Regiocontrolled Synthesis of Enantiopure 3,3′-Thiosubstituted Biphenyls

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Sulfenylation of 6,6′-dimethoxy-2,2′-dihydroxybiphenyl, used as a racemic mixture and single enantiomers, by phthalimidesulfenyl chloride afforded the corresponding 3,3′-*N*,*N*′-dithiophthalimide with complete regioselectivity. Simple manipulations of the latter compound allowed access to the corresponding bis-thiol or *o*-thioquinone as useful intermediates for the synthesis of new sulfur-containing open-chain and macrocyclic C_2 enantiopure ligands. The application of this methodology to the preparation of a biphenyl bearing two cysteine units as potential HIV-1 protease inhibitor is also described.

Introduction

Interest in the chemistry of atropisomeric biphenyls is continuously expanding. Their preparation, in racemic[1] or enantiopure[2] form, and their use in asymmetric synthesis,[3] drug discovery,[4] and material science[5] are fields of great development. Moreover the distribution of biphenyls in plant extracts and the biological activities related to several of these natural biphenyls[6] demonstrate their peculiar biocompatibility, making them a stimulating subject of study.

We have reported an original method for introducing an *N*-thiophthalimide group on electron-rich phenols that uses phthalimidesulfenyl chloride **1** (PhthNSCl, Phth = phthaloyl) as the key reagent.[7−9] The *N*-thioarylphthalimides obtained with this procedure can be used for the formation of the corresponding *o*-hydroxythiols[7] and *o*-thioquinones,[8,9] two classes of very useful and versatile intermediates in organic synthesis. Recently we communicated[10] the possibility of applying this methodology to racemic 6,6′-dimethoxy-2,2′-biphenol **2** which reacts with sulfenyl chloride **1** to give the bis-thiophthalimide **3** with complete regioselectivity as shown in Scheme 1. In this paper we report a detailed study on the reactivity of racemic and enantiopure **3**[11] (Scheme 1).

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(11) All the reactions described in this paper were previously performed on racemic derivatives. Most of the transformations were repeated using enantiopure biphenol (*M*)-**2** (in some case and/or *(P)*-**2**) as starting materials.[12] The stereochemistry of biphenyls will be indicated only when the corresponding compound has been actually prepared as single enantiomer. "Flat" biphenyls state racemic mixtures.

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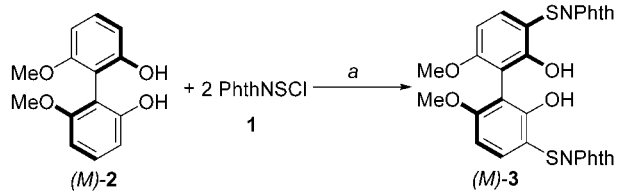
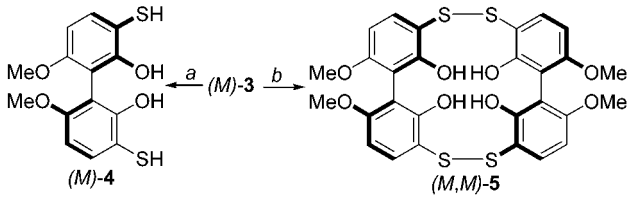
Scheme 1



(M)-**2** *(M)*-**3**

a: $CHCl_3$, rt, 3h, 94%

Scheme 2



(M)-**4** *(M,M)*-**5**

a: $LiAlH_4$ (5.5 equiv), THF, 0 °C, 99%
b: $LiAlH_4$ (1.5-2 equiv), THF, 0 °C, 86%

Results and Discussion

The formation of **3**, shown in Scheme 1, occurs smoothly at room temperature in chloroform. Compound **3** can be purified by flash chromatography on silica gel using dichloromethane as eluent; however this procedure is tedious, due to the poor solubility of **3** in the eluent as well as in most of the common organic solvents. Thus, for multigram-scale preparations, we realized that the purification of **3** can be more conveniently achieved by dissolving the byproducts in boiling chloroform, which causes only a small loss of **3**. When the sulfenylation was performed on enantiopure (*P*)- and (*M*)-**2**,[12] the obtained thiophthalimides (*P*)- and (*M*)-**3** surprisingly were much more soluble in many solvents, including dichloromethane, and even cold chloroform[13] so that flash chromatography is necessary for the purification of enantiopure thiophthalimides **3**. Crystalline products **3** are perfectly stable at room temperature and can be stored for months with neither decomposition nor racemization.

As the first aspect of the reactivity of *N*-thiophthalimide **3**, we considered its transformation into the corresponding thiol. The reduction of **3** was achieved using an excess of $LiAlH_4$ (5.5 equiv) in dry THF.[14] Bis-thiol **4** was thus obtained as a racemic mixture, or as enantiopure compounds, in near quantitative yield. When the reaction was carried out using 1.5−2 equiv of $LiAlH_4$ we could isolate cyclic disulfide **5** as single compound in good yield (Scheme 2).

We have already reported[7] the use of aryl *N*-thiophthalimides as a source for the corresponding diaryl disulfides. Using a substoichiometric amount of hydride ion, the partial reduction of the sulfenamide generates in solution an intermediate thiolate ion, which is a good nucleophile toward the residual starting sulfenamide causing the formation of the disulfide linkage.

