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2,2′-Dihydroxy-3,3′-dimethoxy-5,5′-dimethyl-6,6′-dibromo-1,1′-biphenyl: preparation, resolution, structure and biological activity

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Abstract—The preparation and resolution of the titled conformationally stable biphenyl **1** has been performed in high chemical yield starting from creosol **2**. Enantiopure biphenyls (a*R*)-(+)-**1** and (a*S*)-(−)-**1** were obtained by the corresponding menthylcarbonate diastereomer and successive reduction. The absolute configuration and specific rotation were correlated by X-ray analysis of the crystal structure of diastereopure menthylcarbonate (a*S*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-(+)-**16**. Preliminary biological evaluation of both racemic enantiomers of **1** has been carried out on melanoma cell lines and significant and selective anticancer activity has been observed for the enantiomer (a*S*)-(−)-**1**.

1. Introduction

The rich structural diversity and complexity of natural products has attracted large interest of synthetic chemists due to the interesting stereochemical features and biological activities.[1] Due to the importance of chirality, great efforts in synthetic strategy have also been devoted to the preparation of enantiopure analogues of natural occurring compounds.[2]

The field of synthetic methods is highly advanced at present but, at the same time, is still lacking in many aspects such as economy and easy feasibility.[3] This aspect is often a restrictive factor in the preparation of naturally occurring compounds of high stereochemical and functional complexity.

Hydroxylated biphenyl units are present in a large number of naturally occurring compounds, such as vancomycin, biphenomycin, ellagitannins; the latter occurs in Nature in more than 500 derivatives.[4–6] Generally, hydroxylated biphenyl derivatives have less complex structures compared to naturally occurring compounds lacking in this unit. In virtue of the axial chirality shown in rotationally hindered hydroxylated biphenyls, simple synthetic strategies and often straightforward resolution methodologies are required in the preparation of this class of compounds.[7] It is generally assumed that the stereogenic axis is involved in pharmacological activities[4–6] of hydroxylated biphenyls as well as in the chirality transfer in catalytic and stoichiometric processes.[8]

Given the importance of the biphenyl hydroxylated unit, increasing attention has been paid to this class of compounds from a synthetic, stereochemical and biological point of view.

In a previous article, we reported the synthesis of the 6,6′-dibromo-dehydrodieugenol **3** in its enantiomerically pure form starting from 2-methoxy-4-allylphenol (eugenol) **4**.[9] Although biphenyl **3** retains the natural configurationally flexible biphenyl dehydrodieugenol **5**, two atropisomers of compound **3** were isolated due to the hindered rotation around the stereogenic biaryl axis. We have observed that both racemic and the enantiomers produce significant antinociceptive effects as revealed by the reduction of the number of acetic acid-induced writhing responses.[10]

Hydroxylated bromo biphenyls play an important role in therapy as antibacterial, anti-HIV-1 agents[11] and more recently have displayed significant cytotoxicity against

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human solid tumour cell lines in bromotyrosine dimer derivatives.[12] It is known that the presence of either a bromo or chloro functionality in hydroxylated biaryls makes them effective chiral ligands or chiral activators in asymmetric catalytic processes since halides improve Lewis acidity.[13] In particular, the presence of a bromo group at the *ortho–ortho′* positions significantly influences the value of the dihedral angle of biphenol and thus provides an important change in the efficiency of asymmetric catalysis.[13,14]

As part of our continuing search among hydroxylated biphenyls[15] as building blocks for the preparation of promising pharmaceutics as well as new ligands, we have selected 2,2′-dihydroxy-3,3′-dimethoxy-5,5′-dimethyl-1,1′-biphenyl **6**, namely dehydrodicreosol, as a scaffold for preparing *ortho–ortho′*-dibromo-dehydrodicreosol derivatives.

5,5′-Disubstituted biphenyl structures (C–C linkages) occur frequently in softwood lignins because they come from the symmetric coupling of the corresponding monomers.[16] Dehydrodicreosol **6**, a conformationally flexible biphenyl, is the symmetrical dimer of 2-methoxy-4-methyl phenol (creosol) **2**.[17] Compound **6** has been intensively studied as a model compound in the coupling of lignin monomers[18] and displays higher cytotoxic activity and antiradical efficiency than that observed in creosol **2** (Fig. 1).[19] High cytotoxic activity was observed when a human submandibular gland carcinoma cell line was treated with dehydrodicreosol **6**, which, on the contrary, manifests sevenfold less cytotoxic activity against human gingival fibroblasts.[20] In virtue of this selectivity, **6** is a promising antitumoural agent. The cytotoxicity of dehydrodicreosol **6** against tumour cells is likely associated with the high production of CH_3^+ intermediates instead of quinone methide radicals as observed for monomer **2** and generally for *O*-methoxy-4-alkylphenols.[21] In fact, the presence of two methyl groups at the 5,5′-positions and four hydroxylated groups seems to be a chemostructural requirement for the high cytotoxic activity.[22]

Our starting point was to insert bromine at the 6,6′-position of dehydrodicreosol **6** 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 **1**. According to the anticancer activity observed in hydroxylated biphenyls containing bromo groups, an increase in the antitumoural activity would be expected in brominated biphenyl **1**, whose structure is similar to dehydrodicreosol **6**.

2. Results and discussion

According to the literature, commercial creosol **2** was treated at 0 °C with a solution of methyltributylammonium permanganate (MTBAP) in dichloromethane to give dehydrodicreosol **6** in 85% yield.[17b] Biphenyl **6** was obtained as a colourless solid.

We have explored different bromination conditions in order to address selective bromination. Our aim was to brominate the reactive 6,6′-positions of the aromatic rings maintaining the methyl groups or to transform the methyl into a bromomethyl group, excluding further ring-bromination. Direct bromination of dehydrodicreosol **6** with 2.2 equiv of Br_2 in ether at rt gave biphenyl **1** in 90% yield. Ether appeared to be the most convenient solvent compared to the other solvents generally used in the bromination reaction in the presence of Br_2 (Scheme 1).[23]

With a slight adaptation of the method reported in the literature for related structures,[24] the hydroxyl groups were protected with tetraethylene glycol to obtain biphenyl **7** starting from the reaction of biphenyl **1** with tetraethylene glycol ditosylate in the presence of K_2CO_3 in DMF at 60 °C (Scheme 1). Biphenyl **7**, obtained in 65% overall yield starting from **6** (Scheme 1, paths a and b), is also achievable with comparable overall yield, by direct protection of the hydroxyl groups of dehydrodicreosol **6** with tetraethylene glycol to give **8** and selective bromination at the 6,6′ positions of the aromatic rings with 2.2 equiv of NBS, benzyl peroxide (BPO) in CCl_4 at rt (Scheme 1, path b–c).

