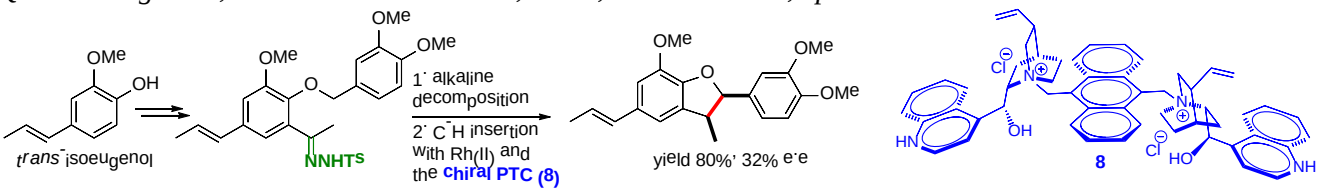

Rh(II)-catalyzed enantioselective synthesis of acuminatin through a C-H insertion reaction of a non-stabilized carbenoid

Cristóbal López-Sánchez, Míriam Álvarez-Corral, Leticia Jiménez-González, Manuel Muñoz-Dorado, and Ignacio Rodríguez-García.*

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ABSTRACT

An efficient and practical asymmetric synthesis of the 2,3-dihydrobenzo[*b*]furan neolignan acuminatin was achieved by using *trans*-isoeugenol as the starting material. The key step is an intramolecular C-H insertion through a non-stabilized carbenoid, prepared by decomposition of a tosylhydrazone in the presence of an anthracenyl-derived cinchonidine quaternary ammonium salt as a chiral phase-transfer catalyst.

Keywords:
Rh(II) catalyst
1,5 C-H insertion
Chiral Phase Transfer Catalyst
Cinchonidine quaternary ammonium salt

1. Introduction

(+)-Acuminatin (**1**) is a dihydrobenzofuran neolignan, a subclass of natural products with a molecular backbone formed by two phenylpropane (C_6C_3) units, whose biological properties have prompted their use as lead compounds for the development of new drugs.[1] It was first isolated in 1972 from *Magnolia acuminata*[2] and later from other plants used in traditional medicine, like *Myristica fragans*,[3,4] *Virola pavonis*,[5] *Machilus obovatifolia*,[6] *Machilus thunbergii*,[7] *Magnolia denudata*,[8] *Piper futokadsura*,[9] and more recently *Magnolia ovata*[10] and *Nectandra amazonum*.[11] The lignan structure initially proposed by Doskotch et al.[2] was later revised as a neolignan with a 2,3-dihydrobenzo[*b*]furan core.[12] The absolute configuration for the natural (+)-enantiomer has been proposed as (2*R*,3*R*)[9,10,12-14] on the basis of the chiroptical properties of the heterocycle.[15]

Among the main biological activities of (+)-acuminatin are the inhibition of DNA-topoisomerases I, II[16] and phospholipase Cγ1,[7] the inhibition of nitric oxide[9] and the inhibition in the production of transaminases,[17] implying, in the last case, potential hepatoprotective properties.

There are two main strategies for the synthesis of acuminatin: the use of the Erdtman methodology[18,19] through phenol oxidative coupling,[12,20] and the cycloaddition of styrene derivatives to quinones.[21] However, both are multistep, low yielding and non stereoselective.

One of the most elegant methods for the preparation of dihydrobenzofuran neolignans is based on the asymmetric Rh-catalyzed C–H insertion reaction developed by Davies et al.,[22-24] which has also been described by Hashimoto[25] and Fukuyama.[26,27] The method has been extended by the use of other metal complexes.[28] In this approach, a diazo compound is treated with a metal salt to give a metal carbene intermediate, which is able to promote intramolecular C-H funtionalization to afford new C-C bonds. The reactivity of the metal carbenes is highly conditioned by the nature of the substituents (Figure 1).

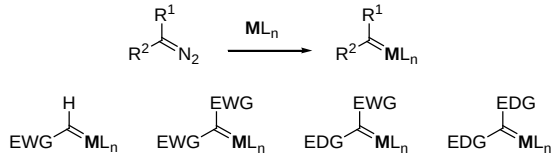

Figure 1 Classes of metal carbenes prepared from diazo compounds.

The acceptor/acceptor carbenes are very reactive species because the acceptor groups do not stabilize the highly electrophilic carbene center, whereas the donor/acceptor metal carbenes are capable of highly selective C–H functionalization. On the other hand, donor/donor metal carbenes have been less studied due to the instability of the required diazo compounds. These can be prepared using the Bamford-Stevens reaction[29] which utilizes tosylhydrazones as safe diazo precursors. In the

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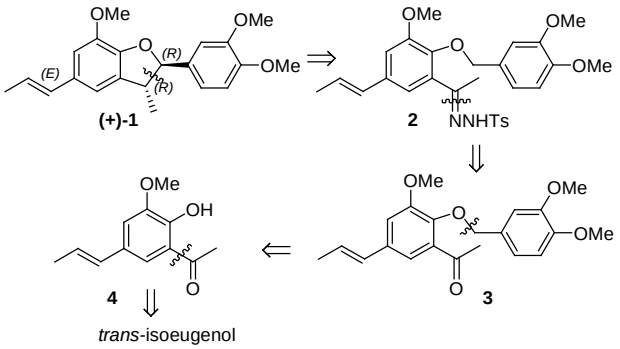
presence of phase-transfer-catalysts (PTC) they can be cleanly converted to diazo compounds under mild reaction conditions.[30]

