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Enantioselective, chemoenzymatic synthesis, and absolute configuration of the antioxidant (−)-gloeosporiol

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ABSTRACT

The natural antioxidant (−)-gloeosporiol, isolated as a peracetylated derivative from a culture of the fungus *Colletotrichum gloeosporioides*, has been enantioselectively prepared from 3,4-dihydroxybenzaldehyde by means of a chemoenzymatic synthesis. The key intermediate was obtained by resolution with a lipase from *Pseudomonas cepacia*. Its stereochemistry, initially assigned as *R*, according to the Kazlaukas empirical rule for secondary alcohols, was independently confirmed by NMR and chirooptic methods. This, in turn, allowed the assignment of compound (−)-**1** as (−)-(2*S*,3*R*,4*R*)-2-(3′,4′dihydroxyphenyl)tetrahydrofuran-3,4-diol.

1. Introduction

The filamentous fungi of the *Colletotrichum* genus are considered major plant pathogens worldwide.[1] The ubiquitous *Colletotrichum gloeosporioides* (Penz.) Penz. & Sacc. (teleomorph *Glomerella cingulata*) has been the subject of a number of studies, including its use in the production of secondary metabolites.[2] As part of our research program on the rational control of phytopathogenic fungi,[3] we are interested in the relationship between the infective capabilities of certain phytopathogenic fungi and the role of their secondary metabolites in the infection mechanisms.

The 3,4-dihydroxylated, 2-(3′,4′-dihidroxyphenyl)tetrahydrofuran derivative (−)-**1**, was recently isolated from a strain of *C. gloeosporioides* and discovered to occur naturally as a single enantiomer through racemic synthesis and resolution of the enantiomeric tetrols.[4] Determination of the enantiomeric composition of a material of natural origin, is useful as there are reports of compounds produced in different enantiomeric proportions, even when obtained from different parts of the same natural source.[5]

An enantioselective synthesis of (−)-**1** would not only provide material for further testing but it would also provide the grounds for an assignment of the absolute stereochemistry of the natural product (−)-**1**.

Enzymes have become standard catalysts in organic synthesis, in order to perform regio-, stereoselective, and enantioselective transformations. Lipases in particular have received the most attention acting with high efficiency in acylation, hydrolysis, and alkoxycarbonylation processes.[6] Recently, hydrolyzes of 1-arylallyl acetates catalyzed by *Candida antartica* lipase were obtained with excellent enantioselectivities.[7] A key feature of enantioselective syntheses is their ability to determine and control the stereochemistry of the chiral materials involved. A number of methods are used to determine absolute configuration and, recently, different NMR spectroscopy based approaches to this problem have emerged.[8,9]

Herein we describe the enantioselective preparation of (−)-gloeosporiol (**1**) and consequently its absolute configuration through the enzymatic resolution of a suitable precursor and the confirmation of its absolute configuration by NMR and chiroptic methods.

2. Results and discussion

The enantioselective synthesis of (−)-(2*S*,3*R*,4*R*)-gloeosporiol (**1**), was achieved as shown in Schemes 1 and 4. The synthetic route was based on the lipases mediated sequential kinetic resolution of the aryl-vinyl acetate **3a**, to yield the enantiomerically pure key intermediate 1-arylvinyl alcohol (**3**). An O-allylation, ring-closing metathesis, dihydroxylation, and deprotection sequence would led

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to the desired enantiomerically pure natural product (−)-**1**, and, in turn, to the elucidation of its absolute stereochemistry.

The treatment of 3,4-dihydroxybenzaldehyde (**2**) with TBDMSCl and imidazole in THF,[10] rendered a protected aldehyde (**2a**). Reaction of compound **2a** with vinyl bromide and magnesium turnings, in THF,[11] yielded 1-[(3′,4′-bis-(*tert*-butyldimethylsilyloxy) phenyl)]prop-2-en-1-ol ((±)-**3**), which can be transformed into the corresponding acetate (±)-**3a**.

The asymmetric synthesis of complex molecules has successfully employed enantiomerically-enriched allylic alcohols and allylic acetates as chiral intermediates.[12] One way of preparing these intermediates is by enantioselective acylation[13] of secondary alcohols or the enantioselective hydrolysis[14] of the corresponding esters employing either enzymatic or non-enzymatic methods. Nevertheless, kinetic resolution of 1-arylallyl alcohols has proven to be challenging[15] and only recently over 99% ee have been described,[7a,b] employing an immobilized *Candida antarctica* lipase.

Lipase mediated kinetic resolution of (±)-**3a** was studied using *Pseudomonas cepacia* lipase (PS lipase or PSL) (Scheme 1). *Pseudomonas fluorescens* lipase (AK lipase) and *Candida rugosa* lipase (CRL) where also considered initially but they failed to react under the evaluated conditions. Selected results obtained with PSL are summarized in Table 1. Enantiomeric excess (ee) was measured by HPLC fitted with a chiral column for enantiomerically enriched alcohol (+)-(*R*)-**3**, while enantiomeric excess for residual acetate (−)-(*S*)-**3a** was measured by GC or GC/MS fitted with a capillary chiral column.

The effect of temperature and time on the enantiomeric excess and yield for both alcohol (+)-(*R*)-**3** and residual acetate (−)-(*S*)-**3a** were evaluated (Table 1). An increase in the temperature disfavors both enantiomeric excess and alcohol yield (+)-(*R*)-**3**, while an optimized time was found for enantiomeric excess (>99%) (Table 1, entry c), which was close to the optimized time for yield (Table 1, entry d). Optimum reaction conditions for enantiomeric excess were employed for further preparative uses, rendering (+)-(*R*)-**3** at a yield of 31% yield and >99% ee; these conditions gave rise to recovered acetate (−)-(*S*)-**3a** at a 50% yield and 96% ee (Table 1, entry c).

Table 1
Kinetic enzymatic resolution of acetate (±)-**3a** by *P. cepacia* lipase (Scheme 1)

Entry	*t* (°C)	*t* (h)	*E*[a]	(−)-(*S*)-**3a**		(+)-(*R*)-**3**	
				(%)[b]	ee(%)[c]	(%)[b]	ee(%)[d]
a	48	3	28	77	4	7	93
b	37	2	32	75	2	17	94
c	25	7	>200	50	96	31	>99
d	25	6	194	53	65	34	98

[a] Calculated from $E=\ln[1-c(1+\mathrm{ee}((+)\text{-}(R)\text{-}\mathbf{3}))]/\ln[1-c(1-\mathrm{ee}((+)\text{-}(R)\text{-}\mathbf{3}))]$, where $c=\mathrm{ee}((-)\text{-}(S)\text{-}3a)/(\mathrm{ee}((-)\text{-}(S)\text{-}\mathbf{3a})+\mathrm{ee}((+)\text{-}(R)\text{-}\mathbf{3}))$.
[b] Isolated yields, following alumina column chromatography.
[c] Enantiomeric excess calculated by chiral GC.
[d] Enantiomeric excess calculated by chiral HPLC.

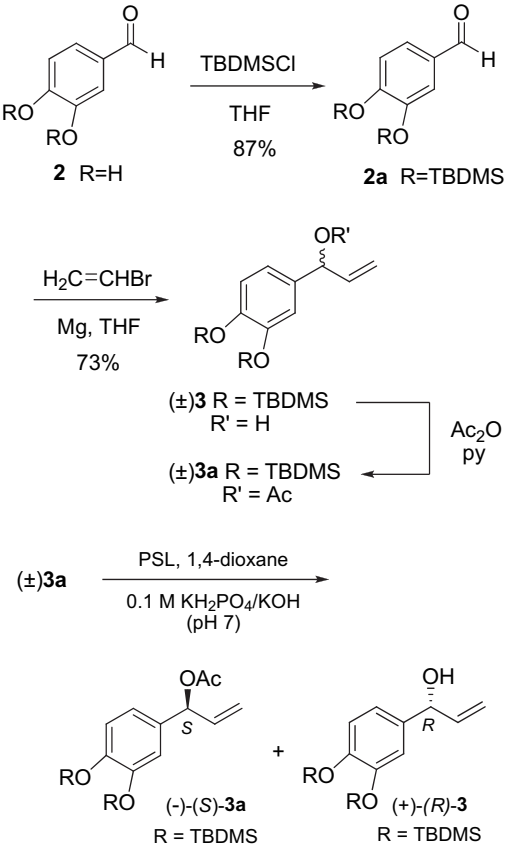
In accordance with the Kazlaukas empirical rule for secondary alcohols,[16] resolved alcohol should be assigned as (+)-(*R*)-**3**. To confirm this assignment, we carried out a variable temperature NMR study of methoxyphenylacetic acid (MPA) derivatives of alcohol (+)-(*R*)-**3**. A survey of the literature produced no examples of assignation of the variable temperature NMR-CDA technique used for the assignment of the absolute stereochemistry of 1-arylallyl alcohols.[9] We therefore carried out a preliminary model study with 1-phenylallyl alcohols of known absolute configuration.

(+)-(*R*)- and (−)-(*S*)-1-Phenylprop-2-en-1-ol (**7**) obtained from commercial sources were independently treated with (*R*)- and (*S*)-MPA, to yield all four possible diastereomers ((+)- and (−)-**8**, (+)- and (−)-**9**) (Scheme 2). The ^{1}H NMR of each of these diastereomeric esters was recorded at 25 °C and −60 °C using TMS as the internal reference for chemical shifts. Differences in chemical shifts ($\Delta\delta^{T1T2}$) between the highest temperature (T_1=25 °C) and the lowest one (T_2=−60 °C) for the proton signals of the groups attached to the chiral center of the alcoholic moiety were recorded as shown in Scheme 2.