Both biphenyls **7** and **8** have a tetraethylene glycol ring that should be a suitable ligand to complex a Na^+ ion.[24,25] Biphenyl **7** is conformationally stable and, thus, two enantiomers can be evidenced at rt. In order to have a multifunctional ligand, we thought to transform the methyl groups of **7** into suitable functional groups that could be subjected to further transformations.[26] According to the general trend of the bromination reaction carried out in the presence of NBS and BPO in CCl_4 on methyl-substituted anisoles, side-chain brominations would be expected

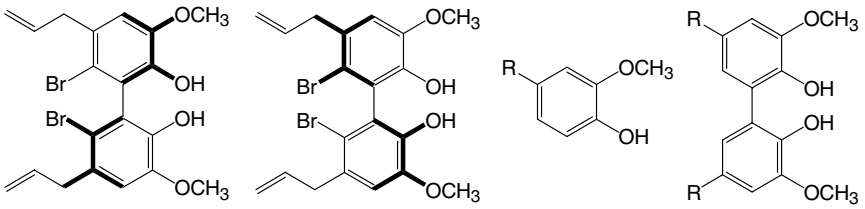
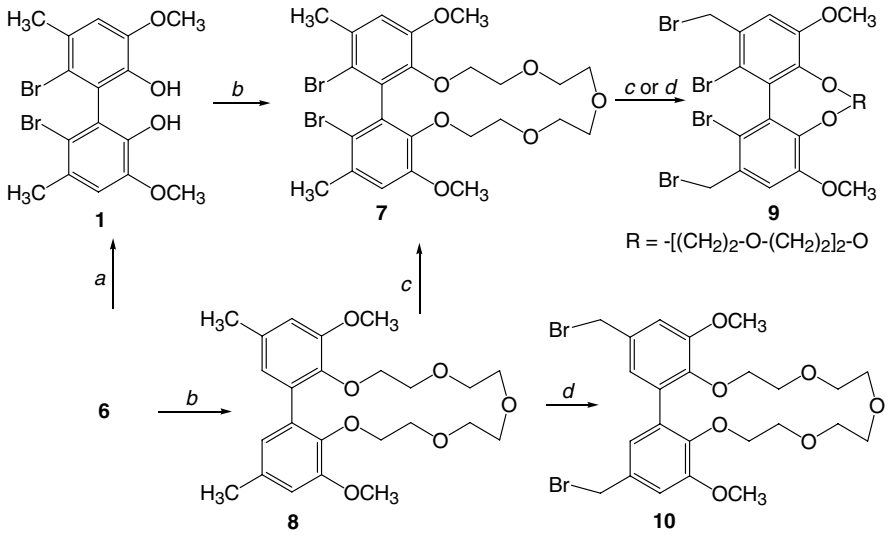


Figure 1.



Scheme 1. Synthesis of hydroxylated biphenyls containing bromo group. Reagents and conditions: (a) 2.2 equiv Br_2, Et_2O, rt, 2 h (90%); (b) $TsO[(CH_2)_2O(CH_2)_2]_2OTs$, K_2CO_3, DMF, 60 °C (**7**: 12 h, 40%; **8**: 14 h, 50%); (c) 2.2 equiv NBS, BPO, CCl_4 (**7**: rt, 12 h, 64%; **9**: rt to 70 °C, 4 h, 60%); (d) 2.2 equiv NBS, hν (200 W), CCl_4, reflux, 1 h (30%).

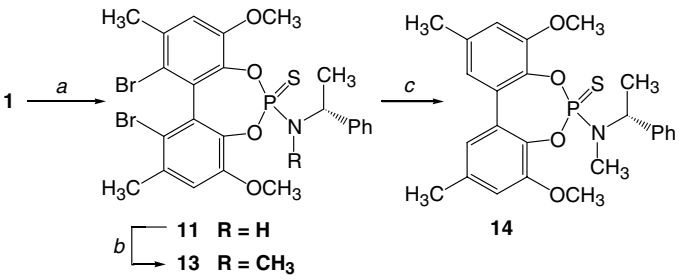
for biphenyl **7**.[23d,e] Biphenyl **9** was obtained in 60% yield after purification by flash chromatography (Scheme 1, path c). Repeated attempts at changing the reaction conditions (stoichiometry of NBS, temperature, time) did not improve the yield of biphenyl **9**.

The light-induced reaction of side-chain bromination of anisole derivatives with NBS in CCl_4 has been studied by Bickelhaupt et al.[23d] According to their report, the side-chain bromination of compound **7** would be preferred to aromatic bromination since radical generation at the methyl group would be more favoured. We subjected biphenyl **7** to light-induced bromination in the presence of NBS in CCl_4 in such a way that a gentle reflux was maintained (Scheme 1, path d). Under these conditions, biphenyl **7** was scarcely reactive, giving only 20% yield of dibromomethyl biphenyl **9**. At first, we attributed this poor reactivity of biphenyl **9** to the bulkiness of the two bromo groups at the *ortho–ortho′* positions that would exert a negative effect ion in the formation of the methide radical, which would be the key intermediate of the side-chain bromination under light irradiation.[23c,d] Nevertheless, only a slight increase in the yield of methyl bromination was observed when we performed the same reaction on biphenyl **8**, which is lacking in bromo atoms at the *ortho–ortho′* positions (Scheme 1, path d). Biphenyl **10** was isolated in 30% yield by flash chromatography and no nuclear aromatic bromination was observed. Other steric and electronic factors should be taken into account in order to justify the unfavourable generation of the methide radical and its resonance stabilization. According to what was observed such as in biphenyl analogues, in biphenyl **10**, the relative orientation of the methoxyl groups with respect to the aromatic ring should also be considered.[27]

All compounds prepared were solids, air stable and easily separated and purified by flash chromatography using appropriate solvent mixtures.

Our aim was to produce hydroxylated biphenyl bromo containing in enantiopure form. Thus, we had planned to resolve them by transformation into diastereomer derivatives, which would allow us to assign also the absolute configuration for each enantiomer.

