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Enantiopure 2,2′-dihydroxy-3,3′-dimethoxy-5,5′-diallyl-6,6′-dibromo-1,1′-biphenyl: a conformationally stable C_2-dimer of a eugenol derivative

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Abstract—The preparation and resolution of the title conformationally stable biphenyl **9** has been performed in high chemical yield starting from eugenol **1**. Enantiopure biphenyls (a*R*)-(+)-**9** and (a*S*)-(−)-**9** were achieved, respectively, by resolution of the corresponding menthylcarbonate diastereomer and subsequent reduction. Absolute configuration and specific rotation were correlated by X-ray analysis of the crystal structure of diastereopure phosphorothioamidate (a*R*,*S*)-(−)-**16**.

1. Introduction

One of the challenges for chemists includes the discovery and development of natural compounds as valuable starting materials or intermediates for the preparation of new drugs,[1] biomaterials,[2] and ligands for catalysis.[3] This research requires the development of synthetic strategies in order to access the analogues of natural products. The field of synthetic methodology development is highly advanced at present but at the same time, still lacking in many aspects such as economy and feasibility.[4] Due to the importance of chirality, great efforts in synthetic strategy are devoted to the preparation of enantiopure analogues of naturally occurring compounds.[5]

The majority of natural products have been isolated from plant origins, mainly due to the ease of the isolation process. Eugenol **1** belongs to the family of natural allyl phenols such as chavicol **2**, estragol **3**, and osmorhyzol **4** (Fig. 1). Eugenol **1** is the main component of clove oil;[6] it occurs in many essential oils and is a valuable starting material for several drugs. In dentistry, eugenol **1** is used as an antiseptic and disinfectant[7] and, in cosmetic and food products, eugenol **1** is used as a flavoring, antimicrobial, and antioxidant agent.[8]

Biphenyl 5,5′ structures (C–C linkages) occur frequently in softwood lignins because they come from the symmetrical coupling of the corresponding monomers.[9] 2,2′-Dihydroxy-3,3′-dimethoxy-5,5′-diallyl-1,1′-biphenyl **5**, namely dehydrodieugenol,[10] is the symmetrical dimer of eugenol **1**, and is a natural *o*,*o*′-dihydroxy biphenyl, conformationally flexible, which manifests biological activity comparable with that observed in eugenol **1** (Fig. 2). *O*-Methyldehydrodieugenol **6** and di-*O*-methyldehydrodieugenol **7** also occur in Nature; they have been isolated from *Ocotea cymbanum*[10b] and *Nectandra polita*.[10c] Magnolol **8**, an active principle mainly isolated from *Magnolia officinalis*[11] is the symmetrical dimer of chavicol **2**. Multiple pharmacological activities have been observed in magnolol and in its numerous natural derivatives and among them, antioxidant and anti-inflammatory properties have been intensively studied.[11b,12] The presence of two allyl chains at the 5,5′ position of **5** and **8** and the four hydroxylated groups seem to be a chemostructural requirement for pharmacological activity.[13]

Because of the wide applicability of eugenol **1** and the observed cytotoxic properties at high concentration, dehydrodieugenol **5** and magnolol **8** have been studied

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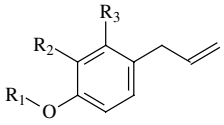
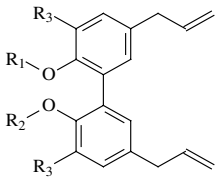


1 $R_1 = H, R_2 = OCH_3, R_3 = H$
2 $R_1 = H, R_2 = H, R_3 = H$
3 $R_1 = CH_3, R_2 = H, R_3 = H$
4 $R_1 = CH_3, R_2 = H, R_3 = CH_3O$

Figure 1.



5 $R_1 = H, R_2 = H, R_3 = OCH_3$
6 $R_1 = H, R_2 = CH_3, R_3 = OCH_3$
7 $R_1 = CH_3, R_2 = CH_3, R_3 = OCH_3$
8 $R_1 = H, R_2 = H, R_3 = H$

Figure 2.

as antioxidant and anti-inflammatory eugenol-related agents.[14] Dehydrodieugenol **5** is less toxic of eugenol **1** and manifests a stronger inhibitory effect on lipid peroxidation and scavenging ability for superoxide radicals with respect to hydroxyl radicals (·OH).[15] Dehydrodieugenol **5** appears to be an interesting starting material to prepare new biphenyls with interesting features and biological activities.

As a part of our ongoing program devoted to the preparation of chiral hydroxylated biphenyls whose structure resembles natural occurring biphenyls,[16] we thought to prepare 2,2′-dihydroxy-3,3′-dimethoxy-5,5′-diallyl-6,6′-dibromo-1,1′-biphenyl **9**, a bromo-dehydrodieugenol derivative. Hydroxylated bromo containing biphenyls have been assuming an important role in therapy as antibacterial as well as anti-HIV-1 agents.[17] The presence of bromo or chloro functionality in hydroxylated biaryls makes them effective chiral ligands or chiral activators in asymmetric catalytic processes since the halo substituent improves the Lewis acidity.[18] The presence of bromo substituents at the *ortho–ortho′* positions increases the dihedral angle of biphenol and thus provides an important change in the efficiency of asymmetric catalysis.[18,19]

Our starting point was to introduce bromines at the 6,6′ positions of dehydrodieugenol **5** in order to achieve configurational stability as well as a more decisive influence on the torsional angle and therefore on the reactivity and stereoselectivity of biphenyl **9**.

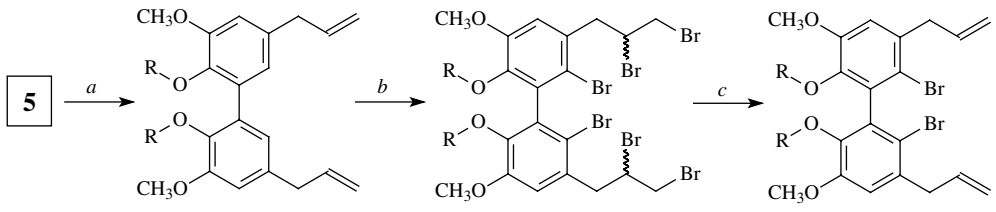
2. Results and discussion

Among the several methods known to prepare **5**,[20] we chose a synthetic method, which uses less toxic reagents and gives the highest yield. Eugenol **1** was treated with a solution of NH_4OH and $K_3Fe(CN)_6$ in acetone–water at room temperature in open air.[20a] Dehydrodieugenol **5** was obtained as a colorless solid in 95% yield after recrystallization from absolute ethanol.

