Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 2131–2136

TETRAHEDRON

Torsional angles in 6,6′-bridged atropoisomeric biphenyls control the electrophilic substitution with phthalimidesulfenyl chloride☆

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Received 21 November 2002; revised 8 January 2003; accepted 30 January 2003

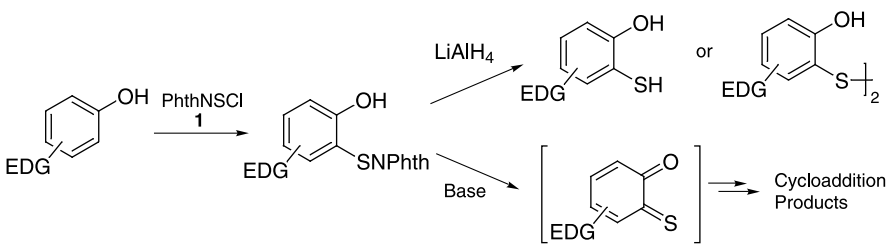
Abstract—The reaction of phthalimidesulfenyl chloride with 2,2′,6,6′-hydroxylated biphenyls allowed the preparation of 3- and/or 3,3′-*N*-thiophthalimide derivatives which can be easily transformed into the corresponding thiols and/or disulfides. Mono- or bis-substitution, as well as the regiochemistry of the sulfenylation, are predictable as a function of the substituents on the biphenyl unit and the length of the 6,6′ bridge. © 2003 Elsevier Science Ltd. All rights reserved.

1. Introduction

In the recent past we demonstrated the utility of the sulfenylation of electron-rich arenes using phthalimidesulfenyl chloride **1**, PhthNSCl (Phth=Phthaloyl), as key reagent. The reaction occurs smoothly at room temperature in chloroform without catalyst to give mono-sulfenylation on the most nucleophilic position.[2] The obtained *S*-arylthiophthalimides are stable crystalline compounds which can be easily transformed into the corresponding thiols and/or disulfides by means of $LiAlH_4$ as reducing agent (Scheme 1).[2] The sulfenylation with **1** of electron-rich phenols affords, with complete regioselectivity, *ortho*-hydroxythiophthalimides which can also be converted to the transient *ortho*-thioquinones, a useful class of electron-poor hetero dienes (Scheme 1).[3–6]

Recently, this chemistry was successfully applied to 2,2′,6,6′-tetramethoxybiphenyl **2**[7] and 2,2′-dihydroxy-6,6′-dimethoxybiphenyl **3**[1,8] with the formation of the bis-thiophthalimides **4** and **5**, respectively; suitable starting materials for the synthesis of the corresponding thiols **6** and **7**, disulfide **8** as well as other valuable sulfur containing biphenylic systems, like **9a–d** and **10** (Fig. 1).

In the light of these results and in consideration of the keen interest around hydroxylated biphenyls for the biological activity exhibited by those commonly isolated from natural sources,[9] and for their use as ligands in asymmetric catalysis,[10] we decided to broaden this study to other accessible electron-rich biphenyl systems. The outcome of this research is reported in this paper.[11]



Scheme 1.

☆ Phthalimidesulfenyl chloride Part 14. For Part 13 see Ref. 1.

Keywords: atropoisomeric biphenyls; phthalimidesulfenyl chloride; S_EAr; reactivity; torsional angle.
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0040–4020/03/$ - see front matter
doi:10.1016/S0040-4020(03)00178-9