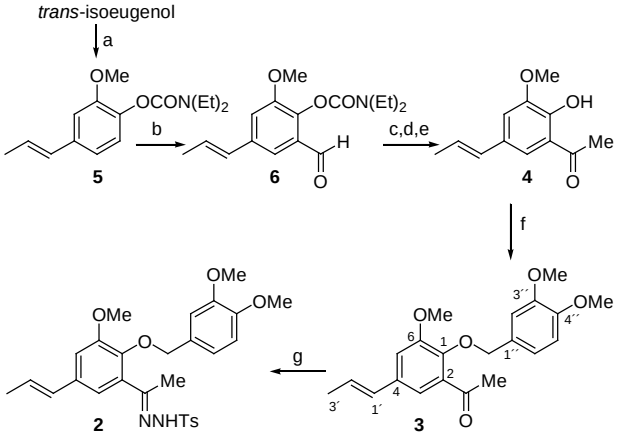
We report here a new method of synthesis of acuminatin based on an intramolecular C-H insertion reaction through rhodium carbenoids intermediates prepared *in situ* by decomposition of tosylhydrazones with base in the presence of a phase transfer catalyst (Scheme 1). The C-H insertion reaction can be performed in a diastereoselective and enantioselective manner using chiral rhodium complexes and chiral phase transfer catalysts.



Scheme 1 Retrosynthetic analysis of (+)-acuminatin (**1**).

2. Results and discussion

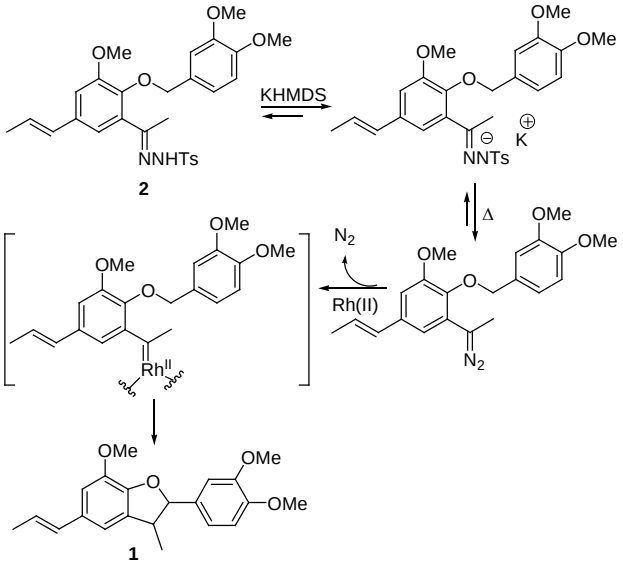
The synthesis of the required tosylhydrazone **2** from *trans*-isoeugenol was achieved in seven high-yielding conventional steps (Scheme 2). Initial attempts to introduce an acyl group in *ortho* position of the phenolic OH through Friedel-Crafts acylation or Fries rearrangement of the acetyl derivative[31-33] in the presence of either $TiCl_4$, $Ti(i\text{-}PrO)_4$ or $Sc(OTf)_4$ did not gave satisfactory results. However, the multi-step process depicted in scheme 2, proved to be useful. First, the phenolic OH was protected with the *ortho*-directing group *N,N´*-diethylcarbamate to form compound **5**. Formilation in *ortho* position to give **6** was optimal when *s*-BuLi as metallating agent and DMF as electrophile were used. Aldehyde **6** was transformed into ketone **4** by a three steps process involving Grignard addition, Dess-Martin oxidation and hydrolysis of the carbamate group in alkaline media. Williamson etherification with 4-(iodomethyl)-1,2-dimethoxybenzene (**7**) and treatment of **3** with tosylhydrazine yielded the desired tosylhydrazone **2**.



a) Et_2NCOCl, py, 100 ºC, 90%; b) *s*-BuLi, DMF, TMEDA,THF, - 90 ºC, 85%; c) Mg, CH_3I, Et_2O, 0 ºC, 93%; d) Dess-Martin oxidation, 95%; e) NaOH, EtOH, Δ, 85%; f) K_2CO_3, **7**, Me_2CO, Δ, 85%; g) $TsNHNH_2$, MeOH, Δ, 92%.

Scheme 2 Preparation of tosylhydrazone **2** from *trans*-isoeugenol.

When the tosylhydrazone **2** is treated with KHMDS in THF at – 80 ºC, cloudiness appears due to the formation of the potassium salt, which, on heating, is unstable and decomposes *in situ* to form the diazo compound derivative (Scheme 3).[30] This diazo compound can be detected by NMR, but our attempts to isolate it failed, possibly because is not stable enough for the standard purification methods used with other diazo compounds bearing electron-withdrawing substituents (like esters or ketones).[34,35]



Scheme 3 Pathway for the C-H insertion reaction through rhodium carbenoids by decomposition of tosylhydrazone **2**.