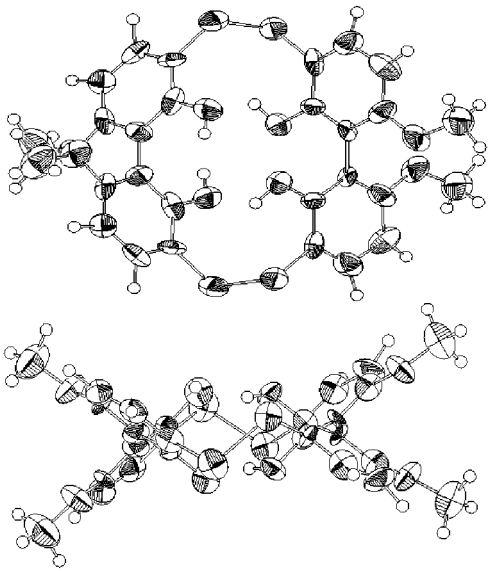


Figure 1. Top and side ORTEP view of racemic disulfide **5**.

The isolation of **5** as the sole product of the partial reduction of **3** is an intriguing result. First, after the formation of the first sulfur−sulfur bond, the intermediate open-chain mono-disulfide could give rise to a mixture of cyclic and linear oligomers through a mix of inter- and intramolecular formation of further disulfide linkages. Instead, starting from **3** only an intramolecular reaction occurs, and the cyclic dimer **5** is obtained as the only product (Scheme 2).

Moreover, the formation of dimer **5**, from racemic **3**, could afford different stereoisomers: a racemic mixture and a *meso* form, depending on the chirality of the biphenyl units link together (the same or the opposite respectively). A single product was obtained from the reduction of racemic **3**, and X-ray analysis[10] demonstrated it was the racemic disulfide **5** (Figure 1). These data seems to indicate that the two biphenyl units are able to recognize each other during the formation of the sulfur−sulfur bonds, which occurs preferentially between two homochiral species affording (*P*,*P*)-**5** and (*M*,*M*)-**5**.

These results can be rationalized by considering at least two independent mechanisms. It is possible to foresee the selective formation of the first sulfur−sulfur bond between two homochiral biphenyls, followed by a highly preferred intramolecular reaction that prevents oligomerization. Alternatively, it can be suggested that both racemic and *meso* compounds **5** are formed in the mixture, and then a fast equilibration, carried out by thiolate ions, occurs leading to the more stable species, among those containing sulfur−sulfur linkages, represented by the homochiral derivatives **5**.[15] As a further interesting aspect related to dimeric disulfide **5**, the reduction of (*M*)-**3** afforded the corresponding (*M*,*M*)-**5**, isolated in 86% yield, which showed $[\alpha]^{20}_D = -735$, indicative of this species being an example of a "high chirality"[16] compound. The X-ray structure of disulfide **5** points out the smallness of its internal cavity, since

(12) Delogu, G.; Fabbri, D. *Tetrahedron: Asymmetry* **1997**, *8*, 759.

(13) The solubility differences between a racemate and the enantiomers is a known, although uncommon, phenomenon. See for example: (a) Jacques, J.; Gabard, J. *Bull. Soc. Chim. Fr.* **1972**, 342. (b) Cervinka, O.; Fabryova, A.; Sablukova, I. *Collect. Czech. Chem. Commun.* **1986**, *51*, 401. In the case of derivative **3** the difference in solubility is really remarkable, for example in chloroform at 20 °C racemic **3** is about 20 times less soluble than (*P*)- or (*M*)-**3**, (4 vs 80 mg/mL).

(14) For the complete reduction of sulfenamide **3** to thiol **4**, dry THF was deoxygenated by bubbling N_2 or Ar (vide infra).

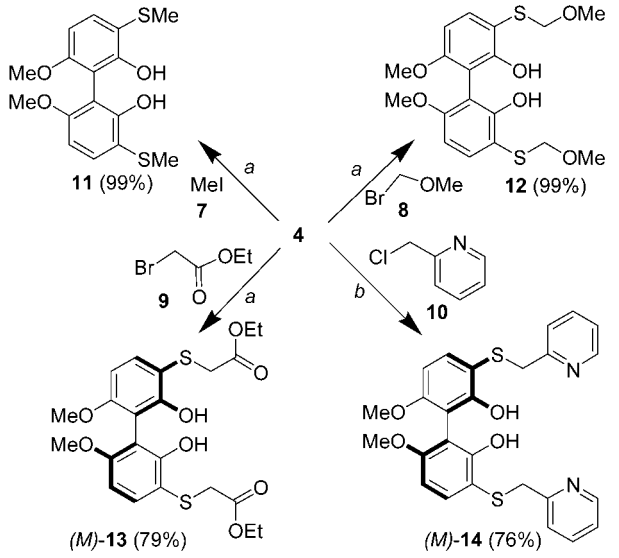
(15) As a demonstration that **5** represents a particular favorite situation, reacting **3** with 2 equiv of sodium methanethiolate or sodium thiophenoxide, no trace of the expected unsymmetric disulfides were detected, while the corresponding dimethyl or diphenyl disulfide and **5** were isolated, respectively. Reasonably in this case, a series of thiolate−disulfide interchanges shifts the equilibrium towards the thermodynamically favored symmetric disulfides.

the four hydroxyl oxygens lay on the vertex of an almost regular tetrahedron with a 3.0−3.2 Å side.[17] Preliminary attempts to use **5** as a cavitand[18,19] for metal cations were unsuccessful[20] as well as our efforts to enlarge the internal[21] cavity which seems inadequate to accommodate even very small metal ions.