We have explored different bromination conditions in order to address selective bromination at the reactive 6,6′ positions of the aromatic rings while maintaining unchanged the allyl chains. It is known that bromination of eugenol **1** in the presence of 1 mol of bromine, gives only aliphatic bromination.[21] In the past, we have successfully used benziltriethylammonium tribromide [BTEA·Br_3] in the regioselective bromination of several methyl protected biphenols bearing different functional groups.[16b,22]

Di-*O*-methyldehydrodieugenol **7** was obtained in virtually quantitative yield by treatment of biphenol **5** with K_2CO_3 in dry DMF and successive addition of iodomethane at 50 °C. Di-*O*-methyldehydrodieugenol **7** was brominated at room temperature by treatment of 2 equiv of [BTEA·Br_3] using a mixture of dichloromethane and methanol as solvent (Scheme 1).

After 6 h at room temperature, a complex mixture of bromo derivatives of di-*O*-methyldehydrodieugenol **7** was obtained for which ^1H NMR spectra showed a significant decrease of the signals attributed to the allylic chains. Repeated attempts at changing the reaction conditions of the bromination (stoichiometry of the brominating agent, temperature, time) did not afford biphenol **10** but a complex mixture of bromo derivatives was obtained.



7 R = CH_3 | **10a**, **10b**, **10c** R = CH_3 | **11** R = CH_3
12 R = (CO)*menthyl* | **13a**, **13b** R = (CO)*menthyl* | **14** R = (CO)*menthyl*
5 R = H | **15a**, **15b**, **15c** R = H | **9** R = H

Scheme 1. Reagents and conditions: when R = CH_3 (a) K_2CO_3, CH_3I, DMF, 60 °C, 8 h, 90% yield; (b) 10 equiv [BTEA·Br_3], 10 equiv $ZnCl_2$, AcOH, 60 °C, 5 h, 85% yield; (c) Zn dust, EtOH 95%, reflux, 12 h, 92% yield. When R = (CO)menthyl: (a) (1*R*,2*S*,5*R*)-(−)-menthyl chloroformate, Et_3N, toluene, rt, 1 h, 95% yield; (b) 10 equiv [BTEA·Br_3], 10 equiv $ZnCl_2$, AcOH, 60 °C, 5 h, 75% yield; (c) Zn dust, AcOH, 80 °C, 24 h, 95% yield. When R = H: (b) Br_2, Et_2O, rt, 3 h, 94% yield; (c) Zn dust, EtOH 95%, reflux, 12h, 91% yield.

When the reaction was carried out under the same conditions using 10 equiv of [BTEA·Br_3] and 10 equiv of $ZnCl_2$ in CH_3COOH, for 3 h at 60 °C, a mixture of three brominated diastereomers **10a**, **10b**, and **10c** in the ratio 1:1:0.2 were identified by ^{1}H NMR spectroscopy. Complete debromination at the two alkyl chains of the mixture **10a**, **10b**, and **10c** was carried out in the presence of Zn dust in aqueous EtOH at reflux to give **11** in 90% yield.[21] Regioselective demethylation at the *ortho–ortho′* position of compound **11** attempted using 0.3 equiv of BBr_3 at −30 °C, failed and partial bromination of the allyl chains was observed.

In order to develop a synthetically useful method to prepare **9** in enantiopure form, biphenyl **5** was treated with 2.2 equiv of (−)-menthyl chloroformate with triethylamine at room temperature using toluene as solvent to give dicarbonate **12** in 85% yield. Previously, we have successfully applied the bromination reaction in a C_2 symmetry flexible biphenol bearing two menthylcarbonate groups at the *ortho–ortho′* positions in order to achieve bromination and configurational stability at the stereogenic axis.[22]

Bromination of biphenyl **12** in the presence of 10 equiv [BTEA·Br_3] using 10 equiv of $ZnCl_2$ in the presence of CH_3COOH afforded a mixture of six diastereomers **13**, which possess both axial and central chirality. The mixture of six atropo-diastereomers **13** was easily separated as a couple of three atropo-diastereomers **13a** and **13b** by stirring the mixture with diethyl ether at room temperature (Scheme 1). Atropo-diastereomers **13a**, ether insoluble, were collected by filtration whereas atropo-diastereomers **13b**, ether soluble, were recovered from the corresponding ether solution. Biphenyls **13a** and **13b** were separately treated with 5 equiv of Zn dust in CH_3COOH to give biphenyl (a*R*)-**14** and (a*S*)-**14**, as diastereomers, in 95% and 90% yield, respectively (Scheme 2).

After reduction of the carbonate group by $LiAlH_4$ in THF at 0 °C, each diastereomer **14** gave the two atropo-enantiomer (+)-**9** and (−)-**9**, respectively. The enantiomeric purity of each biphenol **9** was >99%, and was related to the diastereomeric excess of the corresponding menthylcarbonate **13**, which was verified by ^{1}H NMR. All attempts to achieve suitable crystals from each atropo-diastereomer (a*R*,1*R*,1′*R*,2*S*,2′*S*, 5*R*,5′*R*)-**14** and (a*S*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**14** aimed at correlating the absolute configuration with the specific rotation, failed. Atropo-enantiomer **9** has a quite high interconversion barrier in solution in most solvents. Interconversion was monitored by chiral HPLC at different temperatures and times. Enantiopure biphenol **9** does not racemize in organic solutions even when heated to 115 °C for 10 h. Bromobiphenol **9** is thermally and chemically stable.

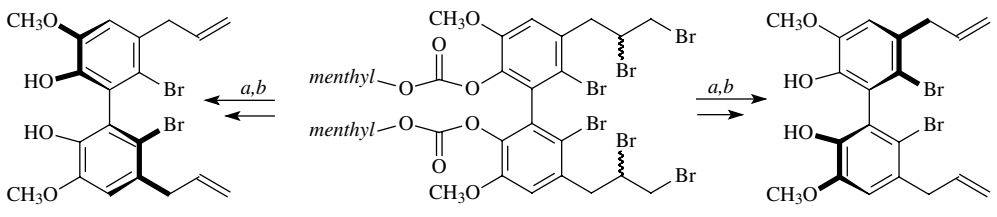
Difficulties encountered in the crystallization of **14** prompted us to modify the reaction path. Bromination of dehydrodieugenol **5** with 8 equiv of bromine in $CHCl_3$ at room temperature afforded the three diastereomers **15a**, **15b**, and **15c** in the ratio 1:0.7:0.9 and in 94% yield (Scheme 1). According to the solvent, such as CCl_4 or Et_2O, different mixtures of **15a**, **15b**, and **15c** were obtained whose ratio was calculated from ^{1}H NMR. Treatment of the mixture **15** with Zn dust in EtOH at 95% provided complete debromination and 2,2′-dihydroxy-3,3′-dimethoxy-5,5′-diallyl-6,6′-dibromo-1,1′-biphenyl **9** was achieved in 91% yield.

We prepared phosphorothioamidate **16** by treating racemic **9** with (*S*)-(−)-C_2P(S)NHCH(CH_3)Ph **17** in the presence of pyridine.[23] In this case we chose a cheaper chiral source, (*S*)-(−)-α-methylbenzylamine, which was used in equimolar ratio and that was expected to be recovered, under reduction conditions, without loss of enantiomeric purity. Repeated attempts devoted to separate the two phosphorothioamidate (a*R*,*S*)-**16** and (a*S*,*S*)-**16** achieved in 84% yield and in equimolar ratio, failed.