Table 1 C-H insertion reaction with several Rh(II) catalysts.[a]

Entry	Catalyst[b]	Yield of **1** (%)	**d.r. (*cis*:*trans*)**
1	$Rh_2(OCOCF_3)_4$	90	100 : 0
2	$Rh_2(OAc)_4$	87	87 : 13
3	$Rh_2(Oct)_4$	35	80 : 20
4	$Rh_2(5S\text{-}MEPY)_4$	70	62 : 38
5	$Rh_2(S\text{-}DOSP)_4$	40	50 : 50

[a] KHMDS was added at – 80 ºC to a THF solution of **2**; then stirred for 30 min. at 25 ºC; next, 1% mol Rh(II) catalyst and *n*-Bu_4NBr were added and refluxed for 12 h.

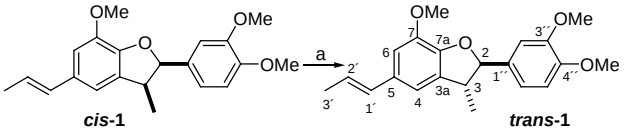
[b] Diastereomeric ratios deduced from the integrals of signals in ^1H NMR of the crude mixtures and confirmed after CC isolation of products.

In the presence of a metal catalyst, the diazo compound reacts with an activated C-H bond through a carbenoid intermediate.[35-40] The process is a 1,5-intramolecular carbon-hydrogen bond insertion[22,24,35,41] to form a five-member heterocycle through a well-established mechanism[42-46] (Scheme 3). The reaction can be highly improved by the presence of phase-transfer catalysts (PTC), like quaternary ammonium salts, because they favour the transformation of the tosylhydrazone salt into the diazo compound and promote the solubility of rhodium catalysts.[30]

Table 1 shows yields, conditions and diastereoselectivity of the reaction of tosylhydrazone **2** with a series of rhodium salts. Mixtures of *cis*/*trans* diastereoisomers are always formed except for $Rh_2(OCOCF_3)_4$, which shows complete *cis* diastereoselectivity. As a general trend, the more electron-donating the rhodium ligands, the less electrophilic the carbenoid carbon atom, with an associated decrease in reaction yield and selectivity. Bulkiness of the ligands has the same effect.

The reaction is chemoselective, as no side products were detected, like those due to sigmatropic rearrangement[47-50] or β-hydride shift.[51,52]

Natural *trans*-acuminatin can be prepared by acidic treatment of either the *cis/trans* mixtures of **1** or the diasteromerically pure *cis*-**1** formed when $Rh_2(OCOCF_3)_4$ is used (Scheme 4).

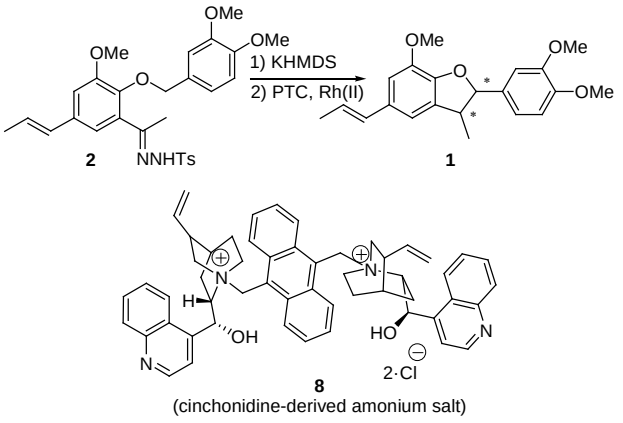


a) Camphorsulphonic acid (cat.), tol, Δ, 95%.

Scheme 4 Isomerization of (±)-*cis*-acuminatin to natural (±)-*trans*-acuminatin in acid media.

3. Asymmetric synthesis of acuminatin

In order to achieve enantioselectivity in the insertion process, several chiral rhodium complexes were tested, although under the standard reaction conditions no enantioselectivity was observed (Table 1, entries 4 and 5). However, when the cyclization step was performed at a lower temperature, excellent diastereoselectivity and moderate enantioselectivity levels were observed (Table 2, entries 1 and 2). The temperature of reaction proved to be critical: a threshold in the range 30-40 ºC was required to complete the transformation of the tosylhydrazone salt into the diazo compound. The results were also improved by the use of the anthracenyl-derived cinchonidine quaternary ammonium salt **8**[53] as phase-transfer catalyst (Scheme 5, Table 2, entries 3 and 4). Surprisingly, when **8** was used in combination with a non chiral rhodium salt, a significant enantiomeric excess was found (table 2, entry 5), thus indicating that this chiral PTC is involved in the cyclization step.



(cinchonidine-derived amonium salt)

Scheme 5 Asymmetric intramolecular C-H insertion reaction.

Table 2 Reaction of **2** with chiral rhodium catalysts and PTC

Entry	T(ºC)	Rhodium catalyst	PTC	yield (%)	d.r (cis:trans)[a]	e.e (%)[b]
1	40	Rh_2(*S*-DOSP)$_4$	*n*-Bu_4NBr	32	92 : 8	24
2	30	Rh_2(*S*-DOSP)$_4$	*n*-Bu_4NBr	29	100 : 0	30
3	40	Rh_2(*S*-DOSP)$_4$	**8**	83	100 : 0	14
4	40	Rh_2(*R*-DOSP)$_4$	**8**	80	100 : 0	20
5	40	$Rh_2(OCOCF_3)_4$	**8**	80	100 : 0	32

[a] Diasteromeric ratios deduced from the integrals of signals in ^{1}H NMR of the crude mixtures

[b] e.e values deduced from chirla HPLC integration

Although the asymmetric induction by chiral PTCs is well documented,[54-56] to the best of our knowledge, this is the first time when a chiral phase-transfer catalyst affords asymmetric induction in an intramolecular C-H bond insertion.