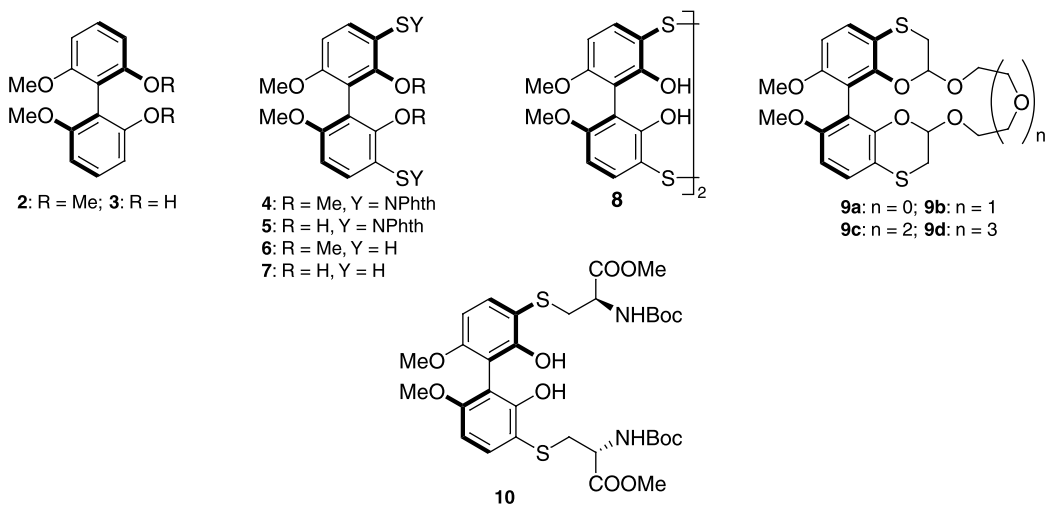


Figure 1. Atropoisomeric thiosubstituted biphenyls prepared using **1**.

2. Results and discussion

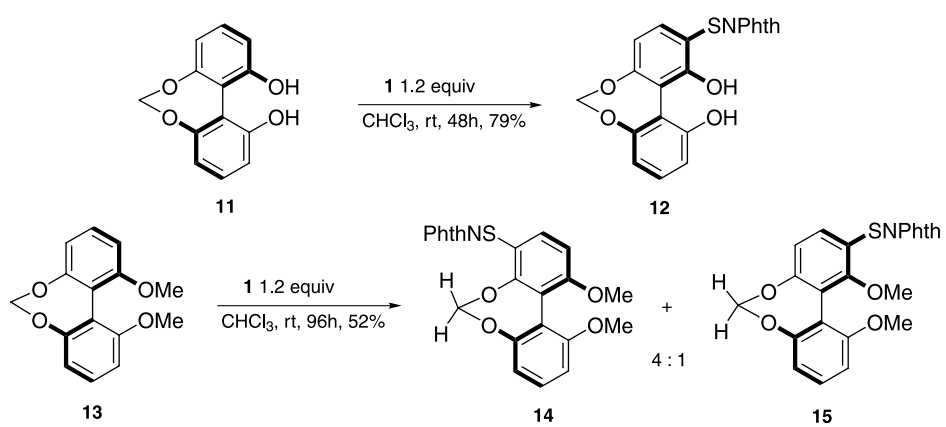
As mentioned, the reaction of **1** with 2,2′,6,6′oxygen-substituted biphenyls **2** and **3** afforded the corresponding bis-thiophthalimides **4** and **5** in good yield under very mild reaction conditions,[7,8] (i.e. chloroform, rt). Surprisingly when the sulfenylation was carried out on biphenyl **11** the mono-substituted derivative **12** was isolated as the only reaction product, as clearly indicated by its ^{1}H and ^{13}C NMR spectra which indicate the lack of a C_2-symmetry axis. On the other hand the formation of only the expected *ortho*-hydroxy substituted regioisomer was verified since one of the two signals for the phenolic hydrogens (6.96 and 9.58 δ, respectively, see Section 4) is typically[2,4,8] deshielded due to an intramolecular hydrogen bond with the imide carbonyls of the adjacent thiophthalimide group.

No evidence of the bis-substituted derivative was detected even when carrying out the reaction using a large excess of **1** at rt or 60°C for long reaction time (24–72 h).