The use of thiol **4** as an efficient nucleophile was then exploited for the synthesis of 3,3′-thiosubstituted biphenyls. To avoid accidental oxidation of thiol **4** to disulfide **5**, air was excluded from the reaction mixtures by bubbling N_2 or Ar. Thiol **4** was reacted in deoxygenated dry THF or DMF, with electrophiles **7**−**10** and Et_3N as base, to give sulfides **11**−**14** in good yields. Bromo ester **9** and 2-picolyl chloride **10** also were reacted with enantiopure (*M*)-**4** to afford (*M*)-**13** and (*M*)-**14**, respectively, as reported in Scheme 3.

The electrophiles were chosen to demonstrate the validity of this methodology in the synthesis of multidonor group containing C_2 biphenyls, since the sulfur atom in these compounds is a donor itself and a very practical means to join the sidearms. Good yield of derivative **14** can be obtained only with excesses of both 2-picolyl chloride **10** (3 equiv) and Et_3N (6 equiv) in DMF. When the reaction of (*M*)-**4** and **10** was performed under the conditions suitable with the other electrophiles, the ^1H NMR analysis of the crude reaction mixture revealed, besides the expected compound (*M*)-**14**, the presence of disulfide (*M*,*M*)-**5** and a third component **15**, which were isolated in 19%, 11%, and 24% yields, respectively (see Experimental Section). ^1H NMR showed that in the latter compound the biphenyl unit and the pyridine ring were

Scheme 3



in 1:1 ratio, suggesting for (*M*)-**15** the structure shown in Figure 2.

We propose that compounds **14**, **15**, or **5** are formed depending upon the relative rates of the nucleophilic substitution vs the sulfur−sulfur bond formation (by adventitious oxidation of thiol **4**) this last becoming a competitive side reaction when the substitution is less efficient. A similar behavior can be observed in the case of fast substitutions by modifying stoichiometry and conditions of the reaction. By reacting thiol **4** with only 1.4 equiv of the bromo ester **9**, after 4 h in nondeoxygenated dry THF, compounds **13** and **16**[23] were isolated in 49% and 44% yields, respectively (with only traces of disulfide **5**), thus validating our previous hypothesis (Figure 2).

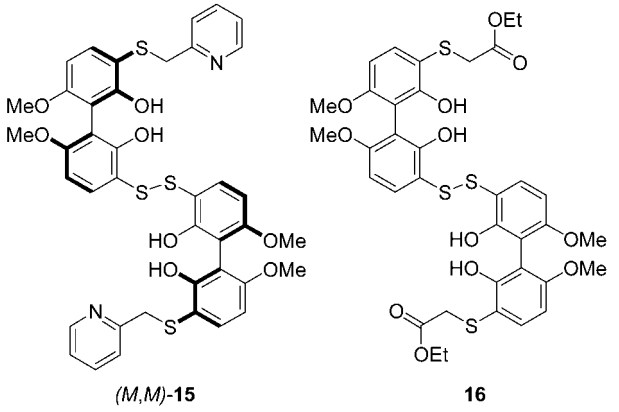


Figure 2. Compounds **15** and **16** obtained from "mixed" substitution and sulfur−sulfur bond formation.

Recently Reetz reported the synthesis of several amino acids containing biphenyl or binaphthyl C_2 symmetric units and their ability to serve as HIV-1 protease inhibitors.[24] The affinity of these species toward the

(16) Kiupel, B.; Niederalt, C.; Nieger, M.; Grimme, S.; Vogtle, F. *Angew. Chem. Int. Ed.* **1998**, *37*, 3031.

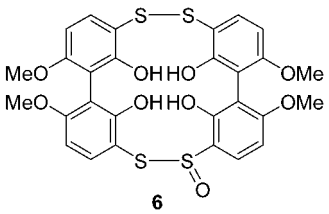
(17) X-ray structure of derivative **5** ruled out the possibility that H-bonding is present between the OH's in the cavity. Independently upon its presence in the final product, the possibility that H-bonding could play a role in the recognition of the two homochiral biphenyl units seems highly improbable since under the reaction conditions required for the synthesis of **5** (see Scheme 2) we likely have in the reaction mixture not the OH's but the corresponding Li/Al salts.

(18) (a) Koenig, K. E.; Lein, G. M.; Stuckler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553. (b) Kaneda, T.; Umeda, S.; Tanigawa, H.; Misumi, S.; Kai, Y.; Morii, H.; Miki, K.; Kasai, N. *J. Am. Chem. Soc.* **1985**, *107*, 4802. (c) Ueda, T.; Adachi, T.; Sumiya, K.; Yoshida, T. *J. Chem. Soc., Chem. Commun.* **1995**, 935.

(19) A referee suggested that compound **5** resembles a calix[4]arene more than a cavitand. Despite several examples of sulfur substituted calixarens are available in the literature (see for example: Hosseini, M., W. In *Calixarenes 2001*; Asfari, Z., Bohmer, V., Harrowfield, Vicens, J. Eds.; Kluwer Academic Publisher: Dordrecht, The Netherlands, 2001; pp110−129 and references therein), compounds with calixarenes containing biphenyl units are hardly ever reported: (a) Yamato, T.; Saruwatari, Y.; Nagayama, S.; Meeda, K.; Tashiro, M. *J. Chem. Soc., Chem. Commun.* **1992**, 861. (b) Yamato, T.; Hasegawa, K−i.; Saruwatari, Y.; Doamekpor, L. K. *Chem. Ber.* **1993**, *126*, 1435.

(20) No trace of complexation between **5** and LiOH was detected by ^1H NMR in $CDCl_3$.