4. Conclusions

We have described a new method for the synthesis of the neolignan acuminatin, in good global yield (40%), through the decomposition of a tosylhydrazone as precursor of the required aryl-methyl diazo compound for a Rh(II) catalyzed C-H insertion. The reaction affords diastereoselectively the *cis* isomer, which can be easily isomerized into the natural *trans*-acuminatin. We have also described the asymmetric intramolecular C-H insertion reaction under the influence of a chiral phase-transfer catalyst, with good yields and moderate enantiomeric excesses.

5. Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 300 spectrometer. Chemical shifts are given in ppm relative to TMS. Carbon substitution degrees were established by DEPT multipulse sequence, and ^{13}C NMR peak assignments were made with the aid of 2D NMR (HMBC, HMQC, COSY and NOESY). Infrared spectra were recorded in liquid film between NaCl plates on a FT-IR Mattson Genesis II spectrometer, and mass spectra were performed on a AutoSpec-Q VG-Analitical (Fisons) (HRMS) instrument, using the Fast Atom Bomb technique (FAB) with a 1% NaI doped matrix of thioglycerol or glycerol.

The reactions were monitored by TLC (unless other technique is specified), using Macherey Nagel Alugram Sil G/UV_{254} plates. UV light and 5% phosphomolibdic or sulphuric acid solutions in methanol were employed for revealing. SDS 60 A CC 35-70 μm silica was used for column chromatography. All solvents were purified and dried following standard procedures. Enantiomeric excesses were calculated from chiral HPLC performed in a Hewlett Packard Series 1100 chromatograph equipped with a circular dichroism detector and a Daicel Chiracel OD-H 150x4.6 mm column and eluting with mixtures of hexane and isopropanol.

(*E*)-2-methoxy-4-(prop-1-enyl)phenyl *N,N´*-diethyl carbamate (**5**). To a solution of *trans*-isoeugenol (2 g, 11.9 mmol) in dry pyridine (25 mL), diethyl carbamoyl chloride (2.4 g, 17.8 mmol) was added. The mixture was stirred at 100ºC for 12 hours. Then, 20 mL of HCl (5%) were added, and the whole extracted with 20 mL of CH_2Cl_2. The organic layer was dried with $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified by column chromatography on silica gel (hexane:Et_2O, 7:3) to afford **5** (2.8 g, 10.7 mmol, 90%) as a yellow oil. IR (film) ν_{max} 1721 (C=O), 1591 (C=C) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.23 [3H, t, ^3J= 7.1 Hz, OCON($CH_2C\underline{H}_3$)$_2$], 1.27 [3H, t, ^3J= 7.1 Hz, OCON($CH_2C\underline{H}_3$)$_2$], 1.94 (3H, dd, ^3J= 6.6 Hz, ^4J= 1.5 Hz, H3´), 3.38 [2H, c, ^3J= 7.1 Hz, OCON($C\underline{H}_2CH_3$)$_2$], 3.42 [2H, c, ^3J= 7.1 Hz, OCON($C\underline{H}_2CH_3$)$_2$], 3.85 (3H, s, O$C\underline{H}_3$), 6.20 (1H, dc, ^3J= 15.7 Hz, ^3J= 6.55 Hz, H2´), 6.37 (1H, dd, ^3J= 15.7 Hz, ^4J= 1.5 Hz, H1´), 6.90 (1H, dd, ^3J= 8.2 Hz, ^4J= 1.7 Hz, H5), 6.92 (1H, d, ^4J= 1.6 Hz, H3), 7.2 (1H, d, ^3J=8.2 Hz, H6). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.36 [OCON($CH_2\underline{C}H_3$)$_2$], 13.97 [OCON($CH_2\underline{C}H_3$)$_2$], 18.37 (CH_3, C3´), 41.94 [OCON($\underline{C}H_2CH_3$)$_2$], 42.20 [OCON($\underline{C}H_2CH_3$)$_2$], 55.80 (O$\underline{C}H_3$), 109.58 (CH, C3), 118.26 (CH, C5), 123.11 (CH, C6), 125.46 (CH, C2´), 130.60 (CH, C1´), 136.21 (C, C4), 139.49 (C, C1), 151.55 (C, C2), 154.15 ($\underline{C}$=O). HRFABMS (*m/z*) calcd. for $C_{15}H_{21}NO_3Na$ 286.1414 [M+Na]$^+$, found 286.1418