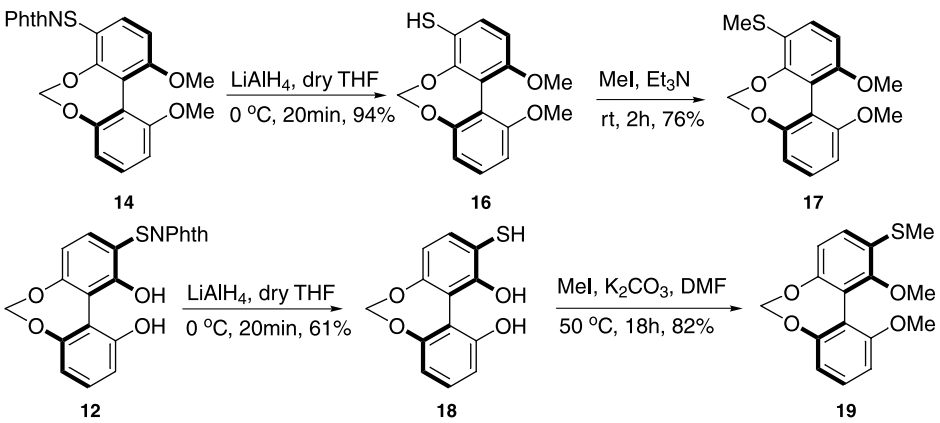
The sulfenylation of the methylated compound **13** led to the formation of two monosubstituted regioisomers **14** and **15**, isolated in 4:1 ratio and 52% overall yield after 96 h at rt (92% conversion yield based on recovered **13**). Also in this case, however, bis-substitution was not observed even when forcing the reaction conditions (Scheme 2).

A less efficient substitution and the formation of a mixture of regioisomers using **13** as an electron-rich arene were not surprising in consideration of the lack of the high activation and *ortho* orientation effect brought about by the hydroxyl group, familiar to us in these reactions.[12] The attribution of the regiochemistry for the two isomers formed in this reaction was initially done in consideration of their ^{1}H NMR spectra since the O–CH_2–O group for the major isomer **14** appears as an AX system (δ_A=5.60; δ_X=5.90; J_{AX}=3.6 Hz) while for the minor isomer **15** this group appears as an AB system (δ_A=5.44; δ_B=5.47; J_{AB}=3.4 Hz). This difference can be attributed to the distance between the thiophthalimide group and the dioxymethylenic hydrogens being greater in **14** than **15**. Indeed the shape of the signals for the O–CH_2–O group of compound **15** was pretty similar to that of derivative **12** which possesses the same relative regiochemistry. Similar considerations can be made for the chemical shifts of the methoxy groups of **14** and **15** which also indicate the regiochemistry reported in Scheme 2.

Major isomer **14** was obtained as a pure compound by column chromatography. Exploiting the chemistry of the



Scheme 2.



Scheme 3.

thiophthalimide group, we had the opportunity to unambiguously confirm the regiochemistry of the reaction. Compound **14** was transformed into the corresponding thiol **16** then methylated to give derivative **17** (Scheme 3). The same sequence carried out on regio-defined derivative **12** (i.e. reduction to thiol **18** and exhaustive methylation) afforded compound **19** (Scheme 3) indeed a regioisomer of **17**, thus confirming the structures reported in Scheme 2 deduced by means of their NMR spectra.

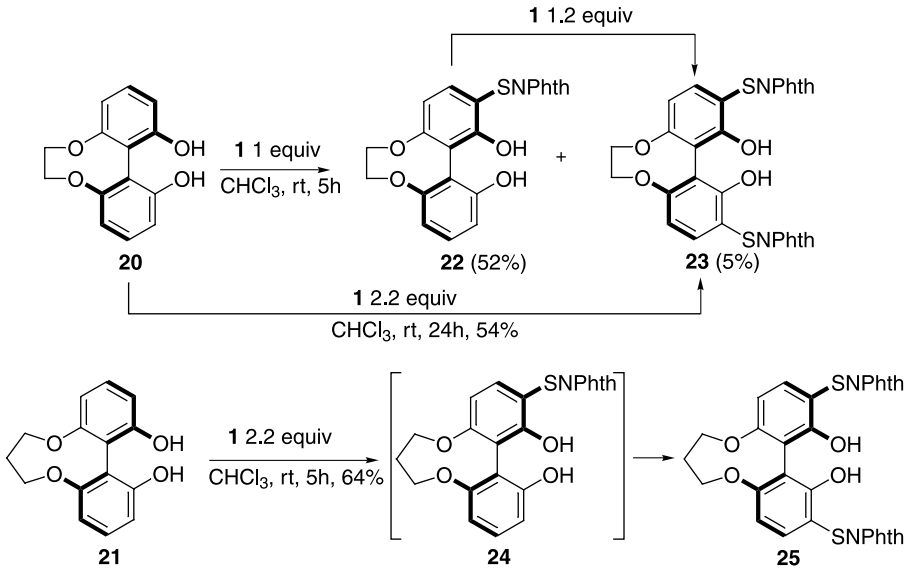
Hence the introduction of a dioxymethylenic bridge in the 6,6′ positions of the biphenyl unit, like in **11** and **13**, causes a clear slowing down of the sulfenylation rate when compared with the rate of the reaction of **1** with the 'unbridged' 6,6′-dimethoxy derivatives **2**[7] and **3**,[8] and more interestingly, does not allow the formation of a bis-substituted thiophthalimide.