(21) Attempts to enlarge this cavity using the disulfide−thiolsulfinate-trisulfide transforming methodology[22] were unsuccessful. The oxidation of **5** to the corresponding thiosulfinate **6** was achieved using *m*-CPBA (see Experimental Section); however, the reaction of **6** with bis(trimethylsilyl)sulfide in boiling chloroform[22] did not afford the expected mono-trisulfide but only a partial reduction back to the disulfide **5**.



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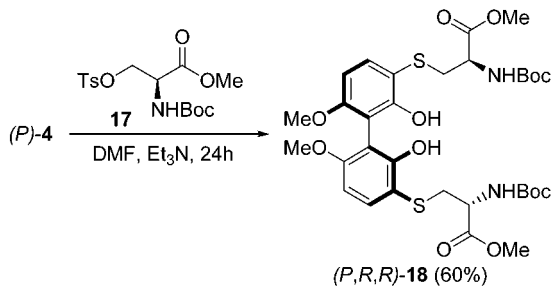
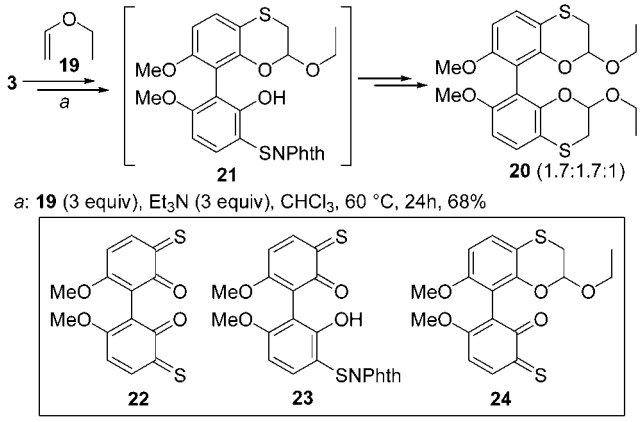
(22) Capozzi, G.; Capperucci, A.; Degl'Innocenti, A.; Del Duce, R.; Menichetti, S. *Tetrahedron Lett.* **1989**, *30*, 2991

(23) Compound **16** was obtained as single diastereomer, spectroscopic data did not allow the attribution of the relative stereochemistry of the biphenyl units.

Scheme 4



Scheme 5



biological target is related to the presence of the C_2 symmetry that is a critical requirement. We proved that our approach is useful to create new potential inhibitors by exploiting the reactivity of thiol **4**. Thus tosylation of (*S*)-*N*-Boc serine methyl ester gave the electrophile **17** that was reacted with racemic and (*P*)-thiol **4** to give the biphenyl-linked cysteine amino acid **18** showing a structure directly related to that of previously mentioned derivatives[24] (Scheme 4).

The study of the reactivity of derivative **3** continued with the evaluation of the possible generation in solution of the corresponding *o*-thioquinone and its trapping as electron-poor bis-heterodiene.[8,9] A suspension in chloroform of thiophthalimide **3** was heated to 60 °C in the presence of 3 equiv of Et_3N and 3 equiv of ethyl vinyl ether (**19**) as potential dienophile. After 24 h, we isolated the cycloadduct **20** in 68% yield as a 1.7:1.7:1 mixture of the three possible diastereomers (Scheme 5).

Bis-benzoxathiin **20** clearly can be derived from two inverse electron demand Diels−Alder reactions of the electron-rich alkene **19** with a dienic *o*-thioquinone species generated "in situ". The reaction was monitored by ^{1}H NMR, and after 5 h of heating, we could detect the presence of a biphenyl derivative of type **21** bearing both a benzoxathiin ring and an *o*-hydroxy-*N*-thiophthalimide moiety. Although we cannot rule out the presence of bis-*o*-thioquinone **22**, a stepwise mechanism with the formation of the final product **20** through two consecutive cycloadditions carried out by the mono-*o*-thioquinones **23** and **24** seems to be the actual route (Scheme 5).

The ratio and relative geometry of the three stereoisomers **20** was obtained on the basis of the ^{1}H NMR spectra of the crude reaction mixture recorded in C_6D_6. By decoupling the three, almost coincident, SCH_2 groups, the acetal protons appear as four separated singlets

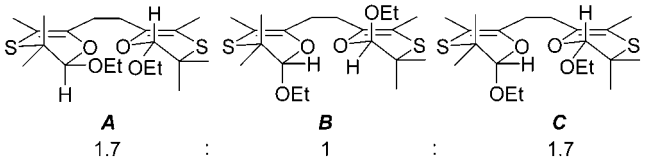
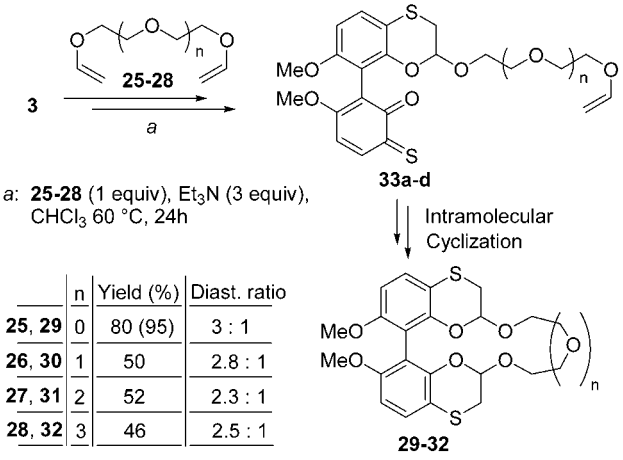


Figure 3. Ratio and relative geometry of the three diastereomers **A**, **B**, **C** of bis-benzoxathiin **20**.