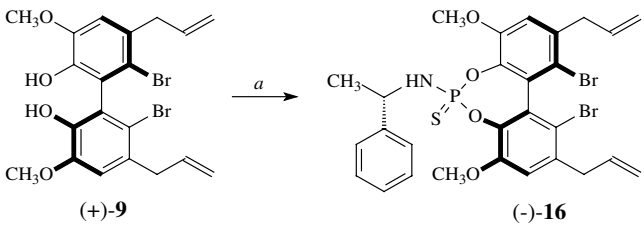
According to our past experience in obtaining suitable crystals for diffraction analysis of biphenol derivatives, we decided to transform biphenol (+)-**9** into the corresponding diastereopure phosphorotioamidate (−)-**16** (Scheme 3). Stable crystals were recovered after recrystallization from EtOH, which, when subjected to X-ray analysis, allowed us to assign unequivocally both the structure and absolute configuration of (a*R*,*S*)-(−)-**16**.

A perspective view of the molecule, showing the atom numbering scheme, is reported in Figure 3.

The dihedral angle τ between the least-squares planes through the biphenyl rings in (a*R*,*S*)-(−)-**16** measures 57.4(1)°. This value is distinctly lower than that



Scheme 2. Reagents and conditions: (a) Zn dust, AcOH, 80 °C, 24 h, 90% yield for compound (a*S*)-**14**, 95% yield for compound (a*R*)-**14**; (b) $LiAlH_4$, THF, 0 °C → rt, 89% yield for compound (a*S*)-(−)-**9**, 90% yield for compound (a*R*)-(+)-**9**.



Scheme 3. Reagents and conditions: (a) (*S*)-(−)-$Cl_2P(S)NHCHCH_3Ph$ **17**, pyridine, reflux, 12 h, 84% yield.

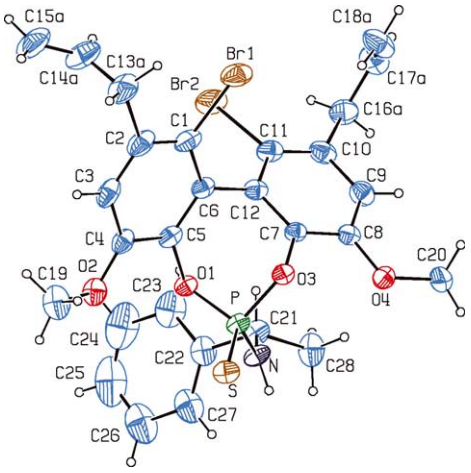


Figure 3. ORTEP plot[24] of diastereomer (a*R*,*S*)-(−)-**16** with atom numbering scheme. Displacement ellipsoids at 20% probability level.

observed in the *ortho–ortho′* dibromo biphenyl derivative previously synthesized,[22] where τ was 86.1(2)° and 87.6(3)° for the two molecules of the asymmetric unit. This remarkable difference is due to the presence in (a*R*,*S*)-(−)-**16** of the phosphorothioamidate seven-membered ring, which constrains the biphenyl to a reduced distortion while increasing the steric repulsion between the *ortho–ortho′* substituents.

A comparison of the crystal structure of (a*R*,*S*)-(−)-**16** with that of related *ortho*-substituted phosphorothioamidate biphenyls[16b,25] nicely illustrates the effect of different substituents on both the conformational features and the associated configurational stability of these compounds. In Table 1 some structural properties of such derivatives are listed.

The increase of the van der Waals radii of the *ortho* substituents along the series (1.5, 1.8, and 1.9 Å for O, S, and Br, respectively[26]) reflects in an increase of both the $r_{X\cdots X'}$ contact distance (X = O, S, Br) and, to a lesser extent, the dihedral angle τ. Owing to the constraint imposed by the seven-membered ring, only a rather small variation in the angle τ is observed, resulting in increasing structural strain on going from the dimethoxy to the dithiomethyl and then to the dibromo derivative. This comes out clearly from the values of the relative approach of the *ortho* substituents with respect to the sum of their van der Waals radii ($\delta r_{X\cdots X'}$), and of the averaged deviation of X, X′ from the least-squares planes through the phenyl rings (Δ). Both these quantities become significantly larger along the series and, in particular, the last one increases by more than 50% from the first to the second compound, and by 11% from the second to the third one. This strain does not affect significantly the structure of the aryl rings, whose slight deviations from the standard geometry are comparable in all three of these derivatives.

3. Conclusions

A straightforward procedure to prepare 2,2′-dihydroxy-3,3′-dimethoxy-5,5′-diallyl-6,6′-dibromo-1,1′-biphenyl **9**, a C_2-configurationally stable eugenol-related dimer, has been realized. The synthetic strategy entailed the preparation of dehydrodieugenol **5**, then, aromatic and alkyl bromination and regioselective debromination of the alkyl chains to give racemic **9** in 81% overall yield. Both enantiomers of bromobiphenol **9** were achieved by a reaction path, which involved trasformation of dehydrodieugenol **5** in the menthylcarbonate **12**, aromatic and alkyl bromination, separation of the two pairs of homochiral atropo-diastereomers **13a** and **13b**, regioselective debromination and final reduction of the menthylcarbonate groups to give enantiopure **9** in 57% overall yield.

We were able to correlate absolute configuration with specific rotation of **9** and to calculate the quite high racemization barrier. Influence of the two bromine atoms at the *ortho–ortho′* positions of biphenol **9** on the conformation of the biphenyl unit was studied by X-ray analysis of the crystal structure of phosphorothioamidate (a*R*,*S*)-(−)-**16**. The crystal data of **16** in comparison with those of other biphenyl phosphorothioamidates confirmed that the introduction of suitable functionalities at the specified positions of the biphenyl structure provides small but significant conformational and elec-

Table 1. Selected structural data for phosphorothioamidate biphenyls with $-OCH_3$, $-SCH_3$ and –Br groups at the *ortho–ortho′* positions[a]

Compound	X···X′	$r_{X\cdots X'}$	τ	$\delta r_{X\cdots X'}$ (%)	Δ
17 of Ref. 16b	O···O′	2.787 (3)	49.93 (9)	7.1	0.153 (2)
18 of Ref. 25	S···S′	3.310 (1)	54.49 (9)	8.0	0.234 (1)
(a*R*,*S*)-(−)-**16**[b]	Br···Br′	3.488 (1)	57.4 (1)	8.2	0.2595 (8)

[a] $r_{X\cdots X'}$ is the contact distance between the *ortho* substituents X, X′; τ is the dihedral angle between the least-squares planes through the phenyl rings; $\delta r_{X\cdots X'}$ is the relative approach of X, X′ with respect to the sum of their van der Waals radii; Δ is the averaged deviation of X, X′ from the least-squares planes through the phenyl rings. Distances in Å, angles in degrees.