During our studies on the phthalimidesulfenylation of electron-rich arenes[1,2,4,7,8] with **1** we verified that such S_EAr reactions never afforded polysubstitution products even when highly activated systems, like 1,3-dimethoxy benzene, resorcinol or 2,6-dihydroxy naphthalene, were reacted with an excess of **1** at high temperature for long reaction time. This behaviour indicates that the introduction of a *N*-thiophthalimide group deactivates the system preventing further substitutions. This distinguishes the phthalimidesulfenyl chloride from simple aliphatic and aromatic sulfenyl chlorides that in S_EAr often suffer of the problem of polysubtitution,[13] and simplifies the work-up.

Keeping this in mind, a possible explanation for the behaviour of derivative **11** and **13** during phthalimide-sulfenylation suggests a partial conjugation between the two rings, due to a small C2–C1–C1′–C2′ torsional angle produced by the short O–CH_2–O bridge, which can be enough to cause a deactivation of the whole system after the first substitution.

In derivatives **2** and **3** the rings can be considered as two unconnected activated arenes since they can stay perpendicular cancelling the conjugation.

We could verify this hypothesis studying the sulfenylation of derivatives **20** and **21** which offer the opportunity to assess the effect of the bridge length on the stoichiometry of the reaction.



Scheme 4.

Sulfenylation of **20** using 1 equiv. of **1** allowed, after 5 h at rt, the isolation of mono-substituted derivative **22** in 52% yield with only a tiny amount (5%) of bis-adduct **23** which can be obtained as a single reaction product either from **20** or **22** using 2.2 or 1.2 equiv. of **1**, respectively, after 24 h at rt (Scheme 4).

On the other hand the reaction of **21** with 1 equiv. of phthalimidesulfenyl chloride monitored by ^{1}H NMR 1 h after the mixing of the reagents showed similar amounts of mono and bis-derivatives **24** and **25**, respectively.[14] The latter was obtained as single compound after 6 h at rt using 2.2 equiv. of **1** (Scheme 4).

Data reported in Scheme 4 are in agreement with the hypothesis of a torsional angle effect since by increasing the length of the bridge between the 6,6′ positions, the two rings, after the first substitution, can more easily approach right-angles, removing the conjugation responsible for the deactivation of the whole system. In fact we observed only mono-substitution for **11**, an appreciable different rate between first and second substitution with **20**, allowing the selective synthesis of mono- or bis-derivatives **22** and **23**, whereas compound **21** parallels the behaviour of unbridged systems **2** and **3** since the first and second substitution reactions occurred at roughly the same rate.

As a matter of fact AM1 semi empirical calculation[15] carried out on mono-derivatives **11**, **22** and **24** showed for the more stable conformers C2–C1–C1′–C2′ torsional angles[16] of 33.1°, 59.2° and 78.1°, respectively, in full accord with the assumption that partial conjugation can be present between the two rings in **11** preventing the second substitution reaction, while **22** and, above all, **24** can be seen as two almost independent electron-rich arenes where the presence of a thiophthalimide group on an aromatic ring does not influence the reactivity of the other electron-rich ring.

The chemistry of biphenylic derivatives **11**, **13**, **20** and **21** has up to now been scarcely studied, however, some reports are available about the role of torsional angles on their efficiency as ligands in asymmetric catalysis.[16] This preliminary work seems to suggest that flexibility around the C1–C1′ bond could have also a relevant role on the chemical behaviour of the two aromatic rings, allowing, in this case, the preparation of mono and/or bis-thiophthalimide derivatives as a function of the 6,6′ bridge's length.

