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Desymmetrization of 2,2′,6,6′-tetramethoxybiphenyl by regioselective sulfenylation reaction

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Abstract—A practical regioselective sulfenylation reaction of the achiral title compound **1** provides desymmetrization and access to C_2-symmetric sulphur derivatives. Resolution of 2,2′,6,6′-tetramethoxy-3,3′-dimercapto-1,1′-biphenyl **7** was achieved by conversion to the corresponding dithiocarbonate diastereomers. The absolute configuration of (a*R*)-(−)-**7** and (a*S*)-(+)-**7** was assigned unambiguously.

1. Introduction

The desymmetrization of an achiral or *meso* compound is a versatile synthetic route to homochiral compounds.[1] Although the majority of synthetic efforts within this area have been directed towards preparing enantiopure molecules with the creation of one or more stereogenic centers,[2] the desymmetrization approach also allows the preparation of axially chiral biaryls, starting from the corresponding achiral derivatives.[3]

Recently, derivatives of 2,2′,6,6′-tetramethoxybiphenyl **1**[4] have attracted attention as a result of their applications in catalysis,[5] asymmetric synthesis[6] and, because of the presence of four methoxyl groups, as building blocks for the preparation of bioactive compounds.[7] Indeed, the structure of **1** resembles several biphenyl structures isolated in plants and marine extracts with pharmacological and agrochemical proprieties.[8] Desymmetrization of biphenyl **1** has already been studied in order to investigate the stereochemical features imposed by different functional groups at the 3- and 3′-positions[9] as well as to achieve a defined stereogenic axis by asymmetric desymmetrization.[10]

Despite the recent progress in the preparation of C_2-symmetric chiral thiosubstituted biphenols,[4,11] most of the methods applied to form the thiol-aryl bond involve tedious and expensive procedures and often require harsh reaction conditions.[12]

We recently applied the chemistry of phthalimidesulfenyl chloride[13] **2** (PhthNSCl, Phth = Phthaloyl) for the sulfenylation of 6,6′-dimethoxy-2,2′-dihydroxy-1,1′-biphenyl **3**.[11b,14] The reaction, which occurs regioselectively at the 3- and 3′-positions (biphenyl **4**), allowed us to obtain, after reduction of the *N*-thiophthalimide residue, a thio-aryl bond (biphenyl **5**) with the possibility to access a large number of different derivatives by chemical manipulation of the thiol group (Scheme 1).

The features of the reaction of biphenyl **1** with **2** are described in the following paper.

2. Results and discussion

The success of the sulfenylation reaction on biphenol **3** encouraged us to use reagent **2** with 2,2′,6,6′-tetramethoxybiphenyl **1**.[15] When **1** was treated with 2.0 equiv. of **2** at rt in dry chloroform, bis-thiophthalimide **6** was obtained with complete regioselectivity at the 3- and 3′-positions (Scheme 2a). Thus, a C_2-symmetric homochiral compound is produced in one reaction with

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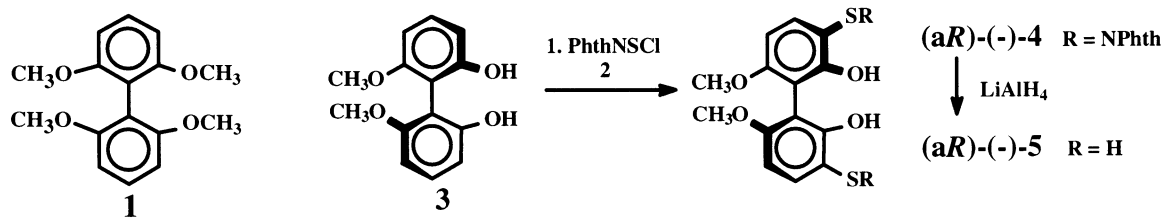


Scheme 1.

concurrent desymmetrization of **1**. Biphenyl **6**, obtained in good yield, is solid, air stable for months and easily purified by chromatography.