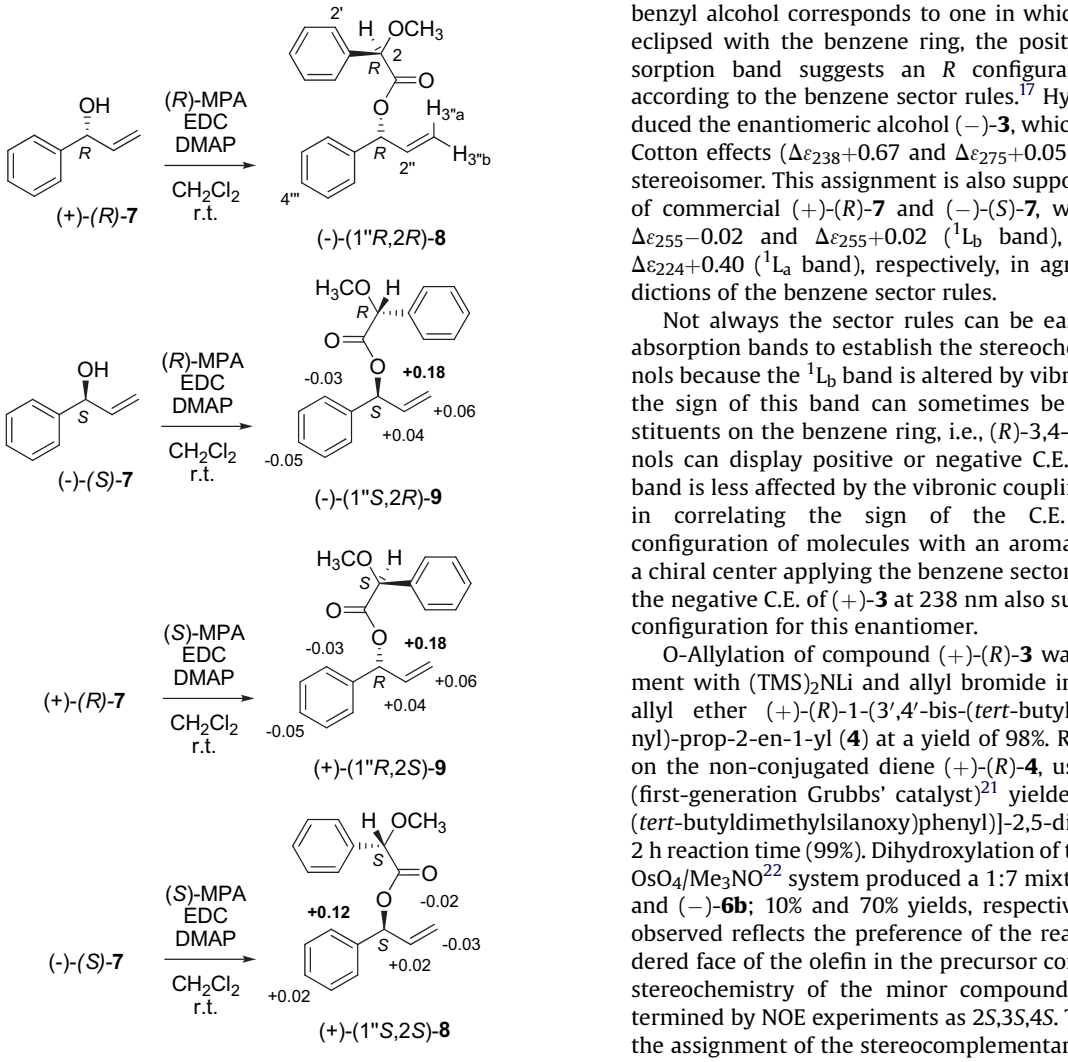
From the data obtained, it can be deduced that, on one hand H-2‴ and H-4‴, protons from the aromatic ring attached to the chiral center on the alcohol (L_1), and on the other hand, H-3″cis and H-3″trans, protons from the methylenic portion of the double bond attached to the chiral center (L_2), undergo observable chemical shift variations consistent with Riguera's rule.[9] H-2″, the most deshielded proton of the ABX spin system and the one from the methynic portion of the double bond attached to the chiral center, does not consistently follows the rule. Probably, in the most stable conformation at each temperature, this proton is too far away to be influenced by shielding of the chiral acidic moiety.

Compound (+)-**3** was independently treated with (*R*)- and (*S*)-MPA, to yield one diastereoisomer in each instance (compounds **10** and **11**). The ^{1}H NMR of each of these diastereomeric esters was recorded at 25 °C and −60 °C, using a TMS as the internal reference for chemical shifts. Differences in chemical shifts ($\Delta\delta^{T1T2}$) between the highest temperature (T_1=25 °C) and the lowest one (T_2=−60 °C) for proton signals of groups attached to the chiral center of the alcoholic moiety were recorded as shown in Scheme 3.

Once each proton of the product was identified, through mono- and bidimensional NMR spectra, comparison of high and low temperature spectra shows changes in chemical shifts, which are consistent with those observed for (*R*)- and (*S*)-MPA esters of (+)-(*R*)-1-phenylprop-2-en-1-ol. Therefore, the structural assignment for compound **3** can be confirmed as (+)-(*R*)-1-(3,4-bis(*tert*-butyldimethylsilyloxi)phenyl)prop-2-en-1-ol, as predicted by the Kazlaukas empirical rule.[16]



Scheme 1. Preparation and kinetic enzymatic resolution of acetate (±)-**3a** by *P. cepacia* lipase (for details see Table 1).

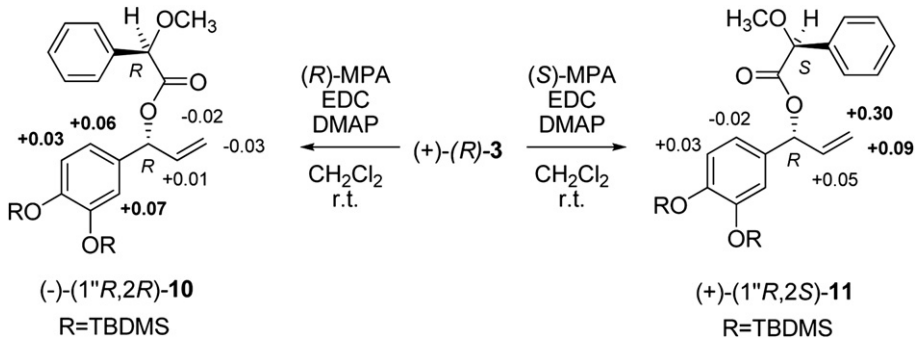


Scheme 2. Preparation of (*R*) and (*S*) methoxyphenylacetic acid (MPA) esters of enantiomers of (+)-(*R*)- and (−)-(*S*) 1-phenylprop-2-en-1-ol. Selected atom numbering is shown for compound (−)-(1″*R*,2*R*)-**8**. Differences in chemical shifts, $\Delta\delta^{T1T2}$ (T_1=25 °C, T_2=−60 °C) are shown for selected protons in compounds (−)-(1″*S*,2*R*)-**9**, (+)-(1″*R*,2*S*)-**9**, and (+)-(1″*S*,2*S*)-**8**.

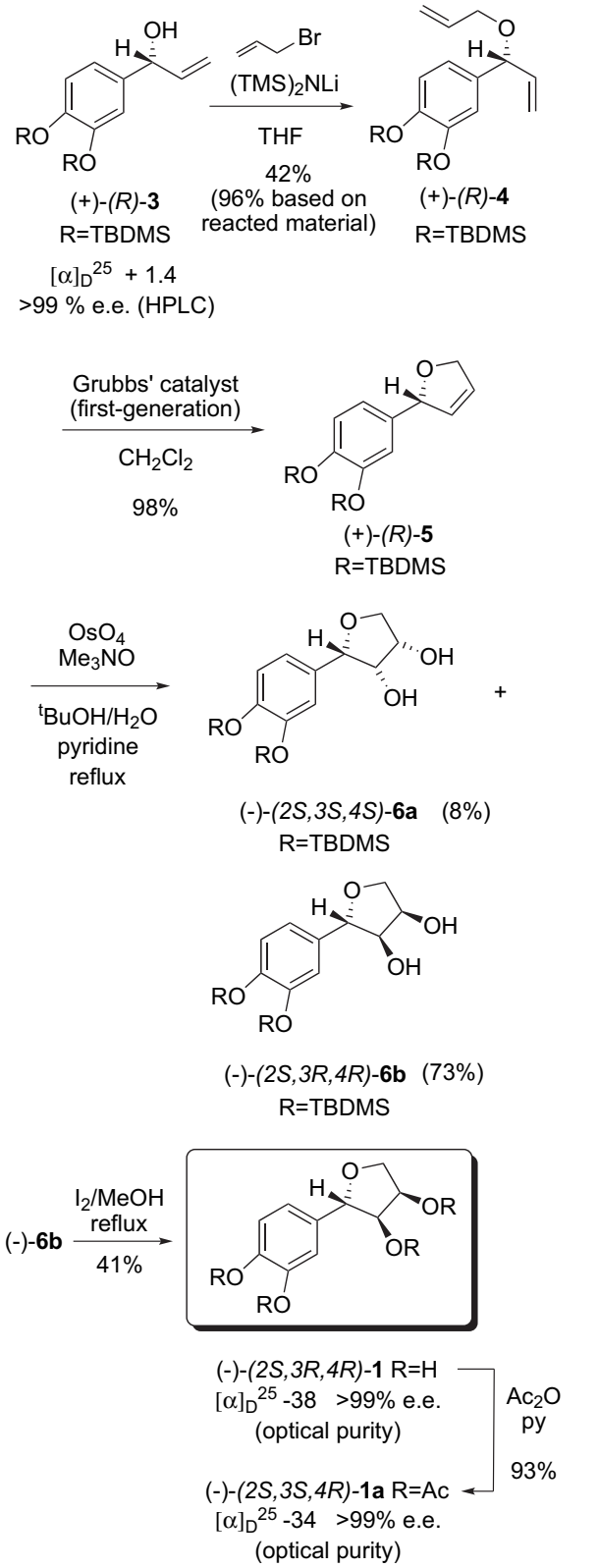
The proposed absolute configuration for **3** was also confirmed by circular dichroism. The CD curve of the (+)-**3** enantiomer displayed two negative Cotton effects (C.E.) at 238 nm ($\Delta\varepsilon$−0.56) and 275 nm ($\Delta\varepsilon$−0.04) associated with the ^1L_b and ^1L_a absorption bands, respectively. Assuming that the preferred conformation of the benzyl alcohol corresponds to one in which the proton is nearly eclipsed with the benzene ring, the positive C.E. of the ^1L_b absorption band suggests an *R* configuration for the carbinol according to the benzene sector rules.[17] Hydrolysis of (−)-**3a** produced the enantiomeric alcohol (−)-**3**, which displays two positive Cotton effects ($\Delta\varepsilon_{238}$+0.67 and $\Delta\varepsilon_{275}$+0.05) as expected for the *S* stereoisomer. This assignment is also supported by the CD spectra of commercial (+)-(*R*)-**7** and (−)-(*S*)-**7**, which displayed C.E. at $\Delta\varepsilon_{255}$−0.02 and $\Delta\varepsilon_{255}$+0.02 (^1L_b band), and $\Delta\varepsilon_{224}$−0.50 and $\Delta\varepsilon_{224}$+0.40 (^1L_a band), respectively, in agreement with the predictions of the benzene sector rules.