3. Conclusion

The phthalimidesulfenylation of 2,2′,6,6′-substituted biphenyls affords with good or complete regioselectivity mono and/or bis-thionated derivatives as a function of the nature of the substituents and the value of the torsional angles. In any case the arylthiophathlimides can be easily converted into the corresponding thiols or disulfides confirming the utility of this strategy for the introduction of sulfur onto electron-rich arenes. Further developments of this methodology are under investigation.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300 and 75 MHz, respectively, using residual $CHCl_3$ at δ_H 7.26 and the central line of $CDCl_3$ at δ_D 77.0 as reference. MS spectra were obtained on a Carlo Erba QM 1000. Melting points are uncorrected. THF, DMF, $CHCl_3$ and Et_3N were dried using standard procedures. Phthalimidesulfenyl chloride[17] **1**, and biphenyls[18,19] **11**, **13** and **21** were prepared as published elsewhere.

4.1.1. 6,7-Dihydro-5,8-dioxa-dibenzo[*a*,*c*]cyclooctene-1,12-diol 20. A solution of 2,2′,6,6′-tetrahydroxy-1,1′-biphenylene (2 g, 9.16 mmol), K_2CO_3 (2.53 g, 18.3 mmol) in dry DMF (10 mL) was stirred at 20°C for 1 h under N_2. A solution of 1,2-dibromoethane (1.72 g, 9.16 mmol) in dry DMF (10 mL) was added dropwise and the heterogeneous mixture was heated at 50°C for 12 h. The reaction mixture was then quenched with 100 mL of H_2O. A solution of 10% HCl was added until neutral pH. The mixture was extracted with ether (5×20 mL), dried over Na_2SO_4 and evaporated to give crude **20** as a colourless solid which was purified by flash chromatography with hexane/CH_2Cl_2=1:1 as eluent (1.14 g, 51%): mp 138–139°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.09 (d, 2H, J=8.4 Hz), 4.41 (d, 2H, J=8.4 Hz), 5.60 (bs, 2H, OH), 6.82 (dd, 2H, J=8.1, 0.9 Hz), 6.85 (dd, 2H, J=8.1, 0.9 Hz), 6.29 (t, 2H, J=8.1 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 66.6 (t), 102.6 (d), 107.2 (d), 108.4 (s), 131.6 (d), 159.5 (s), 160.4 (s). Anal. calcd for $C_{14}H_{12}O_4$: C, 68.85; H, 4.95. Found: C, 69.01; H, 4.78.

Thiophthalimides **12**, **14**, **15**, **22**, **23** and **25** were prepared as reported elsewhere,[7,8] spectroscopic and physical data are as follows.

4.1.2. 2-(1,11-Dihydroxy-6*H*-dibenzo[*d*,*f*]1,3-dioxepin-2-ylthio)isoindoline-1,3-dione 12. Pale yellow solid from column chromatography with CH_2Cl_2 as eluent. Mp 169–170°C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.51 and 5.55 (d, AB system, 2H, J=3.3 Hz); 6.84 (dd, 1H, J=8.1, 1.2 Hz); 6.88 (d, 1H, J=8.1 Hz); 6.96 (s, 1H, OH); 7.02 (dd, 1H, J=8.1, 1.2 Hz); 7.33 (t, 1H, J=8.1 Hz); 7.65–8.00 (m, 4H); 7.98 (d, 1H, J=8.1 Hz); 9.58 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 103.3 (t); 113.6 (s); 115.6 (s); 116.3 (s); 116.6 (d); 117.9 (d); 118.9 (d); 124.4 (d); 130.3 (d); 131.6 (s); 135.1 (d); 139.0 (d); 153.8 (s); 154.2 (s); 154.7 (s); 158.4 (s); 168.5 (s). Anal. calcd for $C_{21}H_{13}NO_6S\cdot H_2O$: C, 59.29; H, 3.56; N, 3.29. Found: C, 59.56; H, 3.91; N, 3.09.