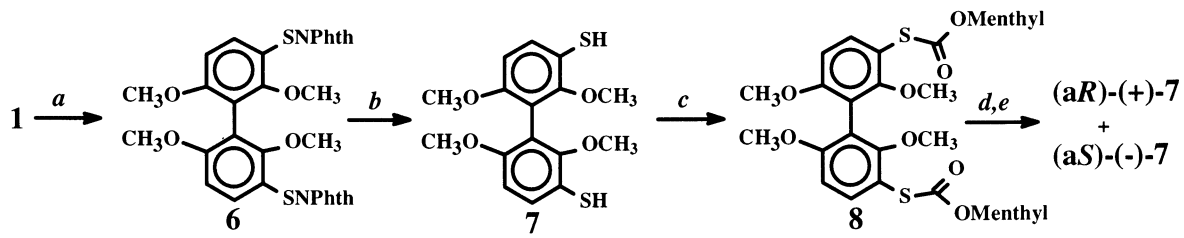
Our strategy was to transform biphenyl **6** into the corresponding dithiol **7** in order to have, after resolution, a new chiral thiol ligand useful both in catalysis[16] and in bioinorganic chemistry.[17] According to the previous preparations,[11b,13] dithiol **7** was thus obtained as a racemic mixture in 62% yield by reduction of **6** in the presence of a small excess of $LiAlH_4$, in dry THF (Scheme 2b). It should be taken into account that, in the reducing conditions, no disulphide derivatives or polymers were detected even after reducing the equivalents of $LiAlH_4$.[18] Probably, the bulk of the four methoxyl groups of **7** prevents dimer formation.

Among the several chiral resolving agents used for the resolution of biaryl dithiols,[19] we preferred to use, according to our experience on this field,[20] (1*R*,2*S*,5*R*)-(−)-menthyl chloroformate as a result of its efficiency in the presence of the thiol group. Treatment of (±)-**7** with 2.2 equiv. of this resolving agent in benzene or toluene and in the presence of Et_3N at rt gave diastereomers (a*R*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**8** and (a*S*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**8** in 85% yield (Scheme 2c). Diastereomers **8** were separated by flash-chromatography, in 94 and 76% d.e., respectively.[21] All attempts to separate the two diastereomers in higher d.e., failed. Reduction of each dithiocarbonate diastereomer **8** with $LiAlH_4$ provided dithiol (+)-**7** and (−)-**7** in virtually quantitative yield (Scheme 2d,e).

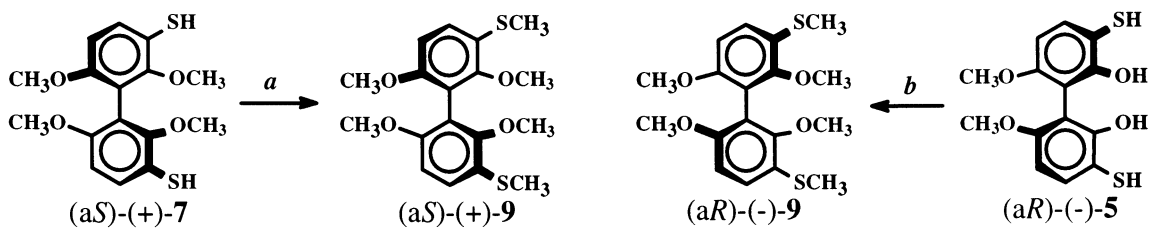
In order to determine the absolute configuration of thiols (+)-**7** and (−)-**7**, we converted enantiomer (+)-**7** into the crystalline dithiomethyl derivate (+)-**9** by treatment with iodomethane in the presence of triethylamine at rt (Scheme 3a). Suitable conditions were achieved in chiral HPLC (Chiracel OD) in the separation of racemic **9** ($\alpha = 1.1$), previously prepared by us.[4] Subsequently, complete methylation of biphenyl (a*R*)-(−)-**5**,[14] performed with iodomethane in the presence of K_2CO_3 at 50°C in DMF, gave (a*R*)-(−)-**9** (Scheme 3b).[22] The latter compound allowed us to correlate optical rotation with absolute configuration of (a*R*)-(−)-**9** and (a*S*)-(+)-**9**, confirmed by the retention time of each enantiomer in chiral HPLC. By reference to biphenyl (a*R*)-(−)-**9** and (a*S*)-(+)-**9**, we can assign the absolute configuration of dithiol (a*R*)-(−)-**7** and (a*S*)-(+)-**7**, unambiguously.