Not always the sector rules can be easily applied to the ^1L_b absorption bands to establish the stereochemistry of chiral carbinols because the ^1L_b band is altered by vibrational transitions and the sign of this band can sometimes be reversed by the substituents on the benzene ring, i.e., (*R*)-3,4-dialkoxy phenyl carbinols can display positive or negative C.E.[18] Fortunately, the ^1L_a band is less affected by the vibronic coupling and is more reliable in correlating the sign of the C.E. with the absolute configuration of molecules with an aromatic ring contiguous to a chiral center applying the benzene sector rules.[19] Consequently, the negative C.E. of (+)-**3** at 238 nm also supports the proposed *R* configuration for this enantiomer.

O-Allylation of compound (+)-(*R*)-**3** was carried out by treatment with $(TMS)_2NLi$ and allyl bromide in THF,[20] producing the allyl ether (+)-(*R*)-1-(3′,4′-bis-(*tert*-butyldimethylsilanoxy)phenyl)-prop-2-en-1-yl (**4**) at a yield of 98%. Ring-closing metathesis on the non-conjugated diene (+)-(*R*)-**4**, using $(PCy_3)_2Cl_2RuCHPh$ (first-generation Grubbs' catalyst)[21] yielded (+)-(*R*)-2-[(3′,4′-bis-(*tert*-butyldimethylsilanoxy)phenyl)]-2,5-dihydrofuran (**5**) after 2 h reaction time (99%). Dihydroxylation of the compound with the OsO_4/Me_3NO[22] system produced a 1:7 mixture of *syn*-diols (−)-**6a** and (−)-**6b**; 10% and 70% yields, respectively. The product ratio observed reflects the preference of the reagent for the least hindered face of the olefin in the precursor compound (+)-(*R*)-**5**. The stereochemistry of the minor compound (−)-**6a** could be determined by NOE experiments as 2*S*,3*S*,4*S*. This, in turn, permitted the assignment of the stereocomplementary compound (−)-**6b** as 2*S*,3*R*,4*R*. Treatment of the major diastereoisomer (−)-(2*S*,3*R*,4*R*)-2-[(3′,4′-bis-(*tert*-butyldimethylsilanoxy)phenyl)]tetrahydrofuran-3,4-diol (**6b**) with I_2/MeOH[23] yielded led to (−)-(2*S*,3*R*,4*R*)-gloeosporiol (**1**), with an enantiomeric excess >99% (optical purity).[24] As shown in Scheme 4, the entire synthesis took place with no loss of enantiomeric purity. Peracetylation of (−)-**1** with Py/Ac_2O yielded (−)-(2*S*,3*S*,4*R*)-2-(3′,4′-diacetoxyphenyl)-3,4-diacetoxytetrahydrofuran (**1a**), which presented physical and spectroscopic data consistent with those observed for the sample obtained by chemical resolution from (±)-**6a**[24] and the isolated tetracetate from the culture of *C. gloeosporioides*.[4]



Scheme 3. Preparation of (*R*)- and (*S*)-MPA esters of (+)-(*R*)-1-(3,4-bis(*tert*-butyldimethylsilyloxi)phenyl)prop-2-en-1-ol (compounds (−)-(1″*R*,2*R*)-**10** and (+)-(1″*R*,2*S*)-**11**). Differences in chemical shifts, $\Delta\delta^{T1T2}$ (T_1=25 °C, T_2=−60 °C) are shown for selected protons in compounds (−)-(1″*R*,2*R*)-**10** and (+)-(1″*R*,2*S*)-**11**).



Scheme 4. Enantioselective preparation of (−)-(2*S*,3*R*,4*R*)-gloeosporiol (**1**) from (+)-(*R*)-**3**.

3. Conclusion

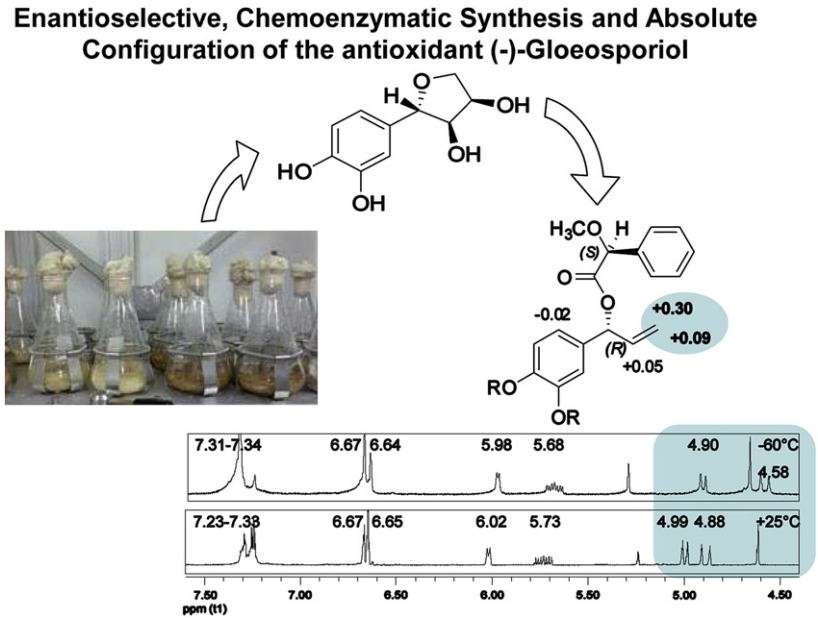
We have achieved enantioselective chemoenzymatic synthesis of the antioxidant (−)-gloeosporiol (**1**). Based on the study of the model compounds, (+)-(*R*)- and (−)-(*S*)-1-phenylprop-2-en-1-ol (**7**), using NMR techniques and chirooptic methods, the stereochemistry of the key intermediate (+)-**3** was unequivocally determined. This, in turn, permitted the assignment of compound (−)-**1** as (−)-(2*S*,3*R*,4*R*)-2-(3′,4′dihydroxyphenyl)tetrahydrofuran-3,4-diol.

4. Experimental

4.1. General experimental procedures

Melting points were measured with a Reichert-Jung Kofler block and are uncorrected. Optical rotations were determined with a Perkin–Elmer 341 polarimeter. IR spectra were recorded on a Perkin–Elmer Spectrum BX FT-IR spectrophotometer. UV spectra were recorded on a UV–vis Varian Cary 50. ^{1}H- and ^{13}C NMR measurements were obtained on Varian INOVA 400 NMR spectrometer with $SiMe_4$ as an internal reference. NMR assignments were made by a combination of 1D and 2D techniques. Multiplicities are described using the following abbreviations: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. In ^{13}C NMR the multiplicities refer to the resonances in the off-resonance spectra and they were elucidated using the distortionless enhancement by polarization transfer (DEPT) spectral editing technique, with secondary pulses at 90° and 135°. Mass spectra were recorded on a Finnigan Voyager mass spectrometer at 70 eV. ESI-MS spectra were recorded on a THERMO- Finnigan LCQ mass spectrometer (4.6 kV, 25 V, 220 °C, N_2). High resolution mass spectra were recorded on a Finnigan MAT95S spectrometer. Purification by semi-preparative HPLC was performed with a Hitachi/Merck L-6270 apparatus equipped with a UV–vis detector (L 4250) and a differential refractometer detector (RI-71). Analytical HPLC was performed with a Elite LaChrom-Hitachi L-2130 apparatus equipped with a UV detector (L-2400). CD spectra were recorded on a Jobin-Ybon MarkIII Dichrograph in ethanol as solvent. Enantiomeric excess determination was accomplished either by HPLC using a Chiracel OD column, Daicel Japan, or by GC using a CycloSil-B column, Agilent J&W, USA; ee were calculated by comparing the area of each peak. TLC was performed on Merck Kiesegel 60 F_{254}, 0.2 mm thick. Silica gel (Merck) was used for column chromatography. For column chromatography, Merck silica gel 60 (0.040–0.063 mm) was used. Dried solvents were obtained from PureSolv® equipment and other materials were obtained from commercial supplies and used without further purification. Petroleum ether refers to the fraction boiling in the range of 60–80 °C. PSL enzyme was obtained from Amano Enzyme, Inc.; PPL and CRL enzymes were obtained from Sigma–Aldrich Co and all of them were used as received.