4.1.3. 2-(1,11-Dimethoxy-6*H*-dibenzo[*d*,*f*]1,3-dioxepan-4-ylthio)isoindoline-1,3-dione 14. Pale yellow solid from column chromatography with CH_2Cl_2 2:1 as eluent, mp 155–156°C

^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.79 (s, 3H); 3.81 (s, 3H); 5.60 (d, 1H, J=3.6 Hz); 5.90 (d, 1H, J=3.6 Hz); 6.82 (d, 1H, J=8.8 Hz); 6.80–6.88 (m, 2H); 7.33 (t, 1H, J=8.0 Hz); 7.80 (d, 1H, J=8.8 Hz); 7.71–7.89 (m, 4H). ^{13}C NMR ($CDCl_3$,

75.5 MHz): δ 56.0 (q); 55.9 (q); 102.6 (t); 108.5 (d); 108.6 (d); 113.3 (d); 118.1 (s); 118.4 (s); 119.7 (s); 123.8 (d); 129.7 (d); 132.1 (s); 134.5 (d); 135.2 (d); 153.3 (s); 153.9 (s); 157.4 (s); 158.5 (s); 167.8 (s). MS (EI): *m/z* (rel. int., %): 435 ($M^{+\cdot}$, 29); 403 (16); 287 (5); 240 (100); 148 (63). Anal. (on the mixture **14**+**15**) calcd for $C_{23}H_{17}NO_6S$: C, 63.44; H, 3.94; N, 3.22. Found: C, 62.97; H, 4.10; N, 2.90.

4.1.4. 2-(1,11-Dimethoxy-6*H*-benzo[*d*]benzo[3,4-*f*]1,3-dioxepan-2-ylthio)isoindoline-1,3-dione 15. A pure sample of compound **15** was eventually obtained by two consecutive columns chromatography with CH_2Cl_2 and hexane/EtOAc=2:1 as eluent, respectively. Pale yellow solid mp 170–171°C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.56 (s, 3H); 3.76 (s, 3H); 5.44 and 5.47 (d, AB system, 2H, *J*=3.4 Hz); 6.81–6.88 (m, 2H); 6.86 (d, 1H, *J*=8.4 Hz); 7.09 (d, 1H, *J*=8.4 Hz); 7.36 (t, 1H, *J*=8.0 Hz); 7.79–8.00 (m, 4H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 55.9 (q) 60.7 (q); 102.3 (t); 108.3 (d); 108.4 (d); 113.1 (d); 118.0 (s); 118.4 (s); 119.7 (s); 124.0 (d); 130.2 (d); 132.1 (s); 134.4 (d); 135.2 (d); 153.2 (s); 153.9 (s); 157.4 (s); 159.5 (s); 167.8 (s).

4.1.5. 2-(1,12-Dihydroxy-6*H*,7*H*-dibenzo[*e*,*g*]1,4-dioxocin-2-ylthio)isoindoline-1,3-dione 22. White solid from column chromatography with CH_2Cl_2/MeOH=200:1 as eluent. Mp 149–150°C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.05–4.13 (m, 2H); 4.33–4.46 (m, 2H); 6.02 (s, 1H, OH); 6.78 (dd, 1H, *J*=8.0, 1.0 Hz); 6.80 (d, 1H, *J*=8.4 Hz); 6.91 (dd, 1H, *J*=8.0, 1.0 Hz); 7.29 (t, 1H, *J*=8.0 Hz); 7.73–7.92 (m, 4H); 7.96 (d, 1H, *J*=8.4 Hz); 9.14 (s, 1H, OH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 73.8 (t); 74.0 (t); 114.6 (s); 114.7 (s); 114.8 (s); 116.0 (d); 116.1 (d); 116.2 (d); 124.3 (d); 130.4 (d); 131.9 (s); 135.0 (d); 139.6 (d); 154.7 (s); 157.9 (s); 159.9 (s); 165.1 (s); 168.5 (s). Anal. calcd for $C_{22}H_{15}NO_6S$: C, 62.70; H, 3.59; N, 3.32. Found: C, 62.67; H, 3.80; N, 3.54.