The racemization time of biphenyl **9** was monitored by chiral HPLC. No interconversion at the stereogenic axis of biphenyl (a*R*)-(−)-**9** occurred in 2-propanol even when heated to 65°C for 12 h.

In conclusion, dithiol **7**, a new hydroxylated biphenyl sulfur-containing compound was readily prepared start-



Scheme 2. (a) PhthNSCl (2.0 equiv.), $CHCl_3$, rt, 60% yield; (b) $LiAlH_4$ (3 equiv.), THF, rt, 62% yield; (c) (−)-menthyl chloroformate, Et_3N, benzene or toluene, rt, 85% yield; (d) separation by flash chromatography; (e) $LiAlH_4$, THF, rt, 90% yield.



Scheme 3. (a) CH_3I (2 equiv.), Et_3N, THF, rt, 65% yield; (b) CH_3I (4.5 equiv.), K_2CO_3, DMF, 50°C, 78% yield.

ing from the synthetically available tetramethoxy biphenyl **1**. Our strategy takes advantage of two key steps: (1) desymmetrization of **1** by regioselective sulfenylation reaction, which affords the C_2-symmetric biphenyl **6**; (2) facile reduction of the sulfenyl group into the thiol group. A practical resolution method allowed the synthesis of dithiols (a*R*)-(−)-**7** and (a*S*)-(+)-**7** in 94 and 76% e.e., respectively.

The possibility of accessing a large number of 3,3′-thio-substituted hydroxylated biphenyls by electrophilic substitution of dithiol **7** makes it a useful synthetic unit to be applied in the preparation of bioactive compounds (ionophores and switches) and as ligands for catalysis. The difference in size and shape of the thio substituents at the 3- and 3′-positions should influence the conformation of the biaryl system, which could result in significant stereochemical modifications on the structure.

3. Experimental section

3.1. 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 VXR 5000 spectrometer at 299.94 and 75.42 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 analyser Perkin–Elmer model 240 C. Optical rotations were measured with a Perkin–Elmer 343 spectropolarimeter. Tetrahydrofuran (THF), benzene and toluene were freshly distilled from sodium–benzophenone ketyl. Triethylamine (Et_3N) was dried over KOH 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 diastereomeric purity of (a*R*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**8** and (a*S*,1*R*,1′*R*,2*S*,2′*S*,5*R*,5′*R*)-**8** was calculated by ^{1}H NMR. Separation of biphenyl **9** in two enantiomers was performed by chiral HPLC using a Chiracel OD column with 97:3 hexane:2-propanol as mobile phase, at a flow rate of 0.6 mL/min and with UV detector at 254 nm.

3.1.1. 2,2′-[[2,2′,6,6′-Tetramethoxy[1,1′-biphenyl]-3,3′-diyl]bis(thio)]bis-1*H*-isoindole-1,3(2*H*)-dione 6. To a suspension of **1** (0.815 g, 2.97 mmol) in dry $CHCl_3$ (30 mL) a solution of sulfenyl chloride **2** (1.292 g, 6.06 mmol) in dry $CHCl_3$ (20 mL) was added dropwise during 30 min. The mixture was stirred at rt for 5 h then diluted with CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ and water. Evaporation of the solvent gave a crude which was purified by flash chromatography (eluent CH_2Cl_2/MeOH = 100/1) to obtain phthalimide derivative **6** (1.15 g, 60%) as a pale grey solid, mp 248°C dec. ^{1}H NMR δ 3.58 (s, 6H), 3.63 (s, 6H), 6.66 (d, 2H Ar, J = 8.8 Hz), 7.48 (d, 2H Ar, J = 8.8 Hz), 7.90–7.70 (m, 8H, Phth); ^{13}C NMR δ 55.9, 61.0, 107.1, 117.7, 120.1, 123.9, 132.2, 132.9, 134.6, 157.8, 159.7, 168.0 Anal. calcd for $C_{32}H_{24}N_2O_8S_2$: C, 61.14; H, 3.85; N, 4.46. Found: C, 61.33; H, 3.99; N, 4.28%.