Scheme 6



	n	Yield (%)	Diast. ratio
25, **29**	0	80 (95)	3 : 1
26, **30**	1	50	2.8 : 1
27, **31**	2	52	2.3 : 1
28, **32**	3	46	2.5 : 1

(between 5.4 and 5.0 ppm), one for each diastereomer in a 1.7:1 ratio possessing the C_2 axis (both homotopic acetal protons in pseudoaxial or pseudoequatorial position, diastereomers **A** and **B**, Figure 3) and two separated singlets for the third diastereomer (one proton pseudoaxial and one pseudoequatorial, diastereomer **C**, Figure 3). Column chromatography permitted the isolation of one major isomer whose acetal protons resonate as a single doublet of doublets at 5.18 ppm (J = 5.8 and 2.4 Hz), indicating that the acetal protons are homotopic (i.e., C_2 axis) and pseudoaxial (isomer **A** Figure 3).[25] This result allowed the attribution of the relative geometry to the three diastereomers **20** as reported in Figure 3.

A promising result of this inverse electron demand Diels−Alder reaction was obtained when bis-enol ethers **25**−**28** were used as dienophiles. In this case we had the opportunity to verify whether an intramolecular cycloaddition could occur after the initial intermolecular reaction, leading to the formation of a macrocyclic compound. The reactions, performed under the conditions reported above (Et_3N, $CHCl_3$, 60 °C) but using 1 equiv of dienophiles **25**−**28**, allowed the isolation of the monomeric cycloadducts **29**−**32** as mixture of only two of the three possible diastereomers (Scheme 6).

These reactions likely proceeded through an intermediate thioquinone of type **33**, bearing the tethered dienophile, so that the intramolecular cycloaddition could be associated with several intermolecular reactions which result in the formation of cyclic and linear oligomers. For cycloadditions carried out with vinyl ethers **26**−**28** (n = 1, 2, 3), ^{1}H NMR analyses of the crude indicated the presence of oligomeric species, although no compound with molecular weight higher than **30**−**32** was isolated from these mixtures. Since the formation of cyclic ethers

(24) Reetz, M.; Merk, C.; Mehler, G. *Chem. Commun.* **1998**, 2075.

(25) For a discussion on the attribution of the pseudoaxial or pseudoequatorial position for the acetal protons of similar oxathiins, see: Capozzi, G.; Fratini, P.; Menichetti, S.; Nativi C. *Tetrahedron* **1996**, *52*, 12233. *Ibid.* **1996**, *52*, 12247.

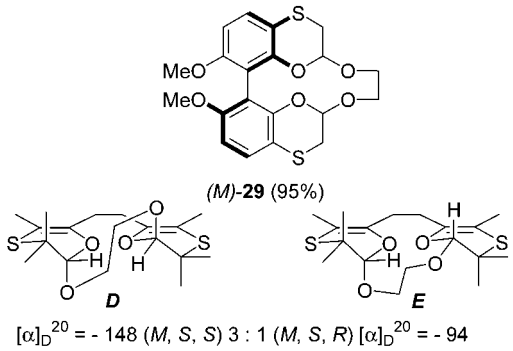


Figure 4. Relative and absolute stereochemistry for the two diastereomers **D** and **E** of 12-membered ring oxathiin (*M*)-**29**.

30−**32** occurred in roughly the same yields (Scheme 6) the ratio of inter- vs intramolecular cycloaddition from thioquinones **33b**−**d** seems almost insensitive to the length of the tethered dienophile (from $n = 1$ to $n = 3$). Thus, cyclization to 15-, 18-, or 21-membered rings (compounds **30**, **31**, and **32**) takes place with similar probability.

Remarkably, when ethylene glycol divinyl ether (**25**, $n = 0$) was the dienophile, the monomeric compound **29** was the unique cycloadduct in the crude reaction mixture, indicating that the formation of the 12-membered ring from thione **33a** represents a highly favorite situation[26] that prevents the oligomerization.[27]

When this reaction was repeated using enantiopure sulfenamide (*M*)-**3**, derivative (*M*)-**29** was isolated in 95% yield, again as 3:1 mixture of two diastereomers isolated by flash chromatography (Scheme 6, Figure 4). Following the same consideration discussed for compound **20** (Figure 3), it has been possible to assign the relative and, in this case, absolute stereochemistry of the two isomers (*M*)-**29**. The major isomer **D** maintains the C_2 axis with both homotopic acetal protons in pseudoequatorial position (apparent triplet at 5.28 ppm, $J = 3.0$ Hz), while the C_2 axis is missed in the minor isomer **E** showing two different signals for the diastereotopic acetal protons (see Experimental Section) (Figure 4).

The same geometric attribution can be done for major and minor diastereomers of derivatives **30**−**32**, which in turn were separated by flash chromatography (see Experimental Section). Thus the inter- *plus* intramolecular cyclization favored the formation of the compounds containing a C_2 axis and with two pseudoaxial acetal carbon−oxygen bonds. It is noteworthy that the same geometry can be found in the minor diastereomer of derivative **20** (see compound **B**, Figure 3), obtained from two intermolecular cycloadditions. Moving from inter- to intramolecular cycloaddition we observed an inversion of the stereochemistry of the major isomers, which however, maintains the C_2 axis (compare isomer **A** of compound **20**, Figure 3, with isomer **D** of compound **29**, Figure 4).

(26) No trace of oligomeric oxathiins were detected even using an excess of bis-enol ether **25**.

(27) As a referee suggests, the formation of **29** as the sole compound is probably due to the "effective molarity" of the second reaction that is much larger on account of the shorter chain holding the reactive groups together. Reasonably with longer more flexible chains, more of an entropic cost has to be paid to bring the reactive groups together, thus allowing the oligomers to be formed during the formation of derivatives **30**−**32**.