(*E*)-2-formyl-6-methoxy-4-(prop-1-enyl)phenyl *N,N´*-diethylcarbamate (**6**). TMEDA (4.8 mL, 32.1 mmol) was added to a solution of compound **5** (2.8 g, 10.7 mmol) in dry THF (30 mL) at -90ºC under nitrogen atmosphere. The mixture was stirred for 5 min., and 11.7 mL (16 mmol) of *s*-BuLi (1.4 M) were added

dropwise. After 6 hours at -90ºC, DMF (5 mL, 64.3 mmol) was added. The reaction was stirred for 12 hours and then, 5 mL of a solution of TsOH/MeOH (50% w/v) was added and the mixture was allowed to reach room temperature. The solvent was removed and the crude dissolved in CH_2Cl_2 (50 mL) was washed with HCl (5%) (3 x 20 mL) and brine (20 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated under reduce pressure. The product was purified by column chromatography on silica gel (hexane:Et_2O, 9:1) to afford **6** (2.6 g, 9.1 mmol, 85%) as a white solid, mp: 81.4ºC; IR (KBr) ν_{max} 1715 (C=O), 1592 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ: 1.23 [3H, t, ^3J= 7.1 Hz, OCON($CH_2C\underline{H}_3)_2$], 1.27 [3H, t, ^3J= 7.1 Hz, OCON($CH_2C\underline{H}_3)_2$], 1.80 (3H, d, ^3J= 6.6 Hz, H3´), 3.38 [2H, c, ^3J= 7.1 Hz, OCON($C\underline{H}_2CH_3)_2$], 3.42 [2H, c, ^3J= 7.1 Hz, OCON($C\underline{H}_2CH_3)_2$], 3.76 (3H, s, $OC\underline{H}_3$), 6.15 (1H, dc, ^3J= 6.6 Hz, ^3J=15.7 Hz, H2´), 6.25 (1H, d, ^3J= 15.7 Hz, H1´), 7.00 (1H, s, H5), 7.3 (1H, s, H3), 10.1 (1H, s, C$\underline{H}$O). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 13.20 [OCON($CH_2\underline{C}H_3)_2$], 14.00 [OCON($CH_2\underline{C}H_3)_2$], 18.30 (CH_3, C3´), 42.10 [OCON($\underline{C}H_2CH_3)_2$], 42.40 [OCON($\underline{C}H_2CH_3)_2$], 56.00 ($O\underline{C}H_3$), 114.60 (CH, C5), 116.80 (CH, C3), 127.10 (CH, C2´), 129.50 (CH, C1´), 129.60 (C, C2), 136.10 (C, C4), 141.90 (C, C1), 152.20 (C, C6), 153.30 (O$\underline{C}$O), 188.80 ($\underline{C}$HO). HRFABMS (*m/z*) calcd. for $C_{16}H_{21}NO_4Na$ 314.1368 $[M+Na]^+$, found 314.1371.

(*E*)-2-(1-hydroxyethyl)-6-methoxy-4-(prop-1-enyl)phenyl N,N'-diethylcarbamate (**9**). To a suspension of Mg (600 mg, 25 mmol) in dry Et_2O (25 mL), MeI (2.5 mL, 27 mmol) was added under nitrogen atmosphere, and the mixture was refluxed until the magnesium turnings disappeared. Then, the reaction was cooled at 0ºC and a solution of 7 (2.6 mg, 8.9 mmol) in dry Et_2O (25 mL) was added slowly. The mixture was refluxed for 3 hours and was quenched by the addition of a solution of NH_4Cl (30%) (100 mL). The organic layer was washed with HCl (5%) (150 mL) and brine (100 mL), dried with $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane:Et_2O, 7:3) yielding **9** (2.6 g, 8.3 mmol, 93%) as a white solid, mp: 66.5ºC; IR (KBr) ν_{max} 3470 (O-H), 1702 (C=O), 1595 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ: 1.23 [3H, t, ^3J=7.1 Hz, OCON($CH_2C\underline{H}_3)_2$], 1.27 [3H, t, ^3J=7.06 Hz, OCON($CH_2C\underline{H}_3)_2$], 1,48 [3H, d, ^3J=6.5 Hz, $C\underline{H}_3$CHOH-], 1.80 (3H, dd, ^3J=6.6 Hz; ^4J=1.5 Hz, H3´), 3.38 [2H, c, ^3J=7.0 Hz, OCON($C\underline{H}_2CH_3)_2$], 3.42 [2H, c, ^3J=7.0 Hz, OCON($CH_2CH_3)_2$], 3.83 (3H, s, $OC\underline{H}_3$), 5.00 (1H, c, ^3J= 6.5 Hz, C$\underline{H}$OH), 6.15 (1H, dc, ^3J= 6.6 Hz; ^3J= 15.6 Hz, H2´), 6.25 (1H, dd, ^3J=15.7 Hz; ^4J= 1.5 Hz, H1´), 6.85 (1H, s, H5), 7.00 (1H, s, H3). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 13.29 [OCON($CH_2\underline{C}H_3)_2$], 13.99 [OCON($CH_2\underline{C}H_3)_2$], 18.31 ($\underline{C}H_3$CHOH-), 22.39 (CH_3, C3´), 42.10 [OCON($\underline{C}H_2CH_3)_2$], 42.37 [OCON($\underline{C}H_2CH_3)_2$], 55.86 ($O\underline{C}H_3$), 63.98 ($\underline{C}$HOH), 108.33 (CH, C5), 115.41 (CH, C3), 125.71 (CH, C2´), 130.73 (CH, C1´), 136.23 (C, C2)*, 136.57 (C, C4)*, 139.01 (C, C1), 151.56 (C, C6), 154.50 (O$\underline{C}$O) *may be interchanged.