3.1.2. 2,2′,6,6′-Tetramethoxy-3,3′-dimercapto-1,1′-biphenyl 7. To a suspension of phthalimide derivative **6** (0.07 g, 0.11 mmol) in dry THF (6 mL) at a 0°C and under N_2, $LiAlH_4$ (0.013 g, 0.33 mmol) was added in one portion. The mixture was kept at 0°C for 20 min then left to reach rt and treated with 3% HCl until pH 1. The aqueous layer was washed with ether, the organic phases, recollected, dried over Na_2SO_4 and evaporated to dryness. The crude was purified by flash chromatography (eluent: CH_2Cl_2) to give thiol **7** as a white solid (0.023 g, 62%), mp 145–6°C. ^{1}H NMR δ 3.48 (s, 6H), 3.67 (s, 2H, *SH*), 3.71 (s, 6H), 6.70 (d, 2H Ar, J = 8.8 Hz), 7.30 (d, 2H Ar, J = 8.8 Hz). ^{13}C NMR δ 56.0, 59.5, 107.5, 116.3, 118.2, 129.9, 155.1, 156.8. Anal. calcd for $C_{16}H_{18}O_4S_2$: C, 56.78; H, 5.36. Found: C, 56.98; H, 5.44%.

3.1.3. [2,2′,6,6′-Tetramethoxy-1,1′-biphenyl]-3,3′-diyl-*S*,*S*′-bis[5-methyl-2-(1-methylethyl)-cyclohexyl]-carbonic ester 8. A solution of 2,2′,6,6′-tetramethoxy-3,3′-dimercapto-1,1′-biphenyl **1** (0.51 g, 1.51 mmol) and Et_3N (2 mL) in benzene or toluene (10 mL) was added, dropwise, to a solution of (−)-(1*R*,2*S*,5*R*)-menthyl chloroformate (0.73 g, 3.32 mmol) in benzene or toluene (10 mL) at rt under N_2. The solution was stirred at rt for 1 h, washed with 10% aqueous HCl and water and the organic phase extracted with CH_2Cl_2. The crude was dried over Na_2SO_4 and concentrated to give a colourless solid that was purified by flash chromatography using a 1:1 mixture of CH_2Cl_2:petroleum ether, to give **8** (0.90 g, 85%) as a mixture of two diastereomers. **8**: first diastereomer eluted, 94% de, oil. ^{1}H NMR δ 0.77 (d, J = 6.6 Hz, 6H), 0.80 (d, J = 6.6 Hz, 6H), 0.91 (d, J = 6.6 Hz, 6H), 0.85–2.10 (series of m, 18H), 3.51 (s, 6H), 3.74 (s, 6H), 4.75 (m, 2H), 6.67 (d, J = 9 Hz, Ar, 2H), 7.53 (d, J = 9 Hz, Ar, 2H); ^{13}C NMR δ 16.63, 20.86, 22.18, 23.77, 26.50, 31.70, 34.34, 41.11, 47.34, 56.16, 61.19, 78.67, 107.27, 113.35, 118.33, 137.77, 145.31, 160.46, 169.70. Anal. calcd for $C_{38}H_{54}O_8S_2$: C, 64.93; H, 7.74. Found: C, 65.12; H, 7.80. $[\alpha]_D^{20}$ −79.6 (*c* 0.3, $CHCl_3$). **8**: second diastereomer eluted, 76% d.e., oil. ^{1}H NMR δ 0.76 (d, J = 6.6 Hz, 6H), 0.88 (d, J = 6.6 Hz, 6H), 0.91 (d, J = 6.6 Hz, 6H), 0.85–2.10 (series of m, 18H), 3.53 (s, 6H), 3.74 (s, 6H), 4.75 (m, 2H), 6.67 (d, J = 9 Hz, Ar, 2H), 7.53 (d, J = 9 Hz, Ar, 2H); ^{13}C NMR δ 15.9, 20.2, 21.7, 23.1, 25.9, 31.7, 40.8, 42.9, 48.1, 57.2, 62.2, 79.7, 106.3, 108.3, 118.4, 136.6, 138.9, 160.5, 169.7. Anal. calcd for $C_{38}H_{54}O_8S_2$: C, 64.93; H, 7.74. Found: C, 65.43; H, 7.85%. $[\alpha]_D^{20}$ −45.8 (*c* 1.9, $CHCl_3$).