4.1.6. 2-[11-(1,3-Dioxoisoindolin-2-ylthio)-1,12-dihydroxy-6*H*,7*H*-dibenzo[*e*,*g*]1,4-dioxocin-2-ylthio]isoindoline-1,3-dione 23. White solid from column chromatography with CH_2Cl_2 as eluent. Mp>300°C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.96 (d, 2H, *J*=8.8 Hz); 4.32 (d, 2H, *J*=8.8 Hz); 6.88 (d, 2H, *J*=8.4 Hz); 7.90 (d, 2H, *J*=8.4 Hz); 7.73–7.92 (m, 8H); 8.53 (s, 2H, OH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 73.8 (t); 114.6 (s); 114.7 (s); 116.4 (d); 124.2 (d); 131.9 (s); 134.8 (d); 139.5 (d); 157.9 (s); 163.8 (s); 168.6 (s). Anal. calcd for $C_{30}H_{18}N_2O_8S_2$: C, 60.19; H, 3.03; N, 4.68. Found: C, 60.33; H, 3.15; N, 4.51.

4.1.7. 2-[12-(1,3-Dioxoisoindolin-2-ylthio)-1,13-dihydroxy-6*H*,7*H*,8*H*-benzo[*f*]benzo[3,4-*h*]1,5-dioxonan-2-ylthio]isoindoline-1,3-dione 25. White solid from column chromatography with CH_2Cl_2 as eluent. Mp>300°C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.83–1.91 (m, 2H); 4.25 (t, 4H, *J*=5.2 Hz); 6.64 (d, 2H, *J*=8.8 Hz); 7.80 (d, 2H, *J*=8.8 Hz); 7.74–7.90 (m, 8H); 8.42 (s, 2H, OH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 29.4 (t); 71.6 (t); 110.1 (s); 112.9 (s); 115.0 (d); 124.2 (d); 132.0 (s); 134.7 (d); 139.0 (d); 158.0 (s); 162.5 (s); 168.6 (s). Anal. calcd for $C_{31}H_{20}N_2O_8S_2$: C, 60.78; H, 3.29; N, 4.57. Found: C, 60.59; H, 3.07; N, 4.48.

4.1.8. 1,11-Dimethoxy-6*H*-dibenzo[*d*,*f*]1,3-dioxepane-4-thiol 16. $LiAlH_4$ (15 mg, 0.39 mmol) was added to a solution of thiophthalimide **14** (78 mg, 0.18 mmol) in dry THF (10 mL) kept at 0°C. After 20 min at 0°C the reaction mixture was diluted with 1 M HCl (10 mL) and extracted with diethyl ether (5×15 mL). The organic phases were recollected, dried over Na_2SO_4 and evaporated to dryness to give a crude material which was purified by column chromatography using CH_2Cl_2 as eluent to obtain thiol **16** (50 mg, 94%) as a yellow solid, mp 162–164°C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.58 (s, 1H, SH); 3.82 (s, 3H); 3.84 (s, 3H); 5.53 (d, 1H, *J*=3.2 Hz); 5.61 (d, 1H, *J*=3.2 Hz); 6.80 (d, 1H, *J*=8.7 Hz); 6.85–6.91 (m, 2H); 7.32 (d, 1H, *J*=8.8 Hz); 7.35 (t, 1H, *J*=8.0 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 55.9 (q); 56.0 (q); 101.2 (t); 108.6 (d); 109.2 (d); 113.2 (d); 114.8 (s); 118.4 (s); 119.5 (s); 129.6 (d); 129.8 (d); 153.7 (s, 2C); 156.0 (s); 157.5 (s).

4.1.9. 1,11-Dimethoxy-4-methylthio-6*H*-dibenzo[*d*,*f*]1,3-dioxepin 17. To a solution of thiol **16** (50 mg, 0.17 mmol) in dry THF (6 mL), methyl iodide (27 mg, 0.19 mmol) and Et_3N (18 mg, 0.18 mmol) were added under nitrogen. After 2 h at rt the mixture was diluted with saturated aqueous NH_4Cl and extracted with diethyl ether (3×15 mL). The organic phases recollected were dried over Na_2SO_4 and evaporated to dryness to give a crude material which was purified by column chromatography using hexane/EtOAc=4:1 as eluent to give methyl derivative **17** as a white solid (39 mg, 76%), mp 134–135°C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.43 (s, 3H); 3.83 (s, 3H); 3.85 (s, 3H, CH_3O); 5.54 and 5.61 (d, AB system *J*=3.6 Hz); 6.90–6.84 (m, 3H); 7.30 (d, 1H, *J*=8.8 Hz);7.34 (t, 1H, *J*=8.2 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 16.6 (q); 56.0 (q); 56.1 (q); 101.7 (t); 108.5 (d); 108.8 (d); 113.2 (d); 116.9 (s, 2C); 121.6 (s); 128.8 (d); 129.5 (d); 153.6 (s, 2C); 156.1 (s); 157.5 (s). Anal. calcd for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30. Found: C, 62.94; H, 5.14.