*4.1.1. 3′,4′-Bis-(tert-butyldimethylsilanoxy)benzaldehyde (**2a**).* A solution of TBDMSCl (14.9 g, 72.4 mmol) in dry THF (20 mL), was added dropwise to a stirred solution of 3,4-dihydroxybenzaldehyde (**2**) (5 g, 36.2 mmol) and imidazol (9.9 g, 144.8 mmol) in dry THF (100 mL), under argon. Stirring is maintained for 48 h and then water (50 mL) and Et_2O (50 mL) were added. The aqueous layer was separated and extracted with Et_2O (2×50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (petroleum ether/ethyl acetate, 95:5) afforded a white solid **2a** (11.5 g, 87%): mp 39–41 °C; ^{1}H NMR (400 MHz, C_6D_6): δ (ppm) 0.13 (s, 12H, 2(−Si(CH_3)$_2$)), 0.98 (s, 18H, 2(−SiC(CH_3)$_3$)), 6.77 (d, *J*=8.2 Hz, 1H, H-5′), 7.11 (dd, *J*=1.6, 8.2 Hz, 1H, H-6′), 7.56 (d, *J*=1.6 Hz, 1H, H-2′), 9.66 (s, 1H, H-1); ^{13}C NMR (100 MHz, C_6D_6): δ (ppm) −4.14 (q, 4C, 2(−Si(CH_3)$_2$)), 18.6 (s, 2C, 2(−SiC(CH$_3$)$_3$)), 25.9 (q, 6C, 2(-SiC(CH_3)$_3$)), 120.6 (d, C-2′), 121.2 (d, C-5′), 125.3 (d, C-6′), 131.8 (s, C-1′), 148.0 (s, C-4′), 153.0 (s, C-3′), 189.7 (d, C-1); selected HMBC correlations: C-1′→H-5′; C-3′→H-2′, H-5′; C-4′→H-2′, H-5′;



IR (neat) ν (cm^{-1}) 1698, 1592, 1256, 841; EIMS *m*/*z* (rel int.): 366 $[M]^{+\cdot}$ (0.58), 309 (59), 253 (12), 195 (21), 193 (15), 179 (15), 73 (100); HREIMS: *m*/*z* calcd for $C_{19}H_{34}O_3Si_2$=366.2046; found 366.1993.

*4.1.2. (±)-(1S(R))-1-[(3′,4′-Bis-(tert-butyldimethylsilanoxy)phenyl)] prop-2-en-1-ol ((±)-**3**).* A solution of vinyl bromide (24.3 mL, 24.3 mmol, 1 M solution) and compound **2a** (2.97 g, 8.10 mmol) was added dropwise to a magnetically stirred suspension of magnesium turnings (602.9 mg, 24.3 mmol) in THF (1 mL), under argon. The magnesium had previously been activated by adding a few crystals of iodine and then stirring under a protective atmosphere for 12 h. After 0.5 h, the reaction was quenched by carefully adding a saturated solution of NH_4Cl in water (20 mL) followed by Et_2O (50 mL). The aqueous and organic layers were separated and the aqueous layer then extracted with Et_2O (2×50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Flash chromatography using a gradient of solvents from petroleum ether to petroleum ether/ethyl acetate (96:4) yielded compound (±)-**3** as a yellow oil (2337 mg, 73%); ^{1}H NMR (400 MHz, C_6D_6): δ (ppm) 0.20 (s, 12H, 2(−Si(C*H*$_3$)$_2$)), 1.04 (s, 18H, 2(−SiC(C*H*$_3$)$_3$)), 1.46 (br s, 1H, OH), 4.88 (dd, *J*=1.6, 4.4 Hz, 1H, H-1), 4.97 (ddd, *J*=1.6, 1.6, 10.4 Hz, 1H, H-3b), 5.21 (ddd, *J*=1.6, 1.6, 17.1 Hz, 1H, H-3a), 5.91 (ddd, *J*=4.4, 10.4, 17.1 Hz, 1H, H-2), 6.81 (dd, *J*=1.7, 8.1 Hz, 1H, H-6′), 6.87 (d, *J*=8.1 Hz, 1H, H-5′), 7.07 (d, *J*=1.7 Hz, 1H, H-2′); ^{13}C NMR (100 MHz, C_6D_6): δ (ppm) −4.00 (q, 2C, (−Si(*C*H$_3$)$_2$)*), −3.99 (q, 2C, (−Si(*C*H$_3$)$_2$)*), 18.62 (s, (−SiC(CH$_3$)$_3$)†), 18.64 (s, (−SiC(CH$_3$)$_3$)†), 26.12 (q, 3C, (−SiC(*C*H$_3$)$_3$)‡), 26.14 (q, 3C, (−SiC(*C*H$_3$)$_3$)‡), 74.7 (d, C-1), 114.0 (t, C-3), 119.9 (d, C-2′$^{\#}$), 120.0 (d, C-5′$^{\#}$), 121.3 (d, C-6′), 137.1 (s, C-1′), 141.3 (d, C-2), 146,6 (s, C-3′), 147.3 (s, C-4′). $^{*\dagger\ddagger\#}$Interchangeable signals; selected HMBC correlations: C-1′→H-1; C-3′→H-2′; IR (neat) ν (cm^{-1}) 3350, 1574, 1508, 1254, 835, 780; EIMS *m*/*z* (rel int.) 394 $[M]^{+\cdot}$ (4), 337 (12), 247 (7), 205 (100), 73 (90); HREIMS: *m*/*z* calcd for $C_{21}H_{38}O_3Si_2$=394.2359; found 394.2355.

*4.1.3. (±)-1-[(3′,4′-Bis-(tert-butyldimethylsilanoxy)phenyl)]-prop-2-en-1-yl acetate ((±)-**3a**).* Acetic anhydride (210.3 mg, 2.06 mmol) was added dropwise to a stirred solution of compound (±)-**3** (135.0 mg, 0.34 mmol) in dry pyridine (1 mL). After 24 h the reaction mixture was diluted with EtOAc (50 mL) and washed sequentially with 2 N HCl (2×50 mL), a diluted solution of $CuSO_4$ (2×50 mL) and brine (50 mL), then dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure, to yield compound (±)-**3a** (129.0 mg, 87%). Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.18 (s, 12H, 2(−Si(C*H*$_3$)$_2$)), 0.97 (s, 18H, 2(−SiC(C*H*$_3$)$_3$)), 2.08 (s, 3H, OCOC*H*$_3$), 5.21 (dd, *J*=1.4, 10.3 Hz, 1H, H-3b), 5.23 (dd, *J*=1.4, 16.9 Hz, 1H, H-3a), 5.96 (ddd, *J*=5.8, 10.3, 16.9 Hz, 1H, H-2), 6.15 (d, *J*=5.8 Hz, 1H, H-1), 6.78–6.81 (m, 3H, H-2′, H-5′, H-6′); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) −4.1 (q, 4C, 2(−Si(*C*H$_3$)$_2$)), 18.4 (s, 2C, 2(−Si*C*(CH$_3$)$_3$)), 21.3 (q, OCO*C*H$_3$), 25.9 (q, 6C, 2(−SiC(*C*H$_3$)$_3$)), 75.7 (d, C-1), 116.4 (t, C-3), 120.2 (d, C-2′*), 120.4 (d, C-5′*), 120.8 (d, C-6′*), 131.8 (s, C-1′), 136.5 (d, C-2), 146,8 (s, 2C, C-3′, C-4′), 170.0 (s, O*C*OCH$_3$). *Interchangeable signals; selected HMBC correlations: C-1′→H-5′, H-1, H-2; C-3′, C-4′→H-2′, H-5′, H-6′; IR (neat) ν (cm^{-1}) 2936, 1768, 1747, 1574, 1508, 1254, 1231, 835, 780; EIMS *m*/*z* (rel int.): 436 $[M]^{+\cdot}$ (2), 379 (5), 247 (6), 205 (100), 73 (72).

*4.1.4. (+)-(R)-1-[(3′,4′-Bis-(tert-butyldimethylsilanoxy)phenyl)]-prop-2-en-1-ol ((+)-(R)-**3**) and (−)-(S)-1-[(3′,4′-bis-(tert-butyldimethylsilanoxy)phenyl)]-prop-2-en-1-yl acetate ((−)-(S)-**3a**): optimization procedure[6b,c].* In a typical procedure, PSL (*P. cepacia* lipase, 677 mg) was added to a solution of (±)-**3a** (128 mg, 0.29 mmol) in 1,4-dioxane (1.9 mL) and pH 7 buffer (0.1 M KH_2PO_4/KOH, 9.4 mL). The suspension was shaken at 25 °C, and the progress of the reaction was followed by TLC (petroleum ether/ethyl acetate 90:10). Then, after removal of the enzyme by filtration, the reaction crude was extracted with ethyl acetate (3×15 mL). The organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, and the solvent removed under reduced pressure. Further purification of the residue by column chromatography over neutral alumina (petroleum ether/ethyl acetate, 95:5) afforded alcohol (+)-(*R*)-**3** (35 mg, 31% yield, >99% ee); $[\alpha]_D^{25}$ +1.4 (*c* 0.4, $CHCl_3$); C.D. (ethanol): $\Delta\varepsilon_{238}$−0.56; $\Delta\varepsilon_{275}$−0.04 and residual acetate (−)-(*S*)-**3a** (63 mg, 50% yield, 96% ee); $[\alpha]_D^{25}$ −1.8 (*c* 0.4, $CHCl_3$). Chiral HPLC for compound **3** (Chiracel OD petroleum ether/2-propanol (99.9:0.1), 0.500 mL min^{-1}) t_R=52 min ((−)-(*S*)-**3**), t_R=55 min ((+)-(*R*)-**3**). Chiral GC for compound **3a** (Agilent J&W CycloSil-B column, oven 160 °C isothermal) t_R=145 min ((*S*)-**3a**), t_R=150 min ((*R*)-**3a**).