We prepared phosphorothioamidate **11** treating racemic **1** with (*S*)-(−)-$Cl_2P(S)NHCH(CH_3)Ph$ **12** in the presence of refluxing pyridine.[28] In this case we chose an inexpensive chiral source, (*S*)-(−)-α-methylbenzylamine, which was used in an equimolar ratio and was expected to be recovered, under the reduction conditions, without a loss of enantiomeric purity. The two phosphorothioamidates (a*R*,*S*)-**11** and (a*S*,*S*)-**11** were obtained in 80% yield after flash chromatography. All attempts to isolate one single diastereomer proved unsuccessful (Scheme 2, path a). A sharp difference in the solubility of two diastereomers **11** was reached after N-methylation. When an equimolar mixture of phosphorothioamidates (a*R*,*S*)-**11** and (a*S*,*S*)-**11** was treated with CH_3I under phase-transfer catalysis, *N*-methyl phosphorothioamidates (a*R*,*S*)-**13** and (a*S*,*S*)-**13** were achieved in 74% yield in a 1:1 ratio (Scheme 2, path b). Each diastereomer **13** was separated after flash chroma-



Scheme 2. Synthesis of phosphorothioamidate diastereomers. Reagents and conditions: (a) compound **12**, py, reflux, 12 h (**11**: 80%); (b) CH_3I, TBAOH, CH_2Cl_2, H_2O (**13**: 74%); (c) $LiAlH_4$, THF (94%).

tography in 15% yield with 99% de. Most diastereomers **13** were collected as a mixture of both. Recrystallization of one diastereomer **13** from *n*-hexane allowed us to collect crystals that, unfortunately, were not suitable for X-ray analysis. The cleavage of *N*-methyl phosphothioamidate biphenyl derivatives requires stoichiometric quantities of $LiAlH_4$ in THF under heating at 60 °C. All attempts to deprotect the phenolic hydroxyls of diastereomers **13** under these conditions failed. The reaction afforded, even at room temperature, only debromination products as expected for aromatic rings containing bromo groups when treated with hydrides (Scheme 2, path c).[29] Biphenyl **14** was recovered from the reaction in virtually quantitative yield. The failure to recover pure diastereomers **13** in high yield as well as to collect suitable crystals for diffraction analysis prompted us to investigate another resolving agent.

In a previous article, 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.[30]

We decided to transform dehydrodicreosol **6** in the corresponding bis-menthylcarbonate (1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**15** by treatment with 2.2 equiv of (−)-menthylchloroformate and triethylamine at rt using toluene as a solvent. Bis-menthylcarbonate (1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**15** was achieved in 90% yield (Scheme 3, path a).

When the bromination reaction was carried out on dicarbonate **15** using 4 equiv of [BTEA·Br_3] and 5 equiv of $ZnCl_2$ in CH_3COOH, after 2 h at 60 °C, a mixture of the two diastereomers (a*R*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**16** and (a*S*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**16** was obtained in a 1:1 ratio and 80% yield (Scheme 3, path b). Complete regioselectivity as well as conformational stability of dibromo derivate **16** was achieved in only one reaction step. Both diastereomers of **16** were readily separated by flash chromatography with 99% de. Despite the complex structure of the diastereomers of **16**, the presence of a C_2 symmetry axis allowed us to have simplified NMR spectra and thus calculate the diastereomeric ratio.

Suitable crystals were recovered after recrystallization from *n*-hexane, which, when subjected to X-ray analysis, allowed us to unequivocally assign both the structure and absolute configuration of (a*S*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-(+)-**16**.

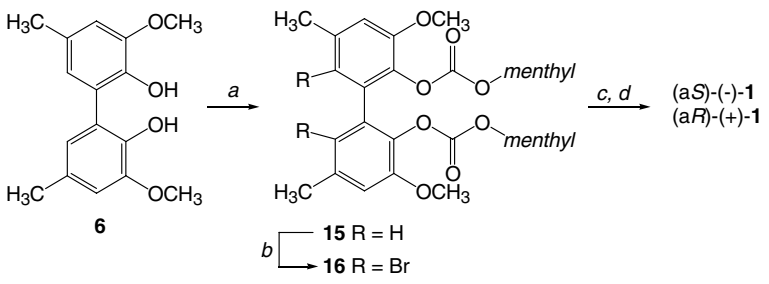
After the reduction of the carbonate group in the presence of a 1 M solution of $LiAlH_4$ in THF at rt, each diastereomer **16** gave the two atropo-enantiomers (+)-**1** and (−)-**1** in 90% yield (Scheme 3). In this case, although these conditions are favourable for the debromination reaction,[29] the high reactivity of the carbonate group allowed us to obtain biphenol **1** in 90% yield with traces of debrominated product.

The enantiomeric purity of each biphenol **1** was >99%, and related to the diastereomeric excess of the corresponding menthylcarbonate **16**.

Atropo-enantiomer **1** has a quite high interconversion barrier in solution in most solvents. Interconversion of biphenyl (a*S*)-**1** was monitored by polarimetric measurements, whereas interconversion of diastereomer (a*R*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-(−)-**16** was detected by ^1H NMR, both at different temperatures and times. Enantiopure biphenol **1** does not racemize in xylene even when heated to 100 °C for 12 h. Bromobiphenol **1** and diastereomer (a*R*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-(−)-**16** are thermally and chemically stable.

2.1. X-ray analysis and computational studies

A perspective view of (a*S*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-(+)-**16** is shown in Figure 2. This compound crystallizes in the rather unusual (for organic compounds) hexagonal $P3_121$ space group with half a molecule in the asymmetric unit. The molecule is completed by the $(-x, -x+y, 1/3-z)$ symmetry operation, denoted here and in Figure 2 by a superscript. The methoxy carbon atom C8 is located significantly far from the plane through the atoms of the aromatic ring (0.44(1) Å). The dihedral angle τ between the least-squares planes through the biphenyl rings, 81.3(2)°, is indicative of high configurational stability. This value is in the range (76–88°) observed for not constrained *ortho–ortho′* dibromo-substituted biphenyls, as found through a survey on the Cambridge Structural Database (CSD version Nov. 2005, no refcode restrictions applied).[32] Among the retrieved structures, the biphenyl derivative previously reported by us,[30] differing from **16** for the absence of the methyl groups at the 5,5′ positions, showed dihedral angles τ slightly larger with respect to **16**, that is 86.1(2)° and 87.6(3)° for the two molecules of the asymmetric unit. No difference, within the experimental error, was otherwise observed between the biphenyl moieties of the



Scheme 3. Resolution of **1** via menthylcarbonate diastereomers. Reagents and conditions: (a) (1*R*,2*S*,5*R*)-(−)-menthyl chloroformate, Et_3N, toluene (**15**: 90%); (b) BTEA·Br_3, $ZnCl_2$, AcOH, 60 °C, 2 h (**16**: 80%); (c) separation of diastereomers by flash chromatography; (d) $LiAlH_4$, THF, 0 °C to rt, 90%.