4.1.10. 2-Sulfanyl-6*H*-dibenzo[*d*,*f*]1,3-dioxepane-1,11-diol 18. $LiAlH_4$ (17 mg, 0.45 mmol) was added to a solution of thiophthalimide **12** (53 mg, 0.13 mmol) in dry THF (15 mL) kept at 0°C. After 20 min at 0°C the reaction mixture was diluted with 1 M HCl (10 mL) and extracted with diethyl ether (5×15 mL). The organic phases were recollected, dried over Na_2SO_4 and evaporated to dryness to give a crude material which was purified using CH_2Cl_2 as eluent to give thiol **18** (20 mg, 61%) as a pale yellow solid, mp 185–187°C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.35 (s, 1H, SH); 4.80 (bs, 1H, OH); 5.53 and 5.54 (d, AB system, 2H, *J*=3.3 Hz); 6.84 (d, 1H, *J*=8.4 Hz); 6.87 (dd, 1H, *J*=8.4, 1.2 Hz); 6.94 (dd, 1H, *J*=8.4, 1.2 Hz); 7.30 (t, 1H, *J*=8.4 Hz); 7.48 (d, 1H, *J*=8.4 Hz); 7.49 (bs, 1H, OH). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 103.3 (t); 110.9 (s); 114.1 (d); 115.1 (d); 115.5 (d); 117.7 (s); 117.8 (s); 130.2 (d); 134.9 (d); 151.3 (s); 153.7 (s); 154.0 (s); 157.6 (s).

4.1.11. 1,11-Dimethoxy-2-methylthio-6*H*-dibenzo-[*d*,*f*]1,3-dioxepin 19. To a solution of thiol **18** (20 mg, 0.08 mmol) in dry DMF (2 mL), methyl iodide (46 mg, 0.32 mmol) and K_2CO_3 (44 mg, 0.32 mmol) were added under argon and the mixture kept at 50°C for 18 h. The mixture was allowed to cool to rt, diluted with saturated aqueous NH_4Cl and extracted with diethyl ether (3×15 mL). The organic phases were recollected and dried over Na_2SO_4 and then evaporated to dryness to give a crude material which was purified by column chromatography using hexane/CH_2Cl_2=1:1 as eluent to give methyl derivative **19** as a white solid (20 mg, 82%), mp 143–145°C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.46 (s, 3H); 3.47 (s, 3H); 3.85 (s, 3H); 5.47 and 5.50 (d, AB system, 2H, J=3.4 Hz); 6.83–6.90 (m, 2H); 6.97 (d, 1H, J=8.6 Hz); 7.17 (d, 1H, J=8.6 Hz); 7.36 (t, 1H, J=8.2 Hz). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 15.1 (q); 56.2 (q); 60.3 (q); 102.3 (t); 108.5 (s); 113.1 (d); 116.2 (s); 116.3 (d); 115.5 (d); 118.5 (s); 126.1 (d); 129.9 (d); 151.2 (s); 153.5 (s); 155.5 (s); 157.4 (s). MS (EI): *m*/*z* (rel. int., %): 304 ($M^{+\cdot}$, 32); 276 (10); 257 (13); 57 (100). Anal. calcd for $C_{16}H_{16}O_4S$: C, 63.14; H, 5.30. Found: C, 62.98; H, 5.44.

Acknowledgements

Work carried out in the framework of the National Project: 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni' supported by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, Rome, by the University of Florence and by CNR-Rome.

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11. All the reactions were carried out on racemic biphenyls, *aR*(*M*) configuration depicted in this paper was arbitrarily chosen.
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14. Attempts to separate by column chromatography derivatives **24** and **25** from mixtures obtained reacting **21** with 0.5–1.5 equiv. of **1** were unsuccessful.
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