Relationships between reaction temperature and reaction times with yields and enantiomeric excess are shown in Table 1.

*4.1.5. (−)-(S)-1-[(3′,4′-Bis-(tert-butyldimethylsilanoxy)phenyl)]-prop-2-en-1-ol ((−)-(S)-**3**).* A solution of KOH (11.5 mg, 0.2 mmol) in H_2O (3 mL) was added to a stirred solution of compound (−)-(*S*)-

3a (45 mg, 0.1 mmol) in MeOH (11.5 mL). The solution was shaken at 25 °C for 5 h. The reaction crude was neutralized with HCl 2 N, and solvent was removed under reduced pressure. The resulting crude was suspended in water (15 mL) and then extracted with ethyl acetate (3×15 mL). The organic layer was washed with brine (30 mL), dried over anhydrous Na_2SO_4, and solvent removed under reduced pressure. Further purification of the residue by column chromatography over neutral alumina (petroleum ether/ethyl acetate, 95:5) afforded alcohol (−)-(*S*)-**3** (12 mg, 29% yield, 96% ee); $[\alpha]_D^{25}$ −1.3 (*c* 0.8, EtOH); C.D. (ethanol): $\Delta\varepsilon_{238}$+0.67; $\Delta\varepsilon_{275}$+0.05.

*4.1.6. (+)-(R)-1-[(3′,4′-Bis-(tert-butyldimethylsilanoxy)phenyl)] prop-2-en-1-yl allyl ether ((+)-(R)-**4**).* A solution of LiHMDS in THF (0.81 mL, 1 M, 0.81 mmol) was added dropwise to a stirred solution of compound (+)-(*R*)-**3** (290 mg, 0.74 mmol) in dry THF (5 mL), kept under argon and at 0 °C. The resulting solution was stirred for 15 min and then allyl bromide (97 mg, 0.81 mmol) was added dropwise. The reaction was then heated to reflux for 12 h, cooled and a saturated solution of NH_4Cl in water (20 mL) was carefully poured onto the reaction mixture and then ethyl acetate (50 mL) was added. The aqueous and organic layers were separated and the aqueous layer was then extracted with ethyl acetate (2×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. Flash chromatography (petroleum ether/ethyl acetate, 97:3) allowed the recovery of 164 mg of starting material (+)-(*R*)-**3** and afforded compound (+)-(*R*)-**4** as a yellow oil (134 mg, 42%, 96% based on reacted material): $[\alpha]_D^{25}$ +20 (*c* 1, MeOH); ^{1}H NMR (400 MHz, C_6D_6): *δ* (ppm) 0.17 (s, 6H, (−Si(CH_3)$_2$)*), 0.22 (s, 6H, (−Si(CH_3)$_2$)*), 1.03 (s, 9H, (−SiC(CH_3)$_3$)†), 1.04 (s, 9H, (−SiC(CH_3)$_3$)†), 3.88 (m, 2H, H-4a, H-4b), 4.64 (m, 1H, H-1), 5.03 (ddd, *J*=1.6, 1.6, 9.6 Hz, 1H, H-3b), 5.05 (tdd, *J*=1.6, 1.6, 9.4 Hz, 1H, H-6b), 5.25 (ddd, *J*=1.6, 1.6, 17.3 Hz, 1H, H-3a), 5.30 (tdd, *J*=1.6, 1.6, 17.2 Hz, 1H, H-6a), 5.88 (m, 1H, H-5), 5.93 (m, 1H, H-2), 6.86 (dd, *J*=1.6, 8.2 Hz, 1H, H-6′), 6.89 (d, *J*=8.2 Hz, 1H, H-5′), 7.15 (d, *J*=1.6 Hz, 1H, H-2′). *†Interchangeable signals; ^{13}C NMR (100 MHz, C_6D_6): *δ* (ppm) −4.0 (q, 4C, 2(−Si(CH_3)$_2$)), 18.6 (s, (−SiC(CH$_3$)$_3$)*), 18.7 (s, (−SiC(CH$_3$)$_3$)*), 26.09 (q, 3C, (−SiC(CH_3)$_3$)†), 26.14 (q, 3C, (−SiC(CH_3)$_3$)†), 69.1 (t, C-4), 81.9 (d, C-1), 115.3 (t, C-3), 115.8 (t, C-6), 120.2 (d, C-2′), 120.7 (d, C-6′), 121.3 (d, C-5′), 135.1 (s, C-1′), 135.5 (d, C-5), 139.9 (d, C-2), 146.7 (s, C-3′‡), 147.4 (s, C-4′‡). *†‡Interchangeable signals; selected HMBC correlations: C-1′→H-6′, H-2, H-1; IR (neat) *ν* (cm^{-1}) 1509, 1255, 840, 781; EIMS *m*/*z* (rel int.): 434 [M]$^+$· (5), 377 (20), 247 (9), 205 (92), 73 (100); HREIMS *m*/*z* calcd for $C_{24}H_{42}O_3Si_2$ 434.2673; found 434.2675.

*4.1.7. (+)-(R)-2-[(3′,4′-Bis-(tert-butyldimethylsilanoxy)phenyl)]-2,5-dihydrofuran ((+)-(R)-**5**).* $(PCy_3)_2Cl_2RuCHPh$ (30 mg, 0.04 mmol) was added to a degassed and stirred solution of compound (+)-(*R*)-**4** (79 mg, 0.2 mmol) in dry CH_2Cl_2 (5 mL) under argon and at 25 °C. The reaction mixture was heated to reflux for 2 h and then the solvent was evaporated under reduced pressure and the crude reaction mixture was immediately purified by flash chromatography (petroleum ether/EtOAc, 98:2) to afford compound (+)-(*R*)-**5** as a yellow oil (27 mg, 98%): $[\alpha]_D^{25}$ +41 (*c* 1.4, MeOH); ^{1}H NMR (400 MHz, C_6D_6): *δ* (ppm) 0.17 (s, 6H, (−SiC(CH_3)$_2$)*), 0.20 (s, 6H, (−SiC(CH_3)$_2$)*), 1.03 (s, 9H, (−SiCC(CH_3)$_3$)†), 1.04 (s, 9H, (−SiCC(CH_3)$_3$)†), 4.53 (dddd, *J*=1.6, 2.4, 4.0, 12.8 Hz, 1H, H-5a), 4.64 (dddd, *J*=1.6, 2.4, 6.0, 12.8 Hz, 1H, H-5b), 5.50 (m, 1H, H-3), 5.58 (m, 1H, H-4), 5.71 (m, 1H, H-2), 6.79 (dd, *J*=2.2, 8.2 Hz, 1H, H-6′), 6.87 (d, *J*=8.2 Hz, 1H, H-5′), 7.04 (d, *J*=2.2 Hz, 1H, H-2′). *†Interchangeable signals; ^{13}C NMR (100 MHz, C_6D_6): *δ* (ppm) −4.02 (q, 2C, (−SiC(CH_3)$_2$)*), −3.95 (q, 2C, (−SiC(CH_3)$_2$)*), 18.61 (s, (−SiC(CH$_3$)$_3$)†), 18.64 (s, (−SiC(CH$_3$)$_3$)†), 26.12 (q, 3C, (−SiC(CH_3)$_3$)‡), 26.16 (q, 3C, (−SiC(CH_3)$_3$)‡), 75.6 (t, C-5), 87.7 (d, C-2), 119.95 (d, C-2′), 120.03 (d, C-6′), 121.4 (d, C-5′), 126.6 (d, C-3), 130.6 (d, C-4), 136.6 (s, C-1′), 146.7 (s, C-4′), 147.3 (s, C-3′). *†‡Interchangeable signals; selected HMBC correlations: C-1′→H-5′, H-2′, H-5a or H-5b; C-4′→H-5′, H-6′; C-3′→H-2′; IR (neat) *ν* (cm^{-1}) 1509, 1255, 840, 781; EIMS *m*/*z* (rel int.): 406 [M]$^+$· (1), 217 (95), 115 (6), 73 (100); HREIMS: *m*/*z* calcd for $C_{22}H_{38}O_3Si_2$=406.2359; found 406.2372.

*4.1.8. (−)-(2S,3S,4S)-2-[(3′,4′-Bis-(tert-butyldimethylsilanoxy)phenyl)] tetrahydrofuran-3,4-diol ((−)-(2S,3S,4S)-**6a**) and (−)-(2S,3R,4R)-2-[(3′,4′-bis-(tert-butyldimethylsilanoxy)phenyl)]tetrahydro-furan-3,4-diol ((−)-(2S,3R,4R)-**6b**).* Trimethylamine *N*-oxide dihydrate (8 mg, 0.07 mmol), pyridine (0.01 mL), and water (0.2 mL) were added to a solution of compound (+)-(*R*)-**5** (20 mg, 0.05 mmol) in *t*-BuOH (2 mL) and stirred at 25 °C. A 2.5% w/w solution of OsO_4 in *t*-BuOH (0.2 mL, 0.02 mmol) was added dropwise and the reaction was heated to reflux for 24 h. The reaction mixture was then cooled to room temperature, sodium bisulfite (20 mL, 20% w/v) was added and the reaction mixture was stirred for a further 1 h. Most of the butanol and water were removed under reduced pressure and the residue was then extracted into Et_2O (3×30 mL). The combined organic layers were washed with brine (1×30 mL), dried over anhydrous Na_2SO_4, and solvent evaporated under reduced pressure. Flash chromatography ($CHCl_3$) afforded a white solid (−)-(2*S*,3*S*,4*S*)-**6a** (2 mg, 8%) and a colorless oil (−)-(2*S*,3*R*,4*R*)-**6b** (16 mg, 73%).