[b] This work.

tronic changes, which make the biphenyl a stereochemical selector.[27]

The high configurational stability and the large dihedral angle show that biphenyl **9** has potential use as ligand, being structurally similar to ligands already synthetized.[28] Investigations to look for the pharmacological activity of **9** in racemic as well as in enantiopure form are in progress.

4. Experimental section

4.1. General procedures

Melting points were determined on a Büchi 530 apparatus and are uncorrected. All ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution with a Varian spectrometer Mercury Plus at 399.93 MHz and 100.57 MHz, respectively. Chemical shifts are given in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), m (multiplet) or dd (double of doublets). Elemental analyses were performed using an elemental analyzer Perkin–Elmer model 240 C. Optical rotations were measured with a Perkin–Elmer 343 spectropolarimeter. The HPLC analyses were performed at rt with a Agilent 1100 Series Liquid Chromatograph/MSD trap using Chiracel OD column (10 μm, 25 cm × 0.46 ID) at flow rate of 1.0 mL/min, 254 UV detection, using a gradient mixture 88:12 w:w *n*-hexane/2-propanol for 20′ and then 85:15 w:w *n*-hexane/2-propanol for 10′ as mobile phase. Tetrahydrofuran (THF) and toluene were freshly distilled from sodium benzophenone ketyl. Pyridine (py) and triethylamine (Et_3N) were dried over KOH and distilled before use. Dimethylformamide (DMF) was dried over molecular sieves (5 Å) and distilled before use. All reagents were of commercial quality and used as purchased. Flash chromatography was carried out with silica gel 60 (230–400 mesh, Kiesgel, EM Reagents) eluting with appropriate solution in the stated v:v proportions. Analytical thin-layer chromatography (TLC) was performed with 0.25 mm thick silica gel plates (Polygram® Sil G/UV$_{254}$, Macherey-Nagel). The purity of all new compounds was judged to be >98% by ^{1}H NMR and ^{13}C NMR spectral determination.

4.2. 2,2′,3,3′-Tetramethoxy-5,5′-diallyl-1,1′-biphenyl 7[10c]

To a solution of **5** (2.70 g, 8.27 mmol) in DMF (20 mL) was added, dropwise, a solution of CH_3I (5.8 g, 41.35 mmol) in DMF (15 mL) at rt under N_2. The solution was stirred at 60 °C for 8 h, washed with water (500 mL), and extracted with ether (2 × 100 mL). The crude, dried over Na_2SO_4 gave a colorless oil that was used in the next reaction without any purification. **7** (2.64 g, 90%): ^{1}H NMR δ 3.36 (d, $J = 6.8$ Hz, 4H), 3.61 (s, 6H), 3.87 (s, 6H), 5.07 (m, 4H), 5.99 (ddt, $J = 20.4$, 10.0, 6.8, Hz, 2H), 6.69 (d, $J = 2$ Hz, Ar, 2H), 6.74 (d, $J = 2$ Hz, Ar, 2H); ^{13}C NMR δ 40.27, 56.03, 60.88, 112.12, 116.10, 123.33, 132.85, 135.32, 137.63, 145.27, 152.74; Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.55; H, 7.39; Found: C, 74.51; H, 7.51.

4.3. 2,2′,3,3′-Tetramethoxy-5,5′-di(2,3-dibromo-propyl)-6,6′-dibromo-1,1′-biphenyl 10

To a solution of **7** (3.96 g, 11.17 mmol) in acetic acid (40 mL) BTEA·Br_3 (48.25 g, 111.7 mmol) and $ZnCl_2$ (15.22 g, 111.7 mmol) were added in one pot. The reaction mixture was stirred at 60 °C for 5 h until the initial orange color faded. Aqueous $Na_2S_2O_5$ and aqueous $NaHCO_3$ were added to the mixture and the solution was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 to obtain a 1:1:0.2 mixture of three diastereoisomers **10a**, **10b**, and **10c** as an orange solid that was purified from impurities by flash chromatography using a 1:1 mixture of CH_2Cl_2/petroleum, as eluent, (7.89 g, 85%): ^{1}H NMR δ (aromatics) diastereomer **10a**: 6.92 (s, Ar, 2H), diastereomer **10b**: 6.98 (s, Ar, 2H); diastereomer **10c**: 7.00 (s, Ar, 2H).

4.4. 2,2′,3,3′-Tetramethoxy-5,5′-diallyl-6,6′-dibromo-1,1′-biphenyl 11

To a solution of **10a**–**c** (mixture of the three diastereoisomers) (1.33 g, 1.60 mmol) in ethanol 95% (20 mL), Zn dust (0.30 g, 4.81 mmol) was added in one pot. The reaction mixture was stirred at reflux for 12 h. Water was added to the mixture and the solution was, then, extracted with CH_2Cl_2. The crude, dried over Na_2SO_4 gave a colorless solid that was purified by flash chromatography using a 1:1 mixture of CH_2Cl_2/petroleum, as eluent, to give **11** (0.75 g, 92%): mp 113 °C; ^{1}H NMR δ 3.54 (m, 4H), 3.67 (s, 6H), 3.88 (s, 6H), 5.10 (m, 4H), 5.91 (ddt, $J = 20.1$, 13.6, 8.8 Hz, 2H), 6.86 (s, Ar, 2H); ^{13}C NMR δ 41.04, 56.04, 60,68, 113.77, 116.69, 116.85, 134.80, 135.26, 136.03, 145.87, 152.09; Anal. Calcd for $C_{22}H_{24}Br_2O_4$: C, 51.59; H, 4.72; Found: C, 51.31; H, 4.90.

4.5. 3,3′-Dimethoxy-5,5′-diallyl-[1,1′-biphenyl]-2,2′-diyl-O,O′-bis[5-methyl-2-(1-methylethyl)-cyclohexyl]-carbonic ester 12

A solution of **5** (2.70 g, 8.27 mmol) and Et_3N (2 mL) in toluene (15 mL) was added, dropwise, to a solution of (−)-(1*R*,2*S*,5*R*)-menthyl chloroformate (3.98 g, 18.19 mmol) in toluene (15 mL) at rt under N_2. The solution was stirred at rt for 12 h, washed with 10% HCl and water and the organic phase extracted with CH_2Cl_2. The crude, dried over Na_2SO_4 gave a colorless solid that was purified by flash chromatography using a 1:1 mixture of CH_2Cl_2/petroleum, as eluent, to give **12** (5.88 g, 95%): mp 113–4 °C; ^{1}H NMR δ 0.69 (d, $J = 7.2$ Hz, 6H), 0.83 (d, $J = 7.2$ Hz, 6H), 0.89 (d, $J = 7.2$ Hz, 6H), 0.80–1.95 (series of m, 18H), 3.34 (d, $J = 6.8$ Hz, 4H) 3.82 (s, 6H), 4.47 (m, 2H), 5.05 (m, 4H), 5.94 (ddt, $J = 20.0$, 10.0, 6.8, Hz, 2H), 6.72 (d, $J = 2$ Hz, Ar, 2H), 6.76 (d, $J = 2$ Hz, Ar, 2H); ^{13}C NMR δ 16.25, 20.65, 21.97,

23.36, 25.93, 31.32, 34.08, 40.07, 40.45, 46.88, 55.91, 78.94, 112.07, 116.21, 122.32, 130.74, 136.25, 136.89, 137.91, 151.41, 152.69; Anal. Calcd for $C_{42}H_{58}O_8$: C, 73.01; H, 8.46; Found: C, 73.12; H, 8.50; $[\alpha]_D^{20} = -16.0$ (*c* 1, $CHCl_3$).