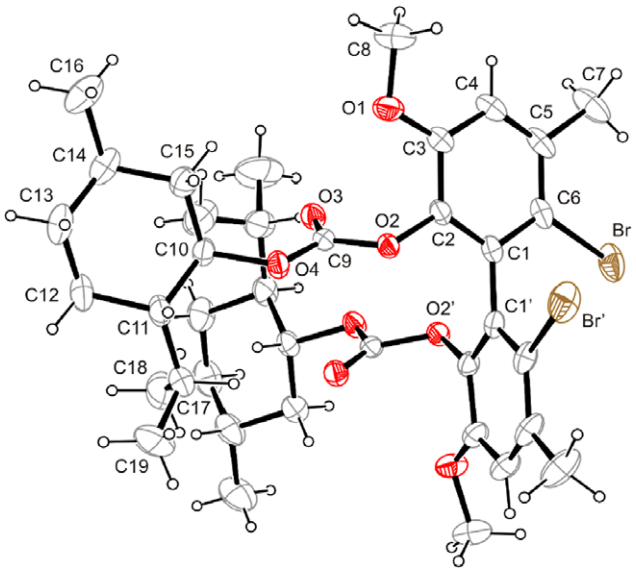


Figure 2. ORTEP plot[31] of diastereomer (a*S*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-(+)-**16**. Displacement ellipsoids are drawn at the 20% probability level.

two structures. Owing to the recognized importance of the methyl groups at the 5,5′-positions in determining the cytotoxic activity of the parent dehydrodicreosol **6**, we decided to undertake a computational study on the two model compounds, aimed at investigating the effect of these groups on the structural and electronic properties of the biphenyl unit.

DFT geometry optimizations were performed on two model compounds obtained from **16** by substituting the menthyl with a methyl group (**16A**) and then removing the methyl groups at the 5,5′ positions (**16B**). Calculations were performed at the B3LYP/6-31G** level with the Gaussian03 package,[33] starting from the X-ray experimental geometry of **16**.

Analysis of the optimized bond distances in **16A** and **16B** indicates that the corresponding experimental structures are well reproduced by calculations (for example, the C–Br distances are reproduced within 0.02 Å). The computed dihedral angle between the least-squares planes through the biphenyl rings is 86.6° in both model compounds, suggesting that the experimentally observed difference is probably attributable to crystal packing effects. Calculations then confirm that no structural differences can be observed between the two compounds. To investigate the changes in the electron distribution arising from the presence of the methyl groups at the 5,5′-biphenyl positions, we have computed the electrostatic potential (EP) of both **16A** and **16B** compounds. Such a property is in fact highly suitable to help understand the initial steps of recognition processes (e.g., drug–receptor interactions), which are in fact electrostatic in nature.[34] In Figure 3, two illustrative plots of EP surfaces of **16A** (left) and **16B** (right) are reported. It can be easily seen that the negative regions associated with the lone pairs of all the oxygen atoms are more extended in **16A**, indicating that an approaching electrophile 'sees' a greater negative area on this side of

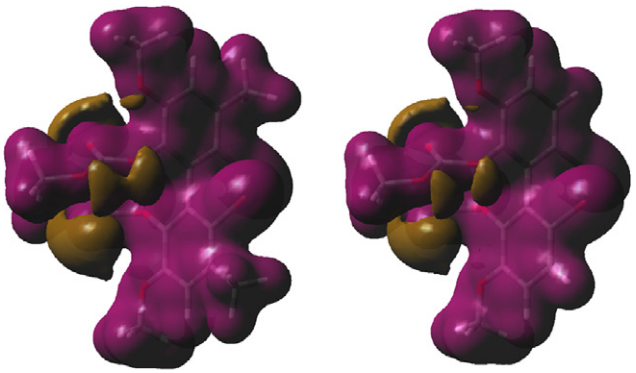


Figure 3. Electrostatic potential surfaces for model compounds **16A** (left) and **16B** (right). Absolute isovalue = 0.05 a.u.; violet: positive isosurface, brown: negative isosurface.

the molecule, with respect to **16B**. In view of this observation, the proximity of two oxygen atoms (at 2,2′ and 3,3′ positions) in such biphenyl derivatives appears to be an important structural factor. No relevant variations of the EP surfaces are observed on the side of the bromine atoms.

2.2. Cell growth inhibition

To investigate the potential anticancer activity of biphenyl (±)-**1**, we performed in vitro cell proliferation assays on three human melanoma cell lines. Cells were grown in the presence of scalar doses of (±)-**1**, (a*R*)-(+)-**1** and (a*S*)-(−)-**1**, as described in the experimental section, to test the capability of these compounds to inhibit cancer cells growth (Fig. 4). The graphic reports results obtained with the CN Mel-A cell line, which are representative for all the melanoma cell lines tested. Results are expressed as a mean percentage of cell growth in the presence of the specific molecule compared to the control (cells not treated). Each bar is representative of three experiments ± standard deviation. The three compounds showed growth inhibition activity, particularly the enantiopure form (a*S*)-(−)-**1**. After 5 days of cell culture in the presence of **1**, we calculated the IC_{50} to be around 25–30 μM for the (a*S*)-(−)-**1** form, IC_{50} above 40 μM for the (a*R*)-(+)-**1** form and IC_{50} higher than 60 μM for the racemic mixture. These results indicate that **1** has a potential anticancer activity in its (a*S*)-(−)-**1** enantiomeric form, since it consistently inhibits melanoma cells proliferation. More accurate investigations are needed to clarify the dose/time of action of (a*S*)-(−)-**1** on different tumours types and its specificity for tumour cells.