*4.1.9. (−)-(2S,3S,4S)-2-[(3′,4′-Bis-(tert-butyldimethylsilanoxy)phenyl)]tetrahydro-furan-3,4-diol ((−)-(2S,3S,4S)-**6a**).* Mp 105–113 °C; $[\alpha]_D^{25}$ −6 (*c* 0.2, MeOH); ^{1}H NMR (400 MHz, CD_3OD): *δ* (ppm) 0.18 (s, 6H, (−Si(CH_3)$_2$)*), 0.20 (s, 6H, (−Si(CH_3)$_2$)*), 0.98 (s, 9H, (−SiC(CH_3)$_3$)†), 0.99 (s, 9H, (−SiC(CH_3)$_3$)†), 3.82 (m, 1H, H-5a‡), 3.85 (m, 1H, H-3), 4.21 (m, 1H, H-4), 4.25 (m, 1H, H-5b‡), 4.54 (d, *J*=7.6 Hz, 1H, H-2), 6.82 (d, *J*=8.4 Hz, 1H, H-5′), 6.86 (dd, *J*=2.0, 8.4 Hz, 1H, H-6′), 6.89 (d, *J*=2.0 Hz, 1H, H-2′). *†‡Interchangeable signals; selected NOESY correlations: H-2→H-3; H-3→H-2, H-4; H-4→H-3, H-5a, H-5b; ^{13}C NMR (100 MHz, CD_3OD): *δ* (ppm) −3.89 (q, 2C, (−Si(CH$_3$)$_2$)*), −3.83 (q, (−Si(CH_3)(CH$_3$))*), −3.79 (q, (−Si(CH$_3$)(CH_3))*), 19.3 (s, (−SiC(CH$_3$)$_3$)†), 19.4 (s, (−SiC(CH$_3$)$_3$)†), 26.47 (q, 3C, (−SiC(CH_3)$_3$)‡), 26.51 (q, 3C, (−SiC(CH_3)$_3$)‡), 72.4 (d, C-4), 74.4 (t, C-5), 79.9 (d, C-3), 83.9 (d, C-2), 120.2 (d, C-2′), 120.4 (d, C-6′), 122.1 (d, C-5′), 135.5 (s, C-1′), 147.6 (s, C-3′$^\#$), 148.0 (s, C-4′$^\#$). *$^{\dagger\ddagger\#}$Interchangeable signals; IR (neat) *ν* (cm^{-1}) 3400, 1509, 1254, 840, 781; EIMS *m*/*z* (rel int.) 440 [M]$^+$ (53), 405 (4), 385 (25), 367 (30), 323 (50), 293 (30), 237 (68), 209 (100), 175 (95), 167 (37), 115 (40);·HREIMS *m*/*z* calcd for $C_{22}H_{40}O_5Si_2$=440.2414; found 440.2433.

*4.1.10. (−)-(2S,3R,4R)-2-[(3′,4′-Bis-(tert-butyldimethylsilanoxy)phenyl)]tetrahydro-furan-3,4-diol ((−)-(2S,3R,4R)-**6b**).* $[\alpha]_D^{25}$ −19 (*c* 1.6, MeOH); >99% ee(optical purity); ^{1}H NMR (400 MHz, CD_3OD): *δ* (ppm) 0.18 (s, 3H, (−Si(CH_3)(CH$_3$))*), 0.19 (s, 3H, (−Si(CH$_3$)(CH_3))*), 0.20 (s, 6H, (−Si(CH_3)$_2$)*), 0.98 (s, 9H, (−SiC(CH_3)$_3$)†), 0.99 (s, 9H, (−SiC(CH_3)$_3$)†), 1.28 (br s, 2H, 2OH), 3.82 (dd, *J*=7.0, 8.4 Hz, 1H, H-5a‡), 3.99 (dd, *J*=7.0, 8.4 Hz, 1H, H-5b‡), 4.09 (m, 1H, H-3), 4.46 (ddd, *J*=4.8, 7.0, 7.0 Hz, 1H, H-4), 4.78 (d, *J*=3.6 Hz, 1H, H-2), 6.81 (2H, H-5′, H-6′), 6.97 (d, *J*=1.6 Hz, 1H, H-2′). *†Interchangeable signals; ^{13}C NMR (100 MHz, CD_3OD): *δ* (ppm) −3.86 (q, 2C, (−Si(CH_3)$_2$)*), −3.82 (q, (−Si(CH_3)(CH$_3$))*), −3.80 (q, (−Si(CH$_3$)(CH_3))*), 19.3 (s, 2C, 2(−SiC(CH$_3$)$_3$)†), 26.5 (q, 3C, (−SiC(CH_3)$_3$)‡), 26.6 (q, 3C, (−SiC(CH_3)$_3$)‡), 72.5 (d, C-5), 73.5 (t, C-4), 74.1 (d, C-3), 84.6 (d, C-2), 121.5 (d, C-5′$^\#$), 121.8 (d, C-6′$^\#$), 122.1 (d, C-2′), 132.5 (s, C-1′), 147.4 (s, C-3′), 147.6 (s, C-4′). *$^{\dagger\ddagger\#}$Interchangeable signals; IR (neat) *ν* (cm^{-1}) 3390, 1513, 1255, 840, 781; EIMS *m*/*z* (rel int.) 440 [M$^+$] (25), 383 (15), 323 (26), 233 (68), 209 (25) (72); 179 (100); 175 (36); 115 (56); 103 (24); HREIMS *m*/*z* calcd for $C_{22}H_{40}O_5Si_2$=440.2414; found 440.2391.

4.2. General procedure for MPA derivatives

A solution of starting material (0.37 mmol) in dry CH_2Cl_2 (1.5 mL) was treated with DMAP (4 mg, 0.03 mmol) and (+)-(2*S*

(*R*))-2-methoxy-2-phenylacetic acid (68 mg, 0.41 mmol). After 15 min stirring at room temperature, EDC (*N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide) (79 mg, 0.41 mmol) was added. Stirring was maintained for 3–24 h. Then, the solvent was removed under reduced pressure. The crude reaction mixture, dissolved in ethyl acetate, was sequentially washed with water, twice with saturated $NaHCO_3$ solution, and twice with water, dried with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification was achieved by flash column chromatography on silica gel 230–400 mesh (elution with 90:10 petroleum ether/ethyl acetate) to obtain compounds (+)-(1″*S*,2*S*)-**8**, (−)-(1″*R*,2*R*)-**8**, (+)-(1″*R*,2*S*)-**9**, (+)-(1″*S*,2*R*)-**9**, (1″*R*,2*R*)-**10** and (+)-(1″*R*,2*S*)-**11**.

*4.2.1. (+)-((1″S,2S)-1-Phenylprop-2-en-1-yl) 2-methoxy-2-phenylacetate ((+)-(1″S,2S)-**8**).* Yellow oil (89 mg, 84% yield). $[\alpha]_D^{25}$ +29 (*c* 5.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ (ppm): 3.42 (s, 3H, −OC*H*$_3$), 4.84 (s, 1H, H-2), 5.23 (ddd, *J*=1.2, 10.5 Hz, 1H, H-3b″), 5.27 (ddd, *J*=1.2, 17.0 Hz, 1H, H-3a″), 5.98 (ddd, *J*=6.2, 10.5, 17.0 Hz, 1H, H-2″), 6.28 (d, *J*=6.2 Hz, 1H, H-1″), 7.04–7.08 (2H, H-2‴, H-6‴), 7.18–7.22 (3H, H-3‴, H-4‴, H-5‴), 7.30–7.35 (3H, H-3′, H-4′, H-5′), 7.38–7.42 (2H, H-2′, H-6′); ^{1}H NMR (400 MHz, CD_2Cl_2/CS_2 (1:4), 25 °C) δ (ppm): 3.31 (s, 3H, −OC*H*$_3$), 4.68 (s, 1H, H-2), 5.14 (ddd, *J*=1.3, 2.2 Hz, 1H, H-3b″), 5.17 (ddd, *J*=1.3, 8.6 Hz, 1H, H-3a″), 5.88 (ddd, *J*=6.2, 10.3, 16.8 Hz, 1H, H-2″), 6.11 (d, *J*=5.9 Hz, 1H, H-1″), 6.97–7.01 (m, 2H, H-2‴, H-6‴), 7.11–7.16 (3H, H-3‴, H-4‴, H-5‴), 7.20–7.24 (3H, H-3′, H-4′, H-5′), 7.24–7.28 (m, 2H, H-2′, H-6′); ^{1}H NMR (400 MHz, CD_2Cl_2/CS_2 (1:4), −60 °C) δ (ppm): 3.32 (s, 3H, −OC*H*$_3$), 4.73 (s, 1H, H-2), 5.16 (ddd, *J*=1.3, 2.4 Hz, 1H, H-3b″), 5.20 (ddd, *J*=1.2, 1.9, 9.2 Hz, 1H, H-3a″), 5.86 (ddd, *J*=5.9, 10.4, 17.0 Hz, 1H, H-2″), 6.05 (d, *J*=6.3 Hz, 1H, H-1″), 6.83–6.91 (m, 2H, H-2‴, H-6‴), 7.08–7.16 (3H, H-3‴, H-4‴, H-5‴), 7.28 (5H, H-2′, H-3′, H-4′, H-5′, H-6′); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ (ppm): 57.3 (c, −OC*H*$_3$), 76.7 (d, C-1″), 82.6 (d, C-2), 117.4 (t, C-3″), 126.5 (d, C-2‴, C-6‴), 127.2 (d, C-2′, C-6′), 127.8 (d, C-3‴, C-5‴), 128.2 (d, C-4‴), 128.4 (d, C-4′), 128.6 (d, C-3′, C-5′), 135.7 (d, C-2″), 135.9 (s, C-1′), 138.2 (s, C-1‴), 169.4 (s, C-1); IR (neat) ν (cm^{-1}) 2931, 1749, 1455, 1245, 1197, 1112, 993, 929, 697; EIMS *m*/*z* (rel int.): 282 $[M]^{+\cdot}$ (0.1), 121 (100), 118 (4), 117 (20), 91 (21), 77 (23); HREIMS calcd for $C_{18}H_{18}O_3$ (M^+): 282.1256; found: 282.1248.