4.6. 3,3′-Dimethoxy-5,5′-bis(2,3-dibromo-propyl)-6,6′-bis(bromo)-[1,1′-biphenyl]-2,2′-diyl-O,O′-bis[5-methyl-2-(1-methylethyl)-cyclohexyl]-carbonic ester 13

To a solution of **12** (10.56 g, 15.3 mmol) in acetic acid (40 mL) BTEA·Br_3 (66.09 g, 153 mmol) and $ZnCl_2$ (20.85 g, 153 mmol) were added in one pot. The reaction mixture was stirred at 60 °C for 5 h until the initial orange color faded. Aqueous $Na_2S_2O_5$ and aqueous $NaHCO_3$ were added to the mixture and the solution was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 to obtain a mixture of six diastereoisomers **13** as an orange solid that was stirred with Et_2O (100 mL) for 1 h. The residue was then filtered to give a brown solid consisting of a 1:1:2 mixture of three diastereomers **13a** (mixture a). The solution was evaporated to obtain a 0.8:1:1 mixture of other three diastereomers as a brown solid **13b** (mixture b) (13.4 g, 75%). The two mixtures **13a** and **13b** (a and b) were used in the next reaction without any purification. ^{1}H NMR δ (aromatics) mixture a: 7.02 (s, Ar, 2H), 7.06 (s, Ar, 2H), 7.25 (s, Ar, 2H); mixture b: 7.04 (s, Ar, 2H), 7.07 (s, Ar, 2H), 7.09 (s, Ar, 2H).

4.7. (a*R*)-(−)-3,3′-Dimethoxy-5,5′-diallyl-6,6′-dibromo-[1,1′-biphenyl]-2,2′-diyl-O,O′-bis[5-methyl-2-(1-methyl-ethyl)-cyclohexyl]-carbonic ester 14

To a solution of **13a** (mixture a) (2.74 g, 2.35 mmol) in acetic acid (40 mL), Zn dust (0.77 g, 11.78 mmol) was added in one pot. The reaction mixture was stirred at 80 °C for 24 h. Aqueous $NaHCO_3$ was added to the mixture and the solution was, then, extracted with CH_2Cl_2. The crude, dried over Na_2SO_4 gave a colorless solid that was purified by flash chromatography using a 1:10 mixture of ethyl acetate/petroleum, as eluent, to give (a*R*)-(−)-**14** (1.89 g, 95%); mp 98–9 °C; ^{1}H NMR δ 0.75 (d, $J = 6.6$ Hz, 6H), 0.86 (d, $J = 6.6$ Hz, 6H), 0.92 (d, $J = 6.6$ Hz, 6H), 0.80–1.90 (series of m, 18H), 3.57 (m, 4H) 3.87 (s, 6H), 4.49 (dt, $J = 4.5$, 11.1 Hz, 2H), 5.15 (m, 4H), 6.01 (ddt, $J = 26.0$, 13.6, 8.8 Hz, 2H), 6.92 (s, Ar, 2H); ^{13}C NMR δ 16.39, 20.61, 22.00, 23.44, 25.93, 31.50, 34.09, 40.29, 40,89, 46.96, 55.98, 79.30, 113.65, 116.01, 117.02, 132.10, 135.27, 136.89, 137.77, 150.61, 151.79; Anal. Calcd for $C_{42}H_{54}Br_2O_8$: C, 59.58; H, 6.43; Found: C, 59.41; H, 6.29; $[\alpha]_D^{20} = -54.1$ (*c* 0.9, $CHCl_3$).

4.8. (a*S*)-(+)-3,3′-Dimethoxy-5,5′-diallyl-6,6′-dibromo-[1,1′-biphenyl]-2,2′-diyl-O,O′-bis[5-methyl-2-(1-methyl-ethyl)-cyclohexyl]-carbonic ester 14

Using the above procedure, mixture of diastereoisomers **13b** gave (a*S*)-(+)-**14** (90%); mp 180–182 °C; ^{1}H NMR δ 0.73 (d, $J = 6.9$ Hz, 6H), 0.82 (d, $J = 6.9$ Hz, 6H), 0.88 (d, $J = 6.9$ Hz, 6H), 0.85–1.96 (series of m, 18H), 3.54 (m, 4H) 3.83 (s, 6H), 4.47 (dt, $J = 4.2$, 10.8 Hz, 2H), 5.18 (m, 4H), 5.98 (ddt, $J = 24.8$, 14.0, 8.8 Hz, 2H), 6.89 (s, Ar, 2H); ^{13}C NMR δ 16.37, 20.66, 22.02, 23.38, 25.89, 31.51, 34.08, 40.27, 40.91, 46.95, 55.98, 79.29, 113.87, 116.87, 117.27, 132.34, 135.51, 137.64, 138.01, 150.85, 152.05; $[\alpha]_D^{20} = +38.0$ (*c* 1.1, $CHCl_3$).

4.9. (a*R*)-(+)-2,2′-Dihydroxy-3,3′-dimethoxy-5,5′-diallyl-6,6′-dibromo-1,1′-biphenyl 9

A solution of (a*R*)-**14** (1 g, 1.17 mmol) in dry THF (30 mL) was cooled at 0 °C under N_2. $LiAlH_4$ 1 M in THF (3 mL, 3 mmol) was added drop to drop with vigorous magnetic stirring. After 12 h at rt, water and 10% HCl were cautiously added. The organic phase was extracted with ether, dried over Na_2SO_4, and evaporated to afford a colorless solid that was purified by flash chromatography using a 1:1 mixture of CH_2Cl_2/petroleum, as eluent to give enantiomerically pure (a*R*)-**9** (0.51 g, 90%) and enantiomerically pure (−)-menthol (0.31 g, 85%). (a*R*)-(+)-**9**: mp 140.2 °C; ^{1}H NMR δ 3.55 (m, 4H), 3.91 (s, 6H), 5.12 (m, 4H), 5.60 (br s, 2H), 6.01 (ddt, $J = 18.9$, 10.0, 8.4 Hz, 2H), 6.81 (s, Ar, 2H); ^{13}C NMR δ 41.01, 56.34, 112.09, 116.58, 117.57, 125.19, 130.95, 136.17, 142.42, 145.90; Anal. Calcd for $C_{14}H_{12}Br_2O_4$: C, 49.61; H, 4.16; Found: C, 49.81; H, 4.00; $[\alpha]_D^{20} = +6.4$ (*c* 0.55, $CHCl_3$); $[\alpha]_{436}^{20} = +22.2$ (*c* 0.55, $CHCl_3$).