3.1.4. (a*S*)-(+)-2,2′,6,6′-Tetramethoxy-3,3′-dimercapto-1,1′-biphenyl 7. A solution of (−)-**8** (second diastereomer eluted, 76% d.e.) (0.5 g, 0.71 mmol) in dry

THF (30 mL) was cooled at 0°C under N_2. $LiAlH_4$ (0.23 g, 6 mmol) was added in portions 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 eluent, (+)-**7** (0.22 g, 91%) and enantiomerically pure (−)-menthol (0.19 g, 85%) were obtained. (+)-**7**: oil. $[\alpha]_D^{20}$ +23.6 (*c* 1, $CHCl_3$).

3.1.5. (a*R*)-(−)-2,2′,6,6′-Tetramethoxy-3,3′-dimercapto-1,1′-biphenyl 7. Using the above procedure, diastereomer (−)-**8** (0.5 g, 0.71 mmol, first diastereomer eluted, 94% de) gave (−)-**7**: (0.20 g, 90%); $[\alpha]_D^{20}$ −28.9 (*c* 0.4, $CHCl_3$). Enantiomerically pure (−)-menthol (0.22 g, 87%) was recovered.

3.1.6. (a*R*)-2,2′,6,6′-Tetramethoxy-3,3′-dimethylmercapto-1,1′-biphenyl 9. Methyl iodide (200 mg, 1.41 mmol) was added to a mixture of biphenyl (a*R*)-(−)-**5**[14] (100 mg, 0.32 mmol, 72% ee) and K_2CO_3 (200 mg 1.30 mmol) in dry DMF (6 mL), under N_2. The mixture was heated at 50°C for 20 h, then diluted with saturated NH_4Cl and extracted with CH_2Cl_2. The crude, after flash-chromatography using a 8:1 mixture of CH_2Cl_2:petroleum ether as eluent, gave (a*R*)-**9** (91 mg, 78%) as a white solid, mp 133–135°C, [lit.[4] mp 126–8°C]. $[\alpha]_D^{22}$ −1.1 (*c* 0.28, $CHCl_3$); $[\alpha]_{365}^{22}$ +16.8 (*c* 0.28, $CHCl_3$). ^1H NMR δ 2.43 (s, 6H), 3.56 (s, 6H), 3.71 (s, 6H), 6.76 (d, 2H Ar, $J=8.7$ Hz), 7.24 (d, 2H Ar, $J=8.7$ Hz). ^{13}C NMR δ 16.1, 55.9, 56.0, 107.1, 118.0, 123.0, 128.2, 155.6, 156.8. Anal. calcd for $C_{18}H_{22}O_4S_2$: C, 58.99; H, 6.05. Found: C, 56.98; H, 5.44%.

3.1.7. (a*S*)-2,2′,6,6′-Tetramethoxy-3,3′-dimethylmercapto-1,1′-biphenyl 9. Methyl iodide (42 mg, 0.30 mmol) was added to a mixture of biphenyl (a*S*)-(+)-**7** (50 mg, 0.15 mmol, 76% e.e.) and Et_3N (30 mg, 0.30 mmol) in dry THF (3 mL), under N_2. The mixture was kept at rt for 3 h, then diluted with saturated NH_4Cl and extracted with CH_2Cl_2. The crude, after flash-chromatography using a 8:1 mixture of CH_2Cl_2: petroleum ether as eluent, gave (a*S*)-**9** in 65% yield. $[\alpha]_D^{22}$ +1.0 (*c* 0.10, $CHCl_3$); $[\alpha]_{365}^{22}$ −17.0 (*c* 0.10, $CHCl_3$).

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18. Previously, we observed that the reduction of **4** can be achieved using an excess (5 equiv.) of $LiAlH_4$, when the reaction was carried out using only 1.5–2 equiv. of $LiAlH_4$, instead of partial formation of thiol **5**, we isolated the corresponding cyclic disulfide as a single compound in good yields. See Refs. 11b and 14.
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21. The separation was obtained loading 1 g of crude in a flash-cromatography column of 50 mm Ø filled with 50 in. of silica gel 60 (400–230 mesh).
22. It was observed low specific rotation [α] of enantiomers (a*R*)-(−)-**9** and (a*S*)-(+)-**9** at the sodium D-line (589 nm) at 20°C, thus, specific rotation [α] was measured also at one mercury Hg-line (365 nm). In the text, the [α] sign of (a*R*)-(−)-**9** and (a*S*)-(+)-**9** was related to the sodium D-line.