3. Conclusions

A straightforward procedure for preparing 2,2′-dihydroxy-3,3′-dimethoxy-5,5′-dimethyl-6,6′-dibromo-1,1′-biphenyl **1**, a C_2-configurationally stable creosol-related dimer, has been set up. The synthetic strategy entailed the preparation of dehydrodicreosol **6** from creosol **2**, then, aromatic bromination to give racemic **1** in 80% overall yield. Both enantiopure bromobiphenols **1** were achieved by a reaction

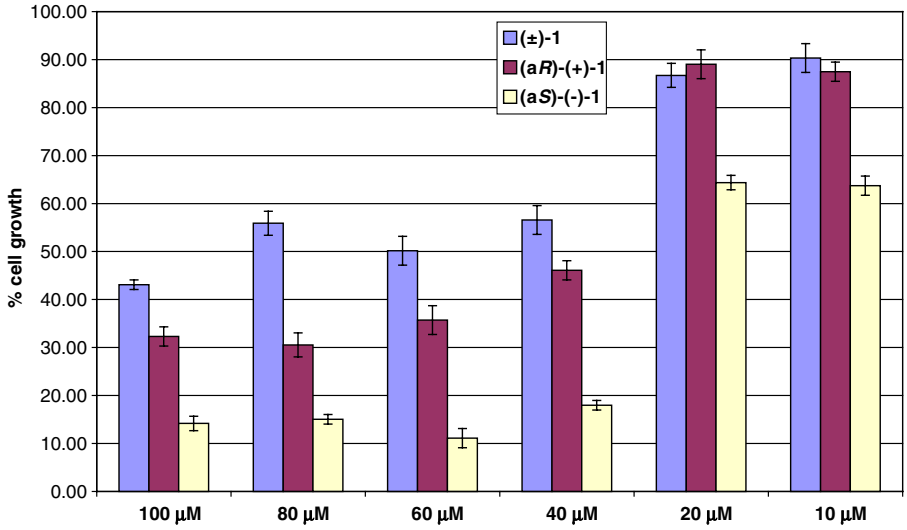


Figure 4. Anti-proliferative effect of (±)-**1**, (a*R*)-(+)-**1** and (a*S*)-(−)-**1** on melanoma cell lines.

path, which involved the transformation of dehydrodicreosol **6** in menthylcarbonate **15**, aromatic bromination, separation of the two homochiral atropo-diastereomers (a*R*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-(−)-**16** and (a*S*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-(+)-**16**, and final reduction of the menthyl carbonate groups to give enantiopure **1** in 65% of overall yield.

We were able to correlate, from the crystal structure of diastereomer (a*S*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-(−)-**16**, the absolute configuration with the specific rotation of **1** and to calculate the quite high racemization barrier. The high configurational stability has also been confirmed by the high value of dihedral angle calculated by the crystal structure of **16**.

Preliminary investigations on the potential anticancer activity of **1** in racemic as well as in enantiopure form have been carried out. Cell proliferation assays showed a strong cell growth inhibition due to treatments of melanoma cells with the (a*S*)-(−)-**1** form, confirming selectivity of atropoisomers (a*S*)-(−)-**1** and (a*R*)-(+)-**1** in the anticancer activity. The biologic activity related to the stereoaxis of hydroxylated biphenyl bromo-containing suggests the influence of this geometrical element in the search of new anticancer therapeutics containing biphenyls.

4. Experimental

4.1. 2,2′-Dihydroxy-3,3′-dimethoxy-5,5′-dimethyl-6,6′-dibromo-1,1′-biphenyl 1

To a stirred solution of **6** (1 g, 3.64 mmol) in dry diethyl ether (25 mL) at 0 °C and under N_2, Br_2 (1.15 g, 7.29 mmol) was added. The cold bath was removed and the mixture stirred at rt for 2 h. Aqueous $Na_2S_2O_5$ was added and the organic phase was extracted with diethyl ether. The organic extract was dried over Na_2SO_4 and concentrated to afford a brown solid. The crude material was purified by flash chromatography using CH_2Cl_2 as an eluent, to give **1** (1.41 g, 90%): mp 246 °C. ^{1}H NMR δ 2.46 (s, 6H), 3.95 (s, 6H), 5.58 (br s, 2H), 6.88 (s, Ar, 2H); ^{13}C NMR δ 23.56, 56.03, 112.57, 117.46, 124.81, 129.45, 141.85, 145.54; Anal. Calcd for $C_{16}H_{16}Br_2O_4$: C, 44.47; H, 3.73. Found: C, 44.73; H, 3.60.

4.2. 3,3′-Dimethoxy-5,5′-dimethyl-[1,1′-biphenyl]-2,2′-diyl-*O*,*O*′-bis[5-methyl-2-(1-methylethyl)-cyclohexyl]-carbonic ester 15

A solution of **1** (7 g, 25.50 mmol) and Et_3N (5 mL) in dry toluene (30 mL) was added, dropwise, to a solution of (−)-(1*R*,2*S*,5*R*)-menthyl chloroformate (12.2 g, 56 mmol) in toluene (30 mL) at rt under N_2. The solution was stirred at rt for 1 h, washed with 10% HCl and water and the organic phase extracted with CH_2Cl_2. The crude was dried over Na_2SO_4 to give **15** as a colourless oil that was used in the following reaction without purification (14.6 g, 90%): ^{1}H NMR δ 0.79 (d, $J = 6.9$ Hz, 6H), 0.95 (d, $J = 6.9$ Hz, 6H), 1.05 (d, $J = 6.9$ Hz, 6H), 0.80–1.95 (series of m, 18H), 2.40 (s, 6H), 3.87 (s, 6H), 4.54 (m, 2H), 6.75 (s, Ar, 2H), 6.80 (s, Ar, 2H); ^{13}C NMR δ 16.24, 20.71, 21.48, 22.03, 23.33, 25.93, 31.35, 34.10, 40.49, 46.87, 55.94, 78.91, 112.70, 122.77, 130.65, 135.70, 135.78, 151.23, 152.86; Anal. Calcd for $C_{36}H_{50}O_8$: C, 70.79; H, 8.25. Found: C, 70.83; H, 8.10.

4.3. 3,3′-Dimethoxy-5,5′-dimethyl-6,6′-dibromo-[1,1′-biphenyl]-2,2′-diyl-*O*,*O*′-bis[5-methyl-2-(1-methylethyl)-cyclohexyl]-carbonic ester 16

To a solution of **15** (1.5 g, 2.35 mmol) in acetic acid (20 mL), BTEA·Br_3 (4 g, 9.4 mmol) and $ZnCl_2$ (1.6 g, 11.7 mmol) were added in one pot. The reaction mixture was stirred at 60 °C for 2 h until the initial orange colour faded. Aqueous $Na_2S_2O_5$ was added to the mixture and the organic phase extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 to obtain a 1:1 mixture of the two diastereomers (a*R*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**16** and (a*S*,1*R*,