Conclusion

The regioselective introduction of two sulfur atoms, performed by applying the chemistry of phthalimidesulfenyl chloride **1**, represents the key step for the further functionalization of the biphenyl skeleton with preservation of the C_2 symmetry. The versatility of the *N*-thiophthalimide moiety offers a straightforward access to a wide range of enantiopure 3,3′-thiosubstituted substrates that represent interesting targets since many thio-biphenyls[28] have found application for their biological activities.[29] Moreover compounds such as biphenyl dimer **5**,[18] C_2 symmetry sulfides **11**−**14**,[30] biphenyl-containing amino acid **18**,[24,31] 1,4-dibenzoxathiin **20**,[32] and macrocyclic polyethers **29**−**32**[33] are the thio-isosters of several derivatives useful in asymmetric catalysis as well as in medicinal chemistry. The potentials of the above-described compounds as well as the extension of this chemistry to further electron-rich biphenyls are under investigation.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded (when not specified) in $CDCl_3$ at 200 and 50 MHz, respectively, using residual $CHCl_3$ at 7.26 ppm for ^{1}H and central peak of $CDCl_3$ at 77 ppm for ^{13}C as reference lines. Mass spectra were recorded in the electron impact ionization mode with an electron energy of 70 eV or, when specified, by electron spray ionization (ESI). Optical rotation were measured using a digital polarimeter with a 10-cm cell. Melting point are uncorrected. $CHCl_3$, CH_2Cl_2, THF, and DMF were dried following standard procedures, all commercial reagents were used without further purification. Phthalimidesulfenyl chloride **1**[8] and biphenol **2**[12] were prepared as reported elsewhere. The following data described only the reaction, when performed, of enantiopure compounds.

(*M*)-2-{3-[3-(1,3-Dioxoisoindolin-2-ylthio)-2-hydroxy-6-methoxyphenyl]-2-hydroxy-4-methoxyphenylthio}-isoindoline-1,3-dione (3). To a solution of biphenol *(M)*-**2** (470 mg, 1.90 mmol) in dry chloroform (15 mL) was added sulfenyl chloride **1** (850 mg, 3.90 mmol), and the mixture was kept for 3 h at room temperature. The mixture was diluted with dichloromethane (30 mL) and washed with saturated aqueous $NaHCO_3$ (1 × 30 mL) and with water (2 × 30 mL). The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude which was purified by flash silica gel chromatography to give bis(thiophthalimide) (*M*)-**3** (935 mg, 82%) as a white solid (eluent: dichloromethane): mp 287

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°C. $[\alpha]^{20}_D = -7.7$ (*c* 0.36, $CHCl_3$). ^1H δ: 8.26 (s, 2H, OH); 7.89 (d, 2H, $J = 8.8$ Hz); 7.87−7.68 (m, 8H); 6.55 (d, 2H, $J = 8.8$ Hz); 3.72 (s, 6H). ^{13}C δ: 168.6 (s); 162.6 (s); 157.8 (s); 139.4 (d); 134.7 (d); 132.0 (s); 124.3 (d); 124.1 (d); 110.8 (s); 103.8 (s); 56.1 (q) δ. Anal. Calcd for $C_{30}H_{20}O_8S_2N_2$: C, 59.99; H, 3.36; N, 4.66. Found: C 59.70; H, 3.36; N, 4.59.

In the same way was obtained derivative (*P*)-**3**, 94%, $[\alpha]^{20}_D = +7.7$ (*c* 0.35, $CHCl_3$). In the case of racemic biphenol **2** the crude obtained after evaporation of the solvent was washed with boiling $CHCl_3$ (10 mL for 1 g) to give pure **3**, 73% yield.

(*M*)-2-(2-Hydroxy-6-methoxy-3-sulfanylphenyl)-3-methoxy-6-sulfanylphenol (4). Nitrogen was bubbled for 10 min in a solution of thiophthalimide *M*-**3** (427 mg, 0.71 mmol) in dry THF (40 mL), and then the mixture was cooled at 0 °C and lithium aluminum hydride (149 mg, 3.92 mmol) added in one portion. The green suspension obtained was kept under nitrogen at 0 °C for 20 min and then at room temperature for 30 min. The mixture was adjusted at pH 2 with 3% aqueous HCl and washed with diethyl ether (5 × 30 mL). The combined organic solvent was dried over Na_2SO_4 and evaporated to dryness. Silica gel flash chromatography (eluent: dichloromethane) gave thiol (*M*)-**4** (220 mg, 99%) as a white solid: mp 158−160 °C. $[\alpha]^{20}_D = -57$ (*c* 0.34, $CHCl_3$). IR (KBr pellet) cm^{-1}: 3437 (O−H stret.); 2254 (S−H stretch). ^1H δ: 7.46 (dd, 2H, $J = 8.8$ and 0.8 Hz); 6.57 (d, 2H, $J = 8.8$ Hz); 6.14 (s, 2H, OH); 3.74 (s, 6H); 3.12 (d, 2H, $J = 0.8$ Hz, *SH*). ^{13}C δ: 158.8 (s); 154.1 (s); 135.1 (d); 108.9 (s); 104.7 (s); 104.1 (d); 56.1 (q). Mass *m*/*z* (rel int, %): 310 ($M^{+\bullet}$,100); 246 (23). Anal. Calcd for $C_{14}H_{14}O_4S_2$: C, 54.18; H, 4.55. Found C, 54.21; H, 4.60.