4.10. (a*S*)-(−)-2,2′-Dihydroxy-3,3′-dimethoxy-5,5′-diallyl-6,6′-dibromo-1,1′-biphenyl 9

Using the above procedure, diastereomer (a*S*)-**14** gave (a*S*)-(−)-**9**, 89%: $[\alpha]_D^{20} = -6.5$ (*c* 0.3, $CHCl_3$), $[\alpha]_{436}^{20} = -22.4$ (*c* 0.3, $CHCl_3$).

4.11. 2,2′-Dihydroxy-3,3′-dimethoxy-5,5′-di(2,3-dibromo-propyl)-6,6′-bis(bromo)-1,1′-biphenyl 15

To a solution of **5** (0.3 g, 0.92 mmol) in Et_2O (40 mL), Br_2 (1.17 g, 7.4 mmol) was added in one pot. The reaction mixture was stirred at rt for 3 h. Aqueous $Na_2S_2O_5$ was added to the mixture and the solution was, then, extracted with Et_2O. The crude, dried over Na_2SO_4 gave a colorless solid that was purified by flash chromatography using a 1:2 mixture of ethyl acetate/petroleum, as eluent to obtain **15** as a 1:0.7:0.9 mixture of three diastereomers **15(a–c)** that was used in the next reaction without separation (0.69 g, 94%): ^{1}H NMR δ (aromatics) diastereomer **15a**: 6.89 (s, Ar, 2H), diastereomer **15b**: 6.94 (s, Ar, 2H), diastereomer **15c**: 6.98 (s, Ar, 2H).

4.12. 2,2′-Dihydroxy-3,3′-dimethoxy-5,5′-diallyl 6,6′-dibromo-1,1′-biphenyl 9

To a solution of **15** (mixture of three diastereoisomers **a–c**) (1.29 g, 1.60 mmol) in ethanol 95% (20 mL), Zn dust

(0.30 g, 4.81 mmol) was added in one pot. The reaction mixture was stirred at reflux for 12 h. Water was added to the mixture and the solution was, then, extracted with CH_2Cl_2. The crude, dried over Na_2SO_4 gave a colorless solid that was purified by flash chromatography using a 1:1 mixture of CH_2Cl_2/petroleum, as eluent, to give **9** (0.7 g, 91%).

4.13. (a*R*,*S*)-(−)-Dibenzo-(d,f)(1,3,2)-dioxaphosphepin-6-amine-1,11- dibromo-2,10-bis(2-propenyl)-4,8-dimethyl-*N*-(1-phenylethyl)-6-sulfide 16

(*S*)-(−)-*N*-((*S*)-α-methylbenzyl)-dichlorothiophosphoroamidate **17** (0.52 g, 2.0 mmol) was added dropwise to a solution of (a*R*)-(+) **9** (0.82 g, 1.70 mmol) in py (50 mL) at rt under N_2. After 12 h under reflux, the reaction mixture was cooled and made acid with 10% H_2SO_4. Water was added and the organic phase was extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated to dryness to obtain a colorless solid. The crude was purified by flash chromatography using a 1:1 mixture of CH_2Cl_2/petroleum, as eluent, to give **16** (0.95 g, 84%): mp 125 °C; ^{1}H NMR δ 1.50 (d, $J = 6.4$ Hz, 3H), 3.41 (s, 3H), 3.4–3.7 (series of m, 5H), 3.92 (s, 3H), 4.71 (m, 1H), 5.11 (m, 4H), 6.01 (ddt, $J = 19.2$, 10.4, 6.4 Hz, 2H), 6.75 (s, Ar, 1H), 6.96 (s, Ar, 1H) 7.20–7.50 (series of m, Ar, 5H); ^{13}C NMR δ aliphatics: 29.71, 41.09, 52.91, 55.45, 56.78; Anal. Calcd for $C_{28}H_{28}O_4$ NPSBr$_2$: C, 50.68; H, 4.26; Found: C, 50.77; H, 4.33; $[\alpha]_D^{20} = -221.7$ (c 0.3, $CHCl_3$), $[\alpha]_{436}^{20} = -506.5$ (*c* 0.3, $CHCl_3$), $[\alpha]_{365}^{20} = -929.1$ (*c* 0.3, $CHCl_3$).

4.14. Interconversion measurements of (a*R*)-(+)-9

Racemic biphenyl **9** has showed a clear separation ($\alpha = 1.36$) in chiral HPLC with Chiracel OD column (10 μm, 25 cm × 0.46 ID) at flow rate of 1.0 mL/min, 254 UV detection, using a gradient mixture 88:12 w:w *n*-hexane/2-propanol for 20′ and then 85:15 w:w *n*-hexane/2-propanol for 10′ as mobile phase. Racemization measurements were performed by injections of dibromo (a*R*)-(+)-**9** at rt in several times,heating on refluxing chloroform and, finally, on *n*-butanol at 115 °C for 10 h. Increase of (a*S*)-(−)-**9** was not detected in all condictions.

4.15. X-ray structure determination of (a*R*,*S*)-(−)-16

Crystal description: colorless prism 0.37 × 0.20 × 0.12 mm. $M_r = 665.36$, orthorhombic, space group $P2_12_12_1$, $a = 8.562(1)$, $b = 17.929(2)$, $c = 19.028(2)$ Å, $V = 2921.0(6)$ Å^3, $Z = 4$, $T = 293(2)$ K, $\mu = 2.934$ mm^{-1}. X-ray data were collected on a Bruker Smart Apex CCD area detector using graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). Data reduction was made using SAINT programs; absorption corrections based on multiscan were obtained by SADABS.[29] The measured reflections 78,750 in number, 6724 independent reflections, 4199 reflections with $I > 2\sigma(I)$, $3.12 < 2\theta < 55.00°$, $R_{int} = 0.084$. The structure was solved by SIR-92[30] and refined on F^2 by full-matrix least-squares using SHELXL-97.[31] Refinement on 6724 reflections, 389 parameters, 58 restraints. Restraints were applied to both the propenyl groups, which assume in the crystal two alternative conformations. Flack parameter[32] for determination of the absolute configuration = 0.000(9). Final $R = 0.0448$, $wR = 0.0916$ for data with $F^2 > 2\sigma(F^2)$, $(\Delta/\sigma)_{max} = 0.001$, $\Delta\rho_{max} = 0.37$, $\Delta\rho_{min} = -0.34$ eÅ^{-3}.