(*E*)-2-acetyl-6-methoxy-4-(prop-1-enyl)phenyl *N,N´*-diethyl carbamate (**10**). Dess-Martin periodinane (3 g, 12.5 mmol) was added to a solution of compound **9** (2.6 g, 8.3 mmol) in CH_2Cl_2 (35 mL) at room temperature. The mixture was stirred for 1 hour, and then it was washed with a saturated solution of $NaHCO_3$ (3 x 20 mL). The organic layer was dried with $MgSO_4$, filtered and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel (hexane:Et_2O, 1:1) yielding **10** (2.4 g, 7.9 mmol, 95%) as a brown-red oil, IR (film) ν_{max} 1588 (C=C), 1714 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ: 1.15 [3H, t, ^3J= 7.0 Hz, OCON($CH_2C\underline{H}_3)_2$], 1.23 [3H, t, ^3J= 7.0 Hz, OCON($CH_2C\underline{H}_3)_2$], 1.81 (3H, dd, ^3J= 6.4 Hz; ^4J= 1.3 Hz, H3´), 2.50 (3H, s, CO$C\underline{H}_3$), 3.33 [2H, c, ^3J= 7.0 Hz, OCON($C\underline{H}_2CH_3)_2$], 3.43 [2H, c, ^3J= 7.0 Hz, OCON($C\underline{H}_2CH_3)_2$], 3.77 (3H, s, $OC\underline{H}_3$), 6.10 (1H, dc, ^3J= 6.3 Hz; ^3J= 15.7 Hz, H2´), 6.20 (1H, d, ^3J= 15.8 Hz, H1´), 7.00 (1H, d, ^4J= 2.0 Hz, H5), 7.20 (1H, d, ^4J= 2.0 Hz, H3). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 13.23 [OCON($CH_2\underline{C}H_3)_2$], 13.94 [OCON($CH_2\underline{C}H_3)_2$], 18.26 (CH_3, C3´), 30.13 ($CO\underline{C}H_3$), 42.03 [OCON($\underline{C}H_2CH_3)_2$], 42.26 [OCON($\underline{C}H_2CH_3)_2$], 56.08 ($O\underline{C}H_3$), 112.54 (CH, C5), 118.26 (CH, C3), 126.60 (CH, C2´), 129.88 (CH, C1´), 132.78 (C, C2), 135.64 (C, C4), 138.00 (C, C1), 152.18 (C, C6), 153.31 (OCO), 198.03 (CO).

(*E*)-2-acetyl-6-methoxy-4-(prop-1-enyl)phenol (**4**). Compound **10** (2.4 g, 7.9 mml) was added to a solution of NaOH (1.27 g, 31.7 mmol) in EtOH (16 mL). The mixture was refluxed during 12 hours. The reaction mixture was cooled to room temperature and a solution of HCl (5%) was added until an acid pH was reached. The solution was extracted with CH_2Cl_2 (3 x 25 mL), and the organic layers were washed with water, dried with $MgSO_4$, filtered and concentrated under reduce pressure. The residue was purified by column chromatography on silica gel (hexane:Et_2O, 6:4) yielding **4** (1.4 g, 6.8 mmol, 85%) as a green oil. IR (film) ν_{max} 1595 (C=C), 1677 (C=O), 3558 (O-H) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ: 1.84 (3H, dd, ^3J=6.5 Hz, ^4J=1.2 Hz, H3´), 2.58 (3H, s, CO$C\underline{H}_3$), 3.86 (3H, s, $OC\underline{H}_3$), 6.10 (1H, dc, ^3J= 6.5 Hz; ^3J=15.7 Hz, H2´), 6.27 (1H, d, ^3J=15.7 Hz, H1´), 7.02 (1H, d, ^4J=1.6 Hz, H5), 7.14 (1H, d, ^4J=1.6 Hz, H3), 12.49 (1H, sa, O$\underline{H}$). ^{13}C NMR (75 MHz, $CDCl_3$), δ: 18.24 (CH_3, C3´), 26.91 ($CO\underline{C}H_3$), 55.98 ($O\underline{C}H_3$), 113.60 (CH, C5), 119.20 (CH, C3), 119.39 (CH, C2´), 124.51 (CH, C1´), 128.52 (C, C2)*, 129.83 (C, C4)*, 148.75 (C, C1), 151.83 (C, C6), 204.88 (CO) *may be interchanged. HRFABMS (*m/z*) calcd. for $C_{12}H_{14}O_3Na$ 229.0841 $[M+Na]^+$, found 229.0835.

4-(iodomethyl)-1,2-dimethoxybenzene (**7**). Imidazol (0.82 g, 12 mmol) and PPh_3 (3.1 g, 12 mmol) were added to a solution of (3,4-dimethoxyphenyl)methanol (1.7 g, 10 mmol) in 25 mL of THF. After stirring for 10 min, iodine (3 g, 12 mmol) was added in darkness and the mixture was stirred at room temperature for 30 min. Solvent was removed *in vacuo*, and the residue was dissolved in CH_2Cl_2. The solution was washed with 20 mL $NaHSO_3$ (5%) and brine (2 x 15 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography 1:1 (hexane:Et_2O) yielding **7**[57] (2,5 g, 9 mmol, 90% of yield).