1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**16** as a brown solid. The two diastereomers were purified and separated by flash chromatography using a 4:6 mixture of CH_2Cl_2–petroleum as an eluent (1.49 g, 80%): (a*R*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**16**: first diastereomer eluted, 99% de: mp 199 °C. ^{1}H NMR δ 0.74 (d, $J = 6.4$ Hz, 6H), 0.85 (d, $J = 6.4$ Hz, 6H), 0.92 (d, $J = 6.6$ Hz, 6H), 0.85–2.10 (series of m, 18H), 2.47 (s, 6H), 3.81 (s, 6H), 4.50 (m, 2H), 6.94 (s, 2H); ^{13}C NMR δ 16.47, 20.67, 22.07, 23.46, 24.04, 25.99, 31.54, 34.13, 40.35, 47.08, 56.03, 79.20, 114.22, 116.75, 131.87, 136.32, 136.93, 150.37, 151.94; Anal. Calcd for $C_{38}H_{52}Br_2O_8$: C, 57.29; H, 6.58. Found: C, 57.22; H, 6.50; $[\alpha]_D^{20} = -72.9$ (*c* 1, $CHCl_3$). (a*S*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**16**: second diastereomer eluted, 99% de: mp 102 °C. ^{1}H NMR δ 0.72 (d, $J = 6.8$ Hz, 6H), 0.86 (d, $J = 6.8$ Hz, 6H), 0.92 (d, $J = 6.8$ Hz, 6H), 0.82–2.01 (series of m, 18H), 2.48 (s, 6H), 3.87 (s, 6H), 4.50 (m, 2H), 6.94 (s, Ar, 2H); ^{13}C NMR δ 16.18, 20.74, 22.05, 23.22, 24.02, 25.83, 31.28, 34.06, 40.23, 46.81, 55.90, 79.13, 114.08, 116.48, 131.82, 136.34, 136.78, 150.28, 151.57; Anal. Calcd for $C_{38}H_{52}Br_2O_8$: C, 57.29; H, 6.58. Found: C, 57.33; H, 6.67; $[\alpha]_D^{20} = +38.7$ (*c* 1, $CHCl_3$).

4.4. (a*R*)-(+)-2,2′-Dihydroxy-3,3′-dimethoxy-5,5′-dimethyl-6,6′-dibromo-1,1′-biphenyl 1

A solution of (a*R*)-**16** (99% de) (0.5 g, 0.62 mmol) in dry THF (30 mL) was cooled at 0 °C under N_2. $LiAlH_4$ (1 M in THF) (6 mL, 6 mmol) was added with vigorous magnetic stirring. After 12 h, water and 10% HCl were cautiously added. The organic phase was extracted with ether, dried over Na_2SO_4 and evaporated to afford a colourless solid. After purification by flash chromatography using CH_2Cl_2 as an eluent, enantiomerically pure (a*R*)-**1** (0.24 g, 90%) and enantiomerically pure (−)-menthol (0.82 g, 85%) were obtained. (a*R*)-(+)-**1**: $[\alpha]_D^{20} = +13.1$ (*c* 0.5, $CHCl_3$); $[\alpha]_{365}^{20} = +103.0$ (*c* 0.5, $CHCl_3$).

4.5. (a*S*)-(−)-2,2′-Dihydroxy-3,3′-dimethoxy-5,5′-dimethyl-6,6′-dibromo-1,1′-biphenyl 1

Using the above procedure, diastereomer (a*S*)-**16** (99% de) gave (a*S*)-(−)-**1**: (0.24 g, 90%): $[\alpha]_D^{20} = -13.1$ (*c* 0.8, $CHCl_3$); $[\alpha]_{365}^{20} = -102.9$ (*c* 0.8, $CHCl_3$). Enantiomerically pure (−)-menthol (0.79 g, 82%) was recovered.

4.6. Dibenzo-(*d*,*f*)(1,3,2)-dioxaphosphepin-6-amine-1,11-dibromo-2,10-dimethyl-4,8-dimethoxy-*N*-(1-phenylethyl)-6-sulfide 11

N-((*S*)-α-Methylbenzyl)-dichlorothiophosphoroamidate **12** (1.41 g, 5.5 mmol) was added dropwise to a solution of **1** (2 g, 4.62 mmol) in dry pyridine (50 mL) at rt under N_2. After 12 h at reflux, the reaction mixture was cooled and made acid with 10% H_2SO_4. Water was added and the organic phase extracted with CH_2Cl_2, dried over Na_2SO_4 and evaporated to dryness to obtain a colourless solid. The crude was purified by flash chromatography using a 1:1 mixture of CH_2Cl_2–petroleum, as an eluent, to give **11** (2.7 g, 80%) as a colourless oil (1:1 inseparable diastereomeric mixture). ^{31}P NMR δ (mixture of two diastereomers) 76.25, 77.43; Anal. Calcd for $C_{24}H_{26}Br_2NO_4PS$: C, 46.84; H, 4.26. Found: C, 46.91; H, 4.34.

4.7. Dibenzo-(*d*,*f*)(1,3,2)-dioxaphosphepin-6-amine-1,11-dibromo-2,10-dimethyl-4,8-dimethoxy-*N*,*N*′-methyl-(1-phenylethyl)-6-sulfide 13