Tables of atomic coordinates, anisotropic thermal parameters, bond lengths and angles of (a*R*,*S*)-**16** may be obtained free of charge from The Director CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK, on quoting the deposition number CCDC 219445, the names of the authors and the journal citation (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk; web site: http://www.ccdc.cam.ac.uk).

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References and notes

1. (a) Sévenet, R. *J. Ethnopharm.* **1991**, *32*, 83–90; (b) Vlietinck, A. J.; De Bruye, T.; Apers, S.; Pieters, L. A. *Planta Med.* **1998**, *64*, 97–109; (c) Kinghorn, A. D.; Farnsworth, N. R.; Soejarto, D. D.; Cordell, G. A.; Pezzuto, J. M.; Udeani, G. O.; Wani, M. C.; Wall, M. E.; Navarro, H. A.; Kramer, R. A.; Menendez, A. T.; Fairchild, C. R.; Kane, K. E.; Forenza, S.; Vyas, D. M.; Lam, K. S.; Shu, Y.-Z. *Pure Appl. Chem.* **1999**, *71*, 1611–1618; (d) Gawronski, J.; Gawronka, K. In: *Tartaric and Malic Acid in Synthesis*; Wiley: New York, 1999; (e) Pommier, Y.; Marchand, C.; Neamati, N. *Antiv. Res.* **2000**, *47*, 139–148.
2. (a) Sakai, N.; Brennan, K. C.; Weiss, L.; Matile, S. *J. Am. Chem. Soc.* **1997**, *119*, 8627–8726; (b) Solé, S.; Merkoçi, A.; Alegret, S. *Trends Anal. Chem.* **2001**, *20*, 102–110; (c) Ciszewski, A.; Milczarek, G. *Eletroanalysis* **2001**, *13*, 860–867.
3. Brunner, H.; Zettlmeier, W. In: *Handbook of Enantioselective Catalysis*; VCH: Weinheim, 1993; Vols. I–II.
4. Lednicer, D. *Strategies for Organic Drug Synthesis and Design*; Wiley: New York, 1998.
5. Koskinen, A. *Asymmetric Synthesis of Natural Products*; Wiley: Chichester, England, 1993.
6. (a) Gilbertson, G.; Koenig, R. *Anal. Chem.* **1981**, *53*, 61R–77R; (b) Marotti, M.; Piccaglia, R.; Giovanelli, E. *J. Agric. Food Chem.* **1996**, *44*, 3926–3929; (c) Markowitz, K.; Moynihan, M.; Liv, M.; Kim, S. *Oral Surg. Oral Phatol.* **1992**, *73*, 729–737; (d) Asha, M. K.; Prashanth, D.; Murali, B.; Padmaja, R.; Amit, A. *Fitoterapia* **2001**, *72*, 669–670.
7. (a) Hattori, M.; Hada, S.; Watahiki, A.; Ihara, H.; Shu, Y.-Z.; Kakiuchi, N.; Mizuno, T.; Namba, T. *Chem. Pharm. Bull.* **1986**, *34*, 3885–3893; (b) Himejima, M.; Kubo, I. *J. Nat. Prod.* **1992**, *55*, 620–625; (c) Fujisawa, S.; Atsumi, T.; Satoh, K.; Sakagami, H. *J. Dent. Res.* **2003**, *82*, 43–47.