(*E*)-2-acetyl-6-methoxy-4-(prop-1-enyl)phenyl 3,4-dimethoxybencyl ether (**3**)**.** Compound **4** (1.4 g, 6.8 mmol) and K_2CO_3 (1.4 g, 10.1 mmol) were dissolved in acetone (10 mL). After stirring for 10 minutes, a solution of **7** (2.3 g, 8.1 mmol) in acetone (10 mL) was added. The mixture was refluxed for 12 hours. Solvent was removed *in vacuo*, and the residue was dissolved in CH_2Cl_2 (20 mL). The solution was washed with HCl (5%) (3 x 15 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography 8:2 (hexane:Et_2O) yielding **3** (2.2 g, 6 mmol, 85%). IR (KBr) ν_{max} 1593 (C=C), 1670 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ: 1.88 (3H, d, ^3J= 6.4 Hz, H3´), 2.55 (3H, s, CO$C\underline{H}_3$), 3.89 (6H, s, 2 x $OC\underline{H}_3$), 3.93 (3H, s, OCH_3), 4.99 (2H, s, $OC\underline{H}_2$Ar), 6.21 (1H, dc, ^3J= 6.4 Hz; ^3J= 16.0 Hz, H2´), 6.35 (1H, d, ^3J= 16.0 Hz, H1´), 6.84 (1H, d, ^3J= 8.2 Hz, H5´´), 6.93 (1H, dd, ^3J= 8.2 Hz; ^4J= 1.9 Hz, H6´´), 6.98 (1H, d, ^4J= 1.9 Hz, H2''), 7.05 (1H, d, ^4J= 1.9 Hz, H5), 7.13 (1H, d, ^4J= 1.9 Hz, H3).^{13}C NMR (75 MHz, $CDCl_3$), δ: 18.35 (CH_3, C3´), 31.31($CO\underline{C}H_3$), 55.78 ($O\underline{C}H_3$), 55.83 ($O\underline{C}H_3$), 56.00 ($O\underline{C}H_3$), 75.97 ($O\underline{C}H_2$Ar), 110.81 (CH, C5´´), 111.81(CH, C2´´), 112.52 (CH, C5), 118.21 (CH, C3), 121.14 (CH, C6´´), 126.20 (CH, C2´), 129.49 (C, C1´´), 129.88 (CH, C1´), 134.15 (C, C4)*, 134.46 (C, C2)*, 145.83 (C,

C1), 148.88 (C, C4´´)#, 149.02 (C, C3´´)#, 152.96 (C, C6), 200.74 (CO). * and # may be interchanged. HRFABMS (*m*/z) calcd. for $C_{21}H_{24}O_5Na$ 379.1521 $[M+Na]^+$, found 379.1550.

Tosylhydrazone of 3 (2). To a solution of **3** (2.2 g, 6 mmol) in 18 mL of MeOH, *p*-toluensulfonyl hidrazide (1.1 g, 9 mmol) was added. The mixture was heated under reflux for 15 minutes and then, it was stirred at room temperature for 15 hours. Solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel (hexane:Et_2O, 1:1) yielding **2** (2.5 g, 5.5 mmol, 92%) as a green-yellow foam. IR (KBr) ν_{max} 3270 (N-H), 1596 (-C=N) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.90 (3H, d, ^3J= 6.4 Hz, H3´), 2.05 (3H, s, C$\underline{H}_3$C=N-), 2.39 (3H, s, $SO_2PhC\underline{H}_3$), 3.86 (3H, s, OC$\underline{H}_3$), 3.87 (3H, s, OC$\underline{H}_3$), 3.88 (3H, s, OC$\underline{H}_3$), 4.74 (2H, s, OC$\underline{H}_2$Ar), 6.14 (1H, dc, ^3J= 6.9 Hz; ^3J= 15.7 Hz, H2´), 6.31 (1H, d, ^3J=15.7 Hz, H1´), 6.72 (1H, d, ^4J=1.6 Hz, H3), 6.79 (2H, m, H6´´, H5´´), 6.90 (2H, m, H5, H2´´), 7.29 (2H, d, ^3J= 10.1 Hz, H5´´´, H3´´´), 7.36 (2H, d, ^3J= 10.1 Hz, H6´´´, H2´´´).^{13}C NMR (75 MHz, $CDCl_3$), δ: 17.07 ($\underline{C}H_3$C=N-), 18.33 (CH_3, C3´), 21.49 ($SO_2Ph\underline{C}H_3$), 55.87 (3 x O$\underline{C}H_3$), 75.92 (O$\underline{C}H_2$Ar), 110.41 (CH, C5), 111.86 (CH, C2´´), 118.82 (CH, C3), 121.05 (CH, C6´´), 125.61 (CH, C2´), 127.98 (C), 128.08 (CH, C5´´), 128.22 (CH, C6´´´y C2´´´), 129.46 (C, C1´´), 129.88 (CH, C5´´´y C3´´´), 130.21 (CH, C1´), 133.20 (C), 134.04 (C), 143.99 (C), 144.52 (C), 145.02 (C), 148.81 (C), 148.90 ($ArCH_3\underline{C}$=NNH), 152.73 (C). HRFABMS (*m*/z) calcd. for $C_{28}H_{32}O_5N_2SNa$ 531.1930 $[M+Na]^+$, found 531.1975.