*4.2.2. (−)-(1″R,2R)-(1-Phenylprop-2-en-1-yl) 2-methoxy-2-phenylacetate ((−)-(1″R,2R)-**8**).* Yellow oil (89 mg, 84% yield); $[\alpha]_D^{25}$ −29 (*c* 5.2, $CHCl_3$).

*4.2.3. (+)-(1″R,2S)-(1-Phenylprop-2-en-1-yl) 2-methoxy-2-phenylacetate ((+)-(1″R,2S)-**9**).* Yellow oil (82 mg, 78% yield); $[\alpha]_D^{25}$ +79 (*c* 5.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.40 (s, 3H, −OC*H*$_3$), 4.82 (s, 1H, H-2), 4.97 (ddd, *J*=1.4, 17.2 Hz, 1H, H-3b″), 5.07 (ddd, *J*=1.4, 10.5 Hz, 1H, H-3a″), 5.84 (ddd, *J*=5.5, 10.5, 17.2 Hz, 1H, H-2″), 6.32 (d, *J*=5.5 Hz, 1H, H-1″), 7.31 (m, 2H, H-2‴, H-6‴), 7.33–7.40 (6H, H-3′, H-4′, H-5′, H-3‴, H-4‴, H-5‴), 7.45–7.48 (m, 2H, H-2′, H-6′); ^{1}H NMR (400 MHz, CD_2Cl_2/CS_2 (1:4), 25 °C) δ (ppm): 3.31 (s, 3H, −OC*H*$_3$), 4.66 (s, 1H, H-2), 4.96 (ddd, *J*=1.3, 17.0 Hz, 1H, H-3a″), 5.04 (ddd, *J*=1.4, 10.5 Hz, 1H, H-3b″), 5.78 (ddd, *J*=5.5, 10.5, 17.0 Hz, 1H, H-2″), 6.14 (td, *J*=1.4, 5.5 Hz, 1H, H-1″), 7.16–7.20 (m, 2H, H-2‴, H-6‴), 7.20–7.28 (6H, H-3′, H-4′, H-5′, H-3‴, H-4‴, H-5‴), 7.30–7.34 (m, 2H, H-2′, H-6′); ^{1}H NMR (400 MHz, CD_2Cl_2/CS_2 (1:4), −60 °C) δ (ppm): 3.29 (s, 3H, −OC*H*$_3$), 4.68 (s, 1H, H-2), 4.78 (ddd, *J*=1.2, 17.0 Hz, 1H, H-3b″), 4.98 (ddd, *J*=1.4, 10.6 Hz, 1H, H-3a″), 5.74 (ddd, *J*=5.6, 10.6, 17.0 Hz, 1H, H-2″), 6.10 (ddd, *J*=1.4, 5.0 Hz, 1H, H-1″), 7.19–7.23 (m, 2H, H-2‴, H-6‴), 7.25–7.29 (6H, H-3′, H-4′, H-5′, H-3‴, H-4‴, H-5‴), 7.30–7.36 (m, 2H, H-2′, H-6′); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 57.3 (c, −OCH_3), 76.4 (d, C-1″), 82.5 (d, C-2), 116.7 (t, C-3″), 127.1 (d, C-2‴, C-6‴), 127.2 (d, C-2′, C-6′), 128.2 (d, C-3‴, C-5‴), 128.5 (d, C-4‴), 128.5 (d, C-4′), 128.7 (d, C-3′, C-5′), 135.3 (d, C-2″), 136.1 (s, C-1′),, 138.3 (s, C-1‴), 169.5 (s, C-1); IR (neat) ν (cm^{-1}) 3031, 1749, 1494, 1455, 1246, 1170, 1113, 930, 698; EIMS *m*/*z* (rel int.): 282 $[M]^{+\cdot}$ (0.1), 121 (100), 118 (4), 117 (20), 91 (21), 77 (23); HREIMS calcd for $C_{18}H_{18}O_3$ (M^+): 282.1256; found: 282.1251.

*4.2.4. (−)-(1″S,2R)-(1-Phenylprop-2-en-1-yl) 2-methoxy-2-phenylacetate ((−)-(1″S,2R)-**9**).* Yellow oil (98 mg, 93% yield); $[\alpha]_D^{25}$ −79 (*c* 6.5, $CHCl_3$).

*4.2.5. (−)-(1″R,2R)-(1-(3,4-Bis(tert-butyldimethylsilyloxy)phenyl)-allyl) 2-methoxy-2-phenylacetate ((−)-(1″R,2R)-**10**).* Yellow oil (12 mg, 45% yield); $[\alpha]_D^{25}$ −3 (*c* 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.12 (s, 6H, −Si(C*H*$_3$)$_2$), 0.15 (s, 6H, −Si(C*H*$_3$)$_2$), 0.94 (s, 9H, −SiC(C*H*$_3$)$_3$), 0.95 (s, 9H, −SiC(C*H*$_3$)$_3$), 3.39 (s, 3H, −OC*H*$_3$), 4.79 (s, 1H, H-2), 5.18 (d, *J*=1.3 Hz, 1H, H-3a″), 5.22 (ddd, *J*=1.3, 8.3 Hz, 1H, H-3b″), 5.94 (ddd, *J*=5.7, 10.5, 17.0 Hz, 1H, H-2″), 6.16 (d, *J*=5.7 Hz, 1H, H-1″), 6.54 (dd, *J*=2.2, 8.2 Hz, 1H, H-6‴), 6.64 (d, *J*=8.2 Hz, 1H, H-5‴), 6.68 (d, *J*=2.2 Hz, 1H, H-2‴), 7.27–7.32 (3H, H-3′, H-4′, H-5′), 7.34–7.38 (m, 2H, H-2′, H-6′); ^{1}H NMR (400 MHz, CD_2Cl_2/CS_2 (1:4), 25 °C) δ (ppm): 0.10 (s, 6H, −Si(C*H*$_3$)$_2$), 0.14 (s, 6H, −Si(C*H*$_3$)$_2$), 0.93 (s, 9H, −SiC(C*H*$_3$)$_3$), 0.94 (s, 9H, −SiC(C*H*$_3$)$_3$), 3.30 (s, 3H, −OC*H*$_3$), 4.64 (s, 1H, H-2), 5.11 (dd, *J*=1.4, 2.3 Hz, 1H, H-3a″), 5.14 (dd, *J*=1.4, 2.1 Hz, 1H, H-3b″), 5.85 (ddd, *J*=5.7, 10.2, 17.3 Hz, 1H, H-2″), 6.01 (d, *J*=5.9 Hz, 1H, H-1″), 6.49 (dd, *J*=2.2, 8.2 Hz, 1H, H-6‴), 6.57 (d, *J*=8.2 Hz, 1H, H-5‴), 6.60 (d, *J*=1.9 Hz, 1H, H-2‴), 7.10–7.23 (3H, H-3′, H-4′, H-5′), 7.23–7.28 (m, 2H, H-2′, H-6′); ^{1}H NMR (400 MHz, CD_2Cl_2/CS_2 (1:4), −60 °C) δ (ppm): 0.08 (s, 6H, −Si(C*H*$_3$)$_2$), 0.12 (s, 6H, −Si(C*H*$_3$)$_2$), 0.92 (s, 9H, −SiC(C*H*$_3$)$_3$), 0.93 (s, 9H, −SiC(C*H*$_3$)$_3$), 3.30 (s, 3H, −OC*H*$_3$), 4.67 (s, 1H, H-2), 5.13 (d, *J*=8.8 Hz, 1H, H-3a″), 5.22 (dd, *J*=1.2 Hz, 1H, H-3b″), 5.84 (ddd, *J*=5.8, 10.6, 16.7 Hz, 1H, H-2″), 5.96 (d, *J*=5.7 Hz, 1H, H-1″), 6.43 (dd, *J*=2.2, 8.2 Hz, 1H, H-6‴), 6.54 (d, *J*=9.4 Hz, 1H, H-5‴), 6.54 (br s, 1H, H-2‴), 7.25 (5H, H-2′, H-3′, H-4′, H-5′, H-6′); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): −4.2 (c, 4C, −Si(*C*H$_3$)$_2$), 18.4 (s, 2C, −Si*C*(CH$_3$)$_3$), 25.9 (c, 6C, −SiC(*C*H$_3$)$_3$), 57.4 (c, −OCH_3), 76.5 (d, C-1″), 82.8 (d, C-2), 117.0 (t, C-3″), 120.1 (d, C-6‴), 120.2 (d, C-2‴), 120.7 (d, C-5‴), 127.2 (d, C-2′, C-6′), 128.5 (d, C-3′, C-5′), 128.6 (d, C-4′), 131.1 (s, C-1‴), 135.9 (d, C-2″), 136.0 (s, C-1′), 146.6 (s, C-3‴), 146.8 (s, C-4‴), 169.7 (s, C-1); IR (neat) ν (cm^{-1}) 2858, 1750, 1510, 1295, 1254, 1168, 1117, 904, 840, 731, 697; EIMS *m*/*z* (rel int.): 542 $[M]^{+\cdot}$ (4), 377 (20), 205 (100), 121 (27), 77 (7), 73 (71); HREIMS calcd for $C_{28}H_{44}O_5Si_2$ (M−26): 516.2727; found: 516.9697.