Analogously was obtained derivative (*P*)-**4** (80%) $[\alpha]^{20}_D = +54$ (*c* 0.29. $CHCl_3$).

(*M*,*M*)-3,12,15,24-Tetramethoxy-7,8,19,20-tetrathiapentacyclo[19.3.1.1⟨2,6⟩.1⟨9,13⟩.1⟨14,18⟩]octacosa-1(25),2,4,6-(26),9(27),10,12,14(28),15,17,21,23-dodecaene-25,26,27,28-tetraol (5). To a solution of thiophthalimide *M*-**3** (409 mg, 0.68 mmol) in dry THF (40 mL), kept at 0 °C, was added lithium aluminum hydride (39 mg, 1.03 mmol) in one portion. The yellow suspension obtained was kept under nitrogen at 0 °C for 20 then at room temperature for 1 h. The mixture was adjusted to pH 2 with 3% aqueous HCl and washed with diethyl ether (5 × 30 mL). The combined organic solvent was dried over Na_2SO_4 and evaporated to dryness. Silica gel flash chromatography (eluent: dichloromethane) gave disulfide (*M*,*M*)-**5** (180 mg, 86%) as a yellow solid: mp 290−292 °C. $[\alpha]^{20}_D = -735$ (*c* 0.29, $CHCl_3$). ^1H 7.65 (d, 4H, $J = 8.8$ Hz); 6.55 (d, 4H, $J = 8.8$ Hz); 5.97 (bs, 4H, OH); 3.69 (s, 12H). ^{13}C δ: 159.1 (s); 155.3 (s); 135.8 (d); 114.8 (s); 108.5 (s); 102.3 (d); 54.4 (q). Mass *m*/*z* (rel int, %): 616 ($M^{+\bullet}$, 40); 310 (55); 276 (100). Anal. Calcd for $C_{28}H_{24}O_8S_4$: C, 54.54; H, 3.93. Found: C, 54.22; H, 4.12. Crystal data and structure refinement for compound **5**. (The following crystal structure has been deposited at the Cambridge Crystallographic Data Centre: Ref. Code LIVSEO, NBS ID: 723789). Molecular formula: $C_{28}H_{24}O_8S_4$; formula weight: 616.71; temperature: 293(2) K; wavelength: 0.71070 Å; crystal system: orthorombic; space group: *Pbcn*; unit cell dimensions: $a = 13.889(5)$ Å, $b = 17.615(5)$ Å, $c = 12.871(5)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$; volume: 3148.9 (8) $Å^3$; *Z*: 4; density (calculated): 1.301 Mg/m^3: absorption coefficient: 0.316 mm^{-1}; *F*(000): 1280; θ range for data collection: 8.5 to 198.8°; index ranges: $0 \le h \le 15$, $0 \le k \le 19$, $0 \le l \le 14$; reflections collected: 2343; R1 = 0.007, wR = 0.062.

25,26,27,28-Tetrahydroxy-3,12,15,24-tetramethoxy-7,8,-19,20-tetrathiapentacyclo[19.3.1.1⟨2,6⟩.1⟨9,13⟩.1⟨14,18⟩]-octacosa-1(25),2,4,6(26),9(27),10,12,14(28),15,17,21,23-dodecaen-7-one (6). To a solution of disulfide **5** (84 mg, 0.13 mmol) in dry dichloromethane (14 mL) kept at 0 °C was added *m*-CPBA (19 mg, 0.07 mmol), and the mixture was maintained 2 h at 0 °C and 3 h at room temperature. The mixture was diluted with dichloromethane (25 mL), washed with saturated aqueous $NaHCO_3$, and dried over Na_2SO_4. The crude obtained after evaporation of the solvent was purified by silica gel flash chromatography (eluent: dichloromethane, dichloromethane/methanol:100/1) to give sulfinate **6** (50 mg, 61%, overall) as a 6:1 mixture of 2 diastereoisomers. **Major**. Yellow solid, mp >300 °C ^1H δ: 9.14 (s, 1H, OH); 7.69 (d, 1H, $J = 8.8$ Hz); 7.65 (d, 1H, $J = 8.8$ Hz); 7.41 (d, 1H, $J = 8.8$ Hz); 7.24 (d, 1H, $J = 8.8$ Hz); 6.60 (d, 1H, $J = 8.8$ Hz); 6.53 (d, 2H, $J = 8.8$ Hz); 6.51 (d, 1H, $J = 8.8$ Hz); 5.99 (s, 1H, OH); 5.71 (s, 1H, OH); 5.59 (s, 1H, OH); 3.69 (s, 3H); 3.68 (s, 3H); 3.67 (s, 3H); 3.66 (s, 3H). ^{13}C δ: 162.1 (s); 161.5 (s); 160.6 (s); 160.4 (s); 158.4 (s); 157.9 (s); 157.3 (s); 156.5 (s); 142.8 (d); 137.9 (d); 136.9 (d); 125.0 (d); 118.7 (s); 115.7 (s); 114.8 (s); 108.8 (s); 107.7 (s); 104.2 (d); 104.0 (d); 103.7 (d); 103.0 (d);56.0 (q); 55.9 (q). Mass (ESI) *m*/*z*: (633, MH^+). Anal. Calcd for $C_{28}H_{24}O_9S_4$: C, 53.16; H, 3.83. Found: C, 53.37; H, 4.16. **Minor**. Yellow solid, mp > 300 °C. ^1H δ: 9.13 (s, 1H, OH); 7.69 (d, 1H, $J = 8.8$ Hz); 7.65 (d, 1H, $J = 8.8$ Hz); 7.43 (d, 1H, $J = 8.8$ Hz); 7.21 (d, 1H, $J = 8.8$ Hz); 6.60 (d, 1H, $J = 8.8$ Hz); 6.53 (d, 2H, $J = 8.8$ Hz); 6.50 (d, 1H, $J = 8.8$ Hz); 5.99 (s, 1H, OH); 5.71 (s, 1H, OH); 5.42 (s, 1H, OH); 3.71 (s, 3H); 3.69 (s, 3H); 3.68 (s, 3H); 3.66 (s, 3H) δ.