8. (a) Ohloff, G. *Scent and Fragrance: The Fascination of Odors and Their Chemical Perspectives*; Springer: Berlin, 1993; (b) Yanishlieva, N. V.; Marinova, E. M. *Eur. J. Lipid Sci. Technol.* **2001**, *103*, 752–767; (c) Suppakul, P.; Miltz, J.; Sonneveld, K.; Biger, S. *J. Agric. Food Chem.* **2003**, *51*, 3197–3207.
9. (a) Baucher, M.; Monties, B.; Mantagu, M.; Boerjan, W. *Crit. Rev. Plant Sci.* **1998**, *17*, 125–197; (b) Pinto, M. B. Carbohydrates and Their Derivatives Including Tannins, Cellulose, and Related Lignins. In *Comprehensive Natural Products Chemistry*; Barton, D., Nakanishi, K., Meth-Cohn, O., Eds.; Elsevier: Amsterdam, 1999; Chapter 3.
10. (a) Jones, H. A.; Haller, H. L. *J. Org. Chem.* **1940**, *62*, 2558–2559; (b) De Diaz, A. M. P.; Gottlieb, H. E.; Gottlieb, O. R. *Phytochemistry* **1980**, *19*, 681–682; (c) Suarez, M.; Bonilla, J.; De Diaz, A. M. P.; Achenbach, H. *Phytochemistry* **1983**, *22*, 609–610; (d) Taira, J.; Ikemoto, T.; Yoneya, T.; Hagi, A.; Murakami, A.; Makino, K. *Free Rad. Res. Commun.* **1992**, *16*, 197–204.
11. (a) Namba, T.; Tsunezuka, M.; Hattori, M. *Planta Med.* **1982**, *44*, 100–106; (b) Lo, Y.-C.; Teng, C.-M.; Chen; Chen, C.-C.; Hong, C.-Y. *Biochem. Pharmacol.* **1994**, *47*, 549–553; (c) Yahara, S.; Nishiyori, T.; Kohda, A.; Nohara, T.; Nishioka, I. *Chem. Pharm. Bull.* **1991**, *39*, 2024–2036; (d) Kouno, I.; Morisaki, T.; Hara, Y.; Yang, C.-S. *Chem. Pharm. Bull.* **1991**, *39*, 2606–2608.
12. (a) Hattori, M.; Endo, Y.; Takebe, S.; Kobashi, K.; Fukasaku, N.; Namba, T. *Chem. Pharm. Bull.* **1986**, *34*, 158–167; (b) Konoshima, T.; Kozuka, M.; Tokuda, H.; Nishino, H.; Iwashima, A.; Haruna, M.; Ito, K.; Tanabe, M. *J. Nat. Prod.* **1991**, *54*, 816–822; (c) Fujita, S.; Taira, J. *Free Radical Biol. Med.* **1994**, *17*, 273–277; (d) Haraguchi, H.; Ishikawa, H.; Shirataki, N.; Fukuda, A. *J. Pharm. Pharmacol.* **1997**, *49*, 209–212; (e) Maruyama, Y.; Kuribara, H.; Morita, M.; Yuzurihara, M.; Weintraub, S. T. *J. Nat. Prod.* **1998**, *61*, 135–138; (f) Shen, Y.-C.; Sung, Y.-J.; Chen, C.-F. *Eur. J. Pharmcol.* **1998**, *343*, 79–86; (g) Chang, B. S.; Lee, Y. M.; Ku, Y.; Bae, K. H.; Chung, C. P. *Planta Med.* **1998**, *64*, 367–369; (h) Matsuda, H.; Kageura, T.; Oda, M.; Morikawa, T.; Sakamoto, Y.; Yoshikawa, M. *Chem. Pharm. Bull.* **2001**, *49*, 716–720.
13. (a) Watanabe, H.; Watanabe, K.; Hagino, K. *J. Pharmacobiodyn.* **1983**, *6*, 184–190; (b) Gustafson, K. R.; Cardellina, J. H., II; McMahon, J. B.; Pannell, L. K.; Cragg, G. M.; Boyd, M. R. *J. Org. Chem.* **1992**, *57*, 2809–2811; (c) Zacchino, S. A.; López, S. N.; Pezzenati, G. D.; Furlán, R. L.; Santecchia, C. B.; Muñoz, L.; Giannini, F. A.; Rodríguez, A. M.; Enriz, R. D. *J. Nat. Prod.* **1999**, *62*, 1353–1357.
14. (a) Taira, J.; Ikemoto, T.; Mimura, K.; Hagi, A.; Murakami, A.; Makino, K. *Free Radical Res. Commun.* **1993**, *19*, S71–S77; (b) Fujisawa, S.; Kashiwagi, Y.; Atsumi, T.; Iwakura, I.; Ueha, T.; Hibino, Y.; Yokoe, I. *J. Dentistry* **1999**, *27*, 291–295; (c) Fujisawa, S.; Atsumi, T.; Kadoma, Y.; Sakagami, H. *Toxicology* **2002**, *177*, 39–54.
15. (a) Gerosa, R.; Borin, M.; Menegazzi, G.; Puttini, M.; Cavalieri, G. *J. Endodont.* **1996**, *22*, 532–534; (b) Ogata, M.; Hoshi, M.; Urano, S.; Endo, T. *Chem. Pharm. Bull.* **2000**, *48*, 1467–1469; (c) Fujisawa, S.; Okada, N.; Muraoka, E. *Dent. Mater. J.* **2001**, *20*, 237–242.
16. (a) Delogu, G.; Fabbri, D. *Tetrahedron: Asymmetry* **1997**, *8*, 759–763; (b) Delogu, G.; Fabbri, D.; Dettori, M. A.; Forni, A.; Casalone, G. *Tetrahedron: Asymmetry* **2000**, *11*, 4417–4427; (c) Capozzi, G.; Delogu, G.; Fabbri, D.; Marini, M.; Menichetti, S.; Nativi, C. *J. Org. Chem.* **2002**, *67*, 2019–2026; (d) Delogu, G.; Salaün, J.; de Candia, C.; Fabbri, D.; Piras, P.; Ollivier, J. *Synthesis* **2002**, 2271–2279; Delogu, G.; Dettori, M. A.; Patti, A.; Pedotti, S.; Forni, A.; Casalone, G. *Tetrahedron: Asymmetry* **2003**, *14*, 2467–2474.
17. (a) Van der Meer, S.; Pouwels, H. *J. Med. Chem.* **1969**, *12*, 534; Chen, D.-F.; Zhang, S.-X.; Xie, L.; Xie, J.-X.; Chen, K.; Kashiwada, Y.; Zhou, B.-N.; Wang, P.; Cosentino, L. M.; Lee, K.-H. *Biorg. Med. Chem.* **1997**, *5*, 1715; (b) Fujihashi, T.; Hara, H.; Sakata, T.; Mori, K.; Higuchi, H.; Tanaka, A.; Kaji, H.; Kaji, A. *Antimicrob. Agents Chemother.* **1995**, *39*, 2000.
18. (a) Higashizima, T.; Sakai, N.; Nozaki, K.; Takaya, H. *Tetrahedron Lett.* **1994**, *35*, 2023–2026; (b) Mikami, K.; Matsukawa, S. *Nature* **1997**, *385*, 613; (c) Matsukawa, S.; Mikami, K. *Tetrahedron: Asymmetry* **1997**, *8*, 815–816; (d) Chavarot, M.; Byrne, J.; Chavant, P. Y.; Pardillos-Guindet, J.; Vallée, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 3889–3894.
19. (a) Jendralla, H.; Li, C. H.; Paulus, E. *Tetrahedron: Asymmetry* **1994**, *5*, 1297–1320; (b) Harada, T.; Takeuchi, M.; Hatsuda, M.; Ueda, S.; Oku, A. *Tetrahedron: Asymmetry* **1996**, *7*, 2479–2482.
20. (a) Asano, A.; Gisvold, O. *J. Am. Pharm. Ass.* **1948**, 169–173; (b) Bassoli, A.; Di Gregorio, G.; Rindone, B.; Tollari, S.; Chioccara, F.; Salmona, M. *Gazz. Chim. Ital.* **1988**, *118*, 763–768; (c) De Farias Dias, A. *Phytochemistry* **1988**, *27*, 3008–3009; (d) Krawczyk, A. R.; Lipkowska, E.; Wróbel, J. T. *Collect. Czech. Chem. Commun.* **1991**, *56*, 1147–1150; (e) Marques, F. A.; Simonelli, F.; Oliveira, A. R. M.; Gohr, G. L.; Leal, P. C. *Tetrahedron Lett.* **1998**, *39*, 943–946; (f) Barba, I.; Chinchilla, R.; Gõmez, C. *J. Org. Chem.* **1990**, *55*, 3270–3272.
21. De Souza, N. J.; Kothare, A. N.; Nadkarny, V. V. *J. Org. Chem.* **1966**, *9*, 618–620.
22. Delogu, G.; Fabbri, D.; Dettori, M. A.; Casalone, G.; Forni, A. *Tetrahedron: Asymmetry* **2000**, *11*, 1827–1833.
23. Fabbri, D.; Delogu, G.; De Lucchi, O. *J. Org. Chem.* **1993**, *58*, 1748.
24. Burnett, M. N.; Johnson, C. K. *ORTEP-III: Oak Ridge Thermal Ellipsoid Plot Program for Crystal Structure Illustrations*, Oak Ridge National Laboratory Report ORNL-6895, **1996**.
25. Delogu, G.; Fabbri, D.; Dettori, M. A.; Forni, A.; Casalone, G. *Tetrahedron: Asymmetry* **2001**, *12*, 1451–1458.
26. Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441–451.
27. Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem.* **2000**, *43*, 3443–3447.
28. (a) Kelly, T. R.; Meghani, P.; Ekkundi, V. *Tetrahedron Lett.* **1990**, *24*, 3381–3384; (b) Bonafoux, D.; Hua, Z.; Wang, B.; Ojima, I. *J. Fluor. Chem.* **2001**, *112*, 101–108.
29. Bruker, *SMART*, *SAINT* and *SADABS*; Bruker AXS Inc., Madison, Wisconsin, USA, **1997**.
30. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. *J. Appl. Crystallogr.* **1994**, *27*, 435.
31. Sheldrick, G. M. *SHELX-97. Program for the Refinement of Crystal Structures*, University of Göttingen, Göttingen (Germany), **1997**.
32. Flack, H. D. *Acta Crystallogr. Sect. A* **1983**, *39*, 876–881.