*4.2.6. (+)-(1″R,2S)-(1-(3,4-Bis(tert-butyldimethylsilyloxy)phenyl)-allyl) 2-methoxy-2-phenylacetate ((+)-(1″R,2S)-**11**).* Yellow oil (15 mg, 56% yield); $[\alpha]_D^{25}$ +39 (*c* 0.4, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 0.17 (s, 6H, −Si(C*H*$_3$)$_2$), 0.18 (s, 6H, −Si(C*H*$_3$)$_2$), 0.97 (s, 18H, −SiC(C*H*$_3$)$_3$), 3.38 (s, 3H, −OC*H*$_3$), 4.77 (s, 1H, H-2), 4.87 (ddd, *J*=1.4, 17.1 Hz, 1H, H-3a″), 5.02 (ddd, *J*=1.4, 10.6 Hz, 1H, H-3b″), 5.78 (ddd, *J*=5.2, 10.6, 17.1 Hz, 1H, H-2″), 6.18 (ddd, *J*=1.4, 5.2 Hz, 1H, H-1″), 6.75 (br s, 2H, H-2‴, H-6‴), 6.80 (br s, 1H, H-5‴), 7.31–7.38 (3H, H-3′, H-4′, H-5′), 7.41–7.45 (m, 2H, H-2′, H-6′); ^{1}H NMR (400 MHz, CD_2Cl_2/CS_2 (1:4), 25 °C) δ (ppm): 0.14 (s, 6H, −Si(CH$_3$)$_2$), 0.15 (s, 6H, −Si(CH$_3$)$_2$), 0.95 (s, 18H, −SiC(CH$_3$)$_3$), 3.30 (s, 3H, −OCH$_3$), 4.61 (s, 1H, H-2), 4.89 (ddd, *J*=1.4, 17.1 Hz, 1H, H-3a″), 5.00 (ddd, *J*=2.3, 10.5 Hz, 1H, H-3b″), 5.73 (ddd, *J*=5.3, 10.5, 17.1 Hz, 1H, H-2″), 6.02 (d, *J*=5.3 Hz, 1H, H-1″), 6.65 (br s, 2H, H-2‴, H-6‴), 6.67 (br s, 1H, H-5‴), 7.22–7.27 (3H, H-3′, H-4′, H-5′), 7.28–7.31 (m, 2H, H-2′, H-6′); ^{1}H NMR (400 MHz, CD_2Cl_2/CS_2 (1:4), −60 °C) δ (ppm): 0.13 (s, 6H, −Si(C*H*$_3$)$_2$), 0.15 (s, 6H, −Si(C*H*$_3$)$_2$), 0.95 (s, 18H, −SiC(C*H*$_3$)$_3$), 3.29 (s, 3H, −OC*H*$_3$), 4.58 (d, *J*=16.9 Hz, 1H, H-3a″), 4.66 (s, 1H, H-2), 4.90 (d, *J*=10.8 Hz, 1H, H-3b″), 5.68 (ddd, *J*=4.5, 10.8, 16.7 Hz, 1H, H-2″), 5.98 (d, *J*=4.5 Hz, 1H, H-1″), 6.64 (sa, 2H, H-2‴, H-6‴), 6.67 (sa, 1H, H-5‴), 7.32 (5H, H-2′, H-3′, H-4′, H-5′, H-6′); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): −4.1 (c, 4C, −Si(*C*H$_3$)$_2$), 18.4 (s, 2C, −Si*C*(CH$_3$)$_3$), 25.9 (c, 6C, −SiC(*C*H$_3$)$_3$), 57.3 (c, −OCH_3), 76.2 (d, C-1″), 82.6 (d, C-2), 116.2 (t, C-3″), 120.4 (d, C-5‴), 120.6 (d, C-6‴), 120.8 (d,

C-2‴), 127.3 (d, C-2′, C-6′), 128.6 (d, C-4′), 128.7 (d, C-3′, C-5′), 131.2 (s, C-1‴), 135.5 (d, C-2″), 136.3 (s, C-1′), 146.8 (s, C-3‴), 147.0 (s, C-4‴), 169.6 (s, C-1); IR (neat) ν (cm^{-1}) 2931, 1751, 1510, 1468, 1295, 1254, 1116, 997, 732; EIMS *m*/*z* (rel int.): 542 $[M]^{+\cdot}$ (4), 377 (20), 205 (100), 121 (27), 77 (7), 73 (71); HREIMS calcd for $C_{28}H_{44}O_5Si_2$ (M−26): 516.2727; found: 516.8416.

*4.2.7. (−)-(2S,3R,4R)-2-(3′,4′Dihydroxyphenyl)tetrahydrofuran-3,4-diol ((−)-(2S,3R,4R)-**1**).* A solution of iodine in methanol (3 mL, 1% w/v) and compound (−)-(2*S*,3*R*,4*R*)-**6b** (15 mg, 0.03 mmol) was heated to reflux for 3 h. The reaction was then cooled and $Na_2S_2O_3$ (80 mg) was added to reduce the remaining iodine. The solvent was removed under reduced pressure and the residue extracted into ethyl acetate (3×50 mL), and the solution then washed with brine (50 mL), dried with Na_2SO_4, and the solvent was evaporated under reduced pressure. Flash chromatography (petroleum ether/acetone 80:20) afforded compound (±)-**1** (3 mg, 41%) as a colorless oil: $[\alpha]_D^{25}$ −38 (*c* 0.3, MeOH); >99% ee (optical purity);[24] ^{1}H NMR (400 MHz, CD_3OD): δ (ppm) 3.80 (dd, *J*=2.4, 8.8 Hz, 1H, H-5b), 3.87 (dd, *J*=4.2, 7.6 Hz, 1H, H-3), 4.22 (ddd, *J*=2.4, 4.2, 4.6 Hz, 1H, H-4), 4.25 (dd, *J*=4.6, 8.8 Hz, 1H, H-5a), 4.51 (d, *J*=7.6 Hz, 1H, H-2), 6.70 (2H, H-5′, H-6′), 6.80 (d, *J*=2.0 Hz, H-2′); ^{13}C NMR (100 MHz, CD_3OD): δ (ppm) 72.4 (d, C-4), 74.2 (t, C-5), 79.6 (d, C-3), 84.5 (d, C-2), 114.4 (d, C-2′), 116.1 (d, C-5′*), 119.0 (d, C-6′*), 133.3 (s, C-1′), 142.1 (s, C-3′#), 146.1 (s, C-4′#). *#Interchangeable signals; IR (neat) ν (cm^{-1}) 3334, 1520; EIMS *m*/*z* (rel int.) 212 $[M]^+$ (73), 194 (8), 152 (10), 139 (100); HREIMS *m*/*z* calcd for $C_{10}H_{12}O_5$=212.0685; found 212.0679.

*4.2.8. (−)-(2S,3S,4R)-2-(3′,4′-Diacetoxyphenyl)-3,4-diacetoxytetrahydrofuran ((−)-(2S,3S,4R)-**1a**).* Acetic anhydride (189 mg, 1.8 mmol) was added dropwise to a stirred solution of compound (−)-(2*S*,3*R*,4*R*)-**1** (3 mg, 0.014 mmol) in dry pyridine (1 mL). After 24 h the reaction mixture was diluted with ethyl acetate (50 mL) and washed sequentially with 2 N HCl (2×50 mL), a diluted solution of $CuSO_4$ (2×50 mL) and brine (50 mL) and was then dried over Na_2SO_4, filtered, and the solvent evaporated under reduced pressure. Flash chromatography (petroleum ether/ethyl acetate 80:20) afforded compound (−)-(2*S*,3*S*,4*R*)-**1a** as a colorless oil (5 mg, 93%). $[\alpha]_D^{25}$ −34 (*c* 0.5, $CHCl_3$); >99% ee (optical purity).[24] The synthetic material exhibits the same spectral data and optical activity as the natural product (−)-**1a**, (see Supplementary data) isolated form the fungus *C. gloeosporioides* 20122.[4]

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Supplementary data

Isolation procedure for compound (−)-**1a** from *C. gloeosporioides* 20122. Experimental details for the preparation of compounds (−)-**12**, (+)-**13** (chemical resolution), (+)-**1**, (−)-**1** (chemical resolution), (+)-**1a**, (−)-**1a** (chemical resolution). ^{1}H NMR and ^{13}C NMR spectra for compounds.(−)-**1**,(−)-**1a** (synthetic), (−)-**1a** (isolated from *C. gloeosporioides*), **2a**, (±)-**3**, (+)-**4**, (+)-**5**, (−)-**6a**, (−)-**6b**, (+)-**8**, (+)-**9**, (−)-**10**, (+)-**11**, (−)-**12**, (+)-**13**. C.D. spectra for compounds (−)-(*S*)-**3**, (+)-(*R*)-**3**, (−)-(*S*)-**7**, (+)-(*R*)-**7**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.07.074. These data include MOL files and InChIKeys of the most important compounds described in this article.

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24. Material for comparison of optical purity was obtained by chemical resolution of racemic (±)-**6b**, prepared from unresolved racemic alcohol (±)-(**3**) (see Supplementary data).