To a solution of **11** (1 g, 1.62 mmol) in CH_2Cl_2 (20 mL) and H_2O (15 mL), tetrabutylammonium hydroxide (TBAOH) (4.86 mmol, 40% aqueous solution) and CH_3I (0.7 g, 4.86 mmol) were added. The reaction mixture was stirred at rt under N_2. After 12 h, water and 10% HCl were cautiously added. The organic phase was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 to obtain a colourless solid that was purified by flash chromatography using a 2:8 mixture of ethyl acetate–petroleum, as an eluent, to give **13** (0.75 g, 74%): compound (−)-**13**, first diastereomer eluted: 99% de, mp 98–99 °C. ^{1}H NMR δ 1.53 (d, $^3J_{HP} = 7.2$ Hz, 3H, CH–*CH*$_3$), 2.26 (d, $^3J_{HP} = 10.4$ Hz, 3H, N–*CH*$_3$), 2.46 (s, 3H), 2.51 (s, 3H), 3.64 (s, 3H), 3.99 (s, 3H), 5.59 (m, 1H), 6.81 (s, Ar, 1H), 7.03 (s, Ar, 1H), 7.33 (d, $J = 8.0$ Hz, Ar, 1H), 7.41 (t, $J = 8.0$ Hz, Ar, 2H), 7.55 (d, $J = 8$ Hz, Ar, 2H); ^{13}C NMR δ (aliphatic only) 16.40 (d, $^2J_{CP} = 2.8$ Hz, N–*CH*$_3$), 24.33 (d, $^2J_{CP} = 5.6$ Hz, CH–*CH*$_3$), 28.30, 29.74, 55.65, 56.13 (d, $^2J_{CP} = 10.5$ Hz, *CH*–CH$_3$), 56.70; ^{31}P NMR δ 80.42; $[\alpha]_D^{20} = -136.4$ (*c* 0.5, $CHCl_3$) Anal. Calcd for $C_{25}H_{28}Br_2NO_4PS$: C, 47.71; H, 4.48. Found: C, 47.63; H, 4.44. Compound (+)-**13**, second diastereomer eluted: 99% de, mp 244–245 °C. ^{1}H NMR δ 1.68 (d, $J = 6.8$ Hz, 3H, CH–*CH*$_3$), 2.16 (d, $^3J_{HP} = 9.6$ Hz, 3H, N–*CH*$_3$), 2.51 (s, 6H), 3.89 (s, 3H), 4.00 (s, 3H), 5.76 (m, 1H), 6.91 (s, Ar, 1H), 7.05 (s, Ar, 1H), 7.20–7.40 (series of m, Ar, 5H); ^{13}C NMR δ (aliphatic only) 16.19 (d, $^2J_{CP} = 2.66$ Hz, N–*CH*$_3$), 24.29 (d $^2J_{CP} = 5.6$ Hz, *CH*–CH$_3$), 28.37, 28.38, 55.33 (d, $^2J_{CP} = 7.9$ Hz, CH–*CH*$_3$), 55.85, 56.80; ^{31}P NMR δ 80.96; $[\alpha]_D^{20} = +209.9$ (*c* 0.5, $CHCl_3$); Anal. Calcd for $C_{25}H_{28}Br_2NO_4PS$: C, 47.71; H, 4.48. Found: C, 47.88; H, 4.41.

4.8. Dibenzo-(*d*,*f*)(1,3,2)-dioxaphosphepin-6-amine-2,10-dimethyl-4,8-dimethoxy–*N*,*N*′-methyl-(1-phenylethyl)-6-sulfide 14

A solution of (−)-**13** (99% de) (0.3 g, 0.47 mmol) in dry THF (30 mL) was cooled at 0 °C under N_2. $LiAlH_4$ (1 M in THF) (1 mL, 1 mmol) was added with vigorous magnetic stirring. After 12 h, water and 10% HCl were cautiously added. The organic phase was extracted with ether, dried over Na_2SO_4 and evaporated to afford a colourless solid. After purification by flash chromatography by using CH_2Cl_2 as an eluent, **14** (0.2 g, 90%) was obtained: **14**: mp 99–100 °C. ^{1}H NMR δ 1.68 (d, $J = 6.8$ Hz, 3H, CH–*CH*$_3$), 2.38 (d, $J = 10.4$ Hz, 3H, N–*CH*$_3$), 2.41 (s, 3H), 2.42 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 5.75 (m, 1H), 6.80 (s, Ar, 1H), 6.83 (s, Ar, 1H), 6.89 (s, Ar, 1H), 6.90 (s, Ar, 1H), 7.27 (d, $J = 7.2$ Hz, Ar, 1H), 7.40 (t, $J = 7.2$ Hz, Ar, 2H), 7.53 (d, $J = 7.2$ Hz, Ar, 2H); ^{13}C NMR δ (aliphatic only) 16.39 (d, $^2J_{CP} = 3.1$ Hz, N–*CH*$_3$), 21.56 (d $J = 2.9$ Hz, *CH*–CH$_3$), 28.24, 55.70 (d, $^2J_{CP} = 7.7$ Hz, CH–*CH*$_3$), 56.13, 56.16; ^{31}P NMR δ 84.07;

Anal. Calcd for $C_{25}H_{30}NO_4PS$: C, 63.67; H, 6.41. Found: C, 63.56; H, 6.66.

4.9. 2,2′-(17-*crown*-5)-3,3′-Dimethoxy-5,5′-dimethyl-1,1′-biphenyl 8

To a stirred solution of K_2CO_3 (6 g, 44 mmol) in dry DMF (200 mL) were added under N_2 a solution of **6** (1.22 g, 4.45 mmol) in dry DMF (200 mL) and a solution of tetraethyleneglycol ditosylate (2.23 g, 4.45 mmol) in dry DMF (200 mL) at rt. The mixture was stirred at 60 °C for 12 h. Water (1000 mL) was added, and the organic phase extracted with diethyl ether. The organic extract was dried over Na_2SO_4 and concentrated to afford a brown solid. The crude material was purified by flash chromatography using a 1:1 mixture of ethyl acetate–petroleum, as eluent, to give **8** (0.96 g, 50%): **8**: mp 82–83 °C. ^{1}H NMR δ 2.35 (s, 6H), 3.91 (s, 6H), 3.50–4.20 (series of m, 16H), 6.73 (s, Ar, 4H); ^{13}C NMR δ 21.32, 55.93, 70.11, 70.32, 70.70, 71.62, 112.41, 123.82, 132.21, 132.62, 143.77, 152.49; Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.63; H, 7.46. Found: C, 66.55; H, 7.49.

4.10. 2,2′-(17-*crown*-5)-3,3′-Dimethoxy-5,5′-dimethyl-6,6′-dibromo-1,1′-biphenyl 7

From **1**: To a stirred solution of K_2CO_3 (21 g, 151 mmol) in dry DMF (400 mL) were added a solution of **1** (6.56 g, 15.18 mmol) in dry DMF (200 mL) and a solution of tetraethyleneglycol ditosylate (7.6 g, 15.18 mmol) in dry DMF (200 mL) at rt under N_2. The mixture was stirred at 60 °C for 16 h. Water (1000 mL) was added, and the solution extracted with diethyl ether. The organic extract was dried (Na_2SO_4) and concentrated to afford a brown solid. The crude material was purified by flash chromatography using a 4:6 mixture of ethyl acetate–petroleum, as eluent, to give **7** (3.58 g, 40%). From **8**: To a stirred solution of **8** (3.2 g, 7 mmol) in CCl_4 (100 mL) were added NBS (3 g, 16.3 mmol) and BPO (0.17 g, 0.7 mmol) at rt and under N_2. The solution was stirred at rt for 12 h and then filtered. The solvent was evaporated to obtain a brown solid. The crude material was purified by flash chromatography using a 4:6 mixture of ethyl acetate–petroleum, as eluent, to give **7** (2.64 g, 64%). Compound **7**: mp 124 °C. ^{1}H NMR δ 2.43 (s, 6H), 3.90 (s, 6H), 3.40–4.30 (series of m, 16H), 6.90 (s, Ar, 2H); ^{13}C NMR δ 23.84, 55.91, 69.75, 70.13, 70.99, 71.52, 113.98, 116.81, 133.13, 134.19, 144.62, 151.45; Anal. Calcd for $C_{24}H_{30}Br_2O_7$: C, 48.83; H, 5.12. Found: C, 48.85; H, 5.32.