General procedure to obtain 2-(3,4-dimethoxyphenyl)-7-methoxy-3-methyl-5-[(*E*)-prop-1-enyl]-2,3-dihydrobenzo[*b*] furan (acuminatin) (1). A solution of **2** in dry THF (5 mL/mmol) was cooled at -80ºC and 1.5 equivalents of anhydrous KHMDS were added under nitrogen atmosphere. The reaction was stirred at this temperature for 15 minutes, then 30 minutes at room temperature. After that, the solution initially colourless, changed to yellow. Catalytic amount of *n*-Bu_4NBr (10% mol) and rhodium catalyst (1% mol) were added and the mixture was refluxed for 12 hours, cooled to room temperature, eluted with diethyl ether and washed with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduce pressure. The residue was purified by column chromatography on silica gel (hexane:Et_2O, 98:2) yielding **1** as a yellow oil (see table 1 for diasteromeric ratio). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 0.86 (3H, d, ^3J=7.3 Hz, C$\underline{H}_3$-C_3), 1.89 (3H, dd, ^3J= 6.5 Hz; ^4J= 1.6 Hz, H3´), 3.62 (1H, q, ^3J=7.3 Hz, H3), 3.88 (3H, s, OC$\underline{H}_3$), 3.90 (3H, s, OC$\underline{H}_3$), 3.94 (3H, s, OC$\underline{H}_3$), 5.81 (1H, d, ^3J= 8.9 Hz, H2), 6.10 (1H, dc, ^3J=6.5 Hz; ^3J=15.3 Hz, H2´), 6.38 (1H, d, ^3J=15.4 Hz, H1´), 6.85 (5H, m, Ar-$\underline{H}$).^{13}C NMR (75 MHz, $CDCl_3$), δ: 16.90 ($\underline{C}H_3$-C_3), 18.29 (CH_3, C3´), 41.47 (CH, C3), 55.81 (O$\underline{C}H_3$), 55.88 (O$\underline{C}H_3$), 56.02 (O$\underline{C}H_3$), 88.60 (CH, C2), 109.37 (CH, C6), 109.78 (CH, C2´´)*, 110.75 (CH, C4)*, 114.17 (CH, C5´´), 118.83 (CH, C6´´), 123.35 (CH, C2´), 130.26 (C, C5), 130.89 (CH, C1´), 132.19 (C, C1´´), 134.23 (C, C3a), 144.12 (C, C7a), 146.46 (C, C4´´), 148.50 (C, C3´´), 148.68 (C, C7) * may be interchanged. HRFABMS (*m*/z) calcd. for $C_{21}H_{24}O_4Na$ 363.1572 $[M+Na]^+$, found 363.1586.

trans*-2-(3,4-dimethoxyphenyl)-7-methoxy-3-methyl-5-[(*E*)-prop-1-enyl]-2,3-dihydrobenzo[*b*]furan (*trans*-acuminatin) (1-*trans*).** To a solution of **1-*cis (50 mg, 0.15 mmol) in toluene (10 mL) camphorsulfonic acid (35 mg, 0.15 mmol) was added. The reaction was refluxed for 12 hours. Then, the solvent was removed under reduce pressure, the crude was dissolved in CH_2Cl_2 (10 mL) and washed with a solution of NaOH (2M, 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated to afford **1-*trans*** (47 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.36 (3H, d, ^3J=7.0 Hz, C$\underline{H}_3$), 1.85 (3H, dd, ^3J= 6.5 Hz; ^4J= 1.6 Hz, H3´), 3.43 (1H, q, ^3J=7.0 Hz, H3), 3.86 (3H, s, OC$\underline{H}_3$), 3.90 (3H, s, OC$\underline{H}_3$), 3.92 (3H, s, OC$\underline{H}_3$), 5.10 (1H, d, ^3J= 9.2 Hz, H2), 6.08 (1H, dc, ^3J=6.6 Hz; ^3J=15.5 Hz, H2´), 6.35 (1H, d, ^3J=15.5 Hz, H1´), 6.80 (5H, m, Ar-$\underline{H}$).^{13}C NMR (75 MHz, $CDCl_3$), δ: 17.25 ($\underline{C}H_3$-C_3), 18.40 (CH_3, C3´), 45.68 (CH, C3), 54.83 (O$\underline{C}H_3$), 55.40 (O$\underline{C}H_3$), 55.77 (O$\underline{C}H_3$), 93.51 (CH, C2), 110.11 (CH, C6), 109.90 (CH, C2´´)*, 113.59 (CH, C4)*, 113.17 (CH, C5´´), 119.03 (CH, C6´´), 123.29 (CH, C2´), 134.28 (C, C5), 130.89 (CH, C1´), 132.06 (C, C1´´), 133.20 (C, C3a), 146.12 (C, C7a), 146.46 (C, C4´´), 149.10 (C, C3´´), 147.60 (C, C7) *may be interchanged.

General procedure for the asymmetric synthesis of acuminatin. A solution of **2** in dry THF (5 mL/mmol) was cooled at -80ºC and 1.5 equivalents of anhydrous KHMDS were added under nitrogen. The reaction was stirred at this temperature for 15 minutes and then another 30 minutes at room temperature. After that, the solution initially colourless, changed to yellow. Catalytic amount of PTC (10%) (*n*-Bu_4NBr or **8**) and rhodium catalyst (1-2%) were added and the mixture was heated (see table 2) during 5-7 days. Then, it was cooled to room temperature, eluted with diethyl ether and washed with brine. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduce pressure. The residue was purified by column chromatography on silica gel (hexane:Et_2O, 98:2) yielding **1** as a yellow oil (see table 2). The enantiomeric excesses were determined by chiral HPLC-UV.

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