4.11. 2,2′-(17-*crown*-5)-3,3′-Dimethoxy-5,5′-dibromomethyl-6,6′-dibromo-1,1′-biphenyl 9

To a stirred solution of **7** (1 g, 1.69 mmol) in dry CCl_4 (15 mL) were added NBS (0.66 g, 3,72 mmol) and BPO (0.04 g, 0.17 mmol) at rt under N_2. The solution was stirred at 70 °C for 4 h and then filtered. The solvent was evaporated to obtain a brown solid. The crude material was purified by flash chromatography using a 1:1 mixture of ethyl acetate–petroleum, as eluent, to give **9** (0.76 g, 60%). Compound **9**: mp 144–145 °C. ^{1}H NMR δ 3.89 (s, 6H), 3.40–4.40 (series of m, 16H), 4.63 (AB system, $J = 10$ Hz, 4H), 7.06 (s, Ar, 2H); ^{13}C NMR δ 35.05, 56.00, 69.80, 70.13, 70.84, 71.86, 114.14, 116.93, 132.21, 134.43, 147.03, 151.93; Anal. Calcd for $C_{24}H_{28}Br_4O_7$: C, 38.53; H, 3.77. Found: C, 38.26; H, 3.99.

4.12. 2,2′-(17-*crown*-5)-3,3′-Dimethoxy-5,5′-dibromomethyl-1,1′-biphenyl 10

To a stirred solution of **8** (0.32 g, 0.7 mmol) in dry CCl_4 (15 mL) was added NBS (0.3 g, 1.63 mmol) at rt under N_2. The solution was irradiated with a 200 W lamp for 1 h at reflux and then filtered. The solvent was evaporated to obtain a brown solid. The crude material was purified by flash chromatography using a 2:1 mixture of acetone–petroleum, as eluent, to give **10** (0.21 g, 30%). Compound **10**: mp 64–65 °C. ^{1}H NMR 3.94 (s, 6H), 3.35–4.20 (series of m, 16H), 4.51 (s, 4H), 6.96 (d, $J = 2.4$ Hz, Ar, 2H), 7.01 (d, Ar, $J = 2.4$ Hz, Ar, 2H); ^{13}C NMR δ 34.14, 55.97, 70.15, 70.27, 70.48, 71.96, 112.16, 124.26, 129.88, 131.57, 132.50, 153.06; Anal. Calcd $C_{24}H_{30}Br_2O_7$: C, 48.83; H, 5.12. Found: C, 48.99; H, 5.08.

4.13. Interconversion measurements of (a*R*)-(+)-1

Racemization measurements were performed by detection of the optical rotatory activity of (a*R*)-(+)-**1** in xylene after heating the solution at 100 and 130 °C at 0, 15, 30, 60, 120, 240, and 720 min, respectively. Optical rotatory activity was unaffected at 100 °C after 720 min at least, whereas little but significant decrease of $[\alpha]_D$ value was observed within 15 min when (a*R*)-(+)-**1** was heated at 130 °C.

4.14. Interconversion measurements of (a*R*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-(−)-16

Racemization measurements were performed by detection of the presence of the other diastereomer (a*S*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-(+)-**16** when a solution of (a*R*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-(−)-**16** in DMSO-d_6 was recorded by ^{1}H NMR after heating at 100, 120 and 130 °C.

4.15. X-ray structure determination of (a*S*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-(+)-16

Crystal description: Colourless prism $0.32 \times 0.26 \times 0.23$ mm. $M_r = 796.62$, hexagonal, space group $P3_121$, $a = b = 12.3105(17)$, $c = 23.674(5)$ Å, $V = 3107.0(9)$ Å^3, $Z = 3$, $T = 293(2)$ K, $\mu = 2.002$ 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.[35] 71,155 measured reflections, 7664 independent reflections, 3665 reflections with $I > 2\sigma(I)$, $3.82 < 2\theta < 66.40°$, $R_{int} = 0.052$. The structure was solved by SIR-92[36] and refined on F^2 by full-matrix least-squares using SHELXL-97.[37] Refinement on 7664 reflections, 217 parameters. Flack parameter[38] for determination of the absolute configuration = 0.005(9). Final $R = 0.0407$, $wR = 0.1077$ for data with $F^2 > 2\sigma(F^2)$, $(\Delta/\sigma)_{max} = 0.001$, $\Delta\rho_{max} = 0.51$, $\Delta\rho_{min} = -0.27$ Å^{-3}. The detailed structural

parameters have been deposited with Cambridge Crystallographic Data Centre under the number CCDC 610996.

4.16. Cell lines and proliferation assays of (±)-1, (a*R*)-(+)-1 and (a*S*)-(−)-1

Three human malignant melanoma cell lines (LCM–Mel, GR-Mel, CN Mel–A), obtained from Istituto Dermopatico dell'Immacolata, Department of Molecular and Cellular Biology, Rome, were used to evaluate potential anti-proliferative activity of biphenyl **1**, as racemic mixture (±)-**1** and in enantiopure forms (a*R*)-(+)-**1** and (a*S*)-(−)-**1**. Before testing, cells were grown to confluence in tissue culture flasks using RPMI medium (Invitrogen, Carlsbad, CA, USA) supplemented with 10% FBS and penicillin/streptomycin [100 IU (50 μg)/mL] in a humidified 5% CO_2 atmosphere at 37 °C. For proliferation assays cells were then plated in 96-well plates (3×10^3/well) in their complete medium, in quadruplicate. After 24 h, the medium was removed and replaced on days 1, 3, and 5, by the same medium (control) or supplemented with various doses of **1** at final concentrations comprising between 10 and 100 μM. The cells were observed with an inverted microscope every 24 h to check on morphological changes, suffering or cell death. The percentage of cell proliferation was estimated on day 6 by the colorimetric assay of Kueng et al.[39] modified as follows: cells were fixed for 20 min at room temperature with 4% paraformaldehyde (PFA), stained with 0.1% crystal violet in 20% methanol for 20 min, washed in PBS, solubilized with 10% acetic acid and read at 595 nm in a microplate reader (Versamax™, Molecular Devices, USA).

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