Typical Procedure for the Preparation of Sulfides 11−13. Nitrogen was bubbled for 5 min into a solution of thiol **4** in dry THF (roughly 10^{-2} M), the electrophiles **7**−**9** (2 equiv) and Et_3N (2 equiv) were added via syringe, and the mixture kept at room temperature, under a positive nitrogen pressure, until the complete disappearance of starting materials monitored by TLC. Saturated aqueous NH_4Cl (30 mL) was added, and the mixture extracted with diethyl ether (3 × 20 mL), organic phases recollected, dried over Na_2SO_4, and evaporated to dryness. The crude mixtures were purified by silica gel flash chromatography to isolate compounds **11**−**13**.

2-(2-Hydroxy-6-methoxy-3-methylthiophenyl)-3-methoxy-6-methylthiophenol (11). From thiol **4** (20 mg, 0.06 mmol), methyl iodide (**7**) (16 mg, 0.12 mmol), and Et_3N (12 mg, 0.12 mmol) in dry THF (6 mL). After 30 min at room temperature, workup and flash chromatography, (eluent: dichloromethane) gave compound **11** (20 mg, 99%) as a dark yellow solid: mp 151−153 °C. ^1H δ: 7.51 (d, 2H, $J = 8.8$ Hz); 6.65 (s, 2H, OH); 6.59 (d, 2H, $J = 8.8$ Hz); 3.75 (s, 6H); 2.32 (s, 6H). ^{13}C δ: 159.4 (s); 154.9 (s); 135.0 (d); 113.1 (s); 109.2 (s); 104.0 (d); 56.0 (q); 20.1 (q). Mass *m*/*z* (rel int, %): 338 ($M^{+\bullet}$, 85); 290 (13); 276 (19); 83 (100). Anal. Calcd for $C_{16}H_{18}O_4S_2$: C, 56.78; H, 5.36. Found: C, 56.65; H, 5.74.

2-[2-Hydroxy-6-methoxy-3-(methoxymethylthio)phenyl]-3-methoxy-6-(methoxymethylthio)phenol (12): from thiol **4** (46 mg, 0.15 mmol), bromo methyl methyl ether (**8**) (38 mg, 0.30 mmol), and Et_3N (30 mg, 0.30 mmol) in dry THF (15 mL). After 30 min at room temperature, workup and flash chromatography (eluent: dichloromethane) gave compound **12** (59 mg, 99%) as a dark solid: mp 267−268 °C. ^1H δ: 7.47 (d, 2H, $J = 8.8$ Hz); 7.01 (s, 2H, OH); 6.56 (d, 2H $J = 8.8$ Hz); 4.74 (s, 4H); 3.74 (s, 6H); 3.45 (s, 6H). ^{13}C δ: 159.7 (s); 155.5 (s); 135.8 (d); 110.8 (s); 110.0 (s); 103.7 (d); 79.8 (t); 56.9 (q); 55.9 (q). Mass *m*/*z* (rel int, %): 398 ($M^{+\bullet}$, 46); 366 (23); 334 (48); 322 (100). Anal. Calcd for $C_{18}H_{22}O_6S_2$: C, 54.25; H, 5.56. Found: C, 54.37; H, 5.86.

(*M*)-Ethyl-2-(3-{3-[(ethoxycarbonyl)methylthio]-2-hydroxy-6-methoxyphenyl}-2-hydroxy-4-methoxyphenylthio)acetate (13): from thiol (*M*)-**4** (38 mg, 0.12 mmol), bromo ethyl acetate (**9**) (41 mg, 0.24 mmol), and Et_3N (24 mg, 0.24 mmol) in dry THF (12 mL). After 1 h at room temperature, workup and flash chromatography (eluent: petroleum ether: ethyl acetate/1:1) gave compound (*M*)-**13** (39 mg, 67%) as a yellow solid: mp 129−130 °C. $[\alpha]^{20}_D = -20$ (*c* 0.54, $CHCl_3$). ^1H δ: 7.52 (d, 2H, $J = 8.8$ Hz); 7.20 (s, 2H, OH); 6.55 (d, 2H $J = 8.8$ Hz); 4.15 (q, 4H, $J = 7.0$ Hz); 3.73 (s, 6H); 3.46 (s, 4H); 1.22 (t, 6H, $J = 7.0$ Hz). ^{13}C δ: 170.7 (s); 160.3 (s); 156.3 (s); 136.8 (d); 110.0 (s); 109.9 (s); 103.9 (d); 61.9 (t); 56.0 (q); 39.3 (t); 14.0 (q). Mass *m*/*z* (rel int, %): 482 ($M^{+\bullet}$, 5); 84 (100). Anal. Calcd for per $C_{22}H_{26}O_8S_2$: C, 54.76; H, 5.44. Found: C, 54.79; H, 5.84.

(*M*)-2-[2-Hydroxy-6-methoxy-3-(2-pyridylmethylthio)-phenyl]-3-methoxy-6-(2-pyridylmethylthio)phenol (14). To a solution of thiol (*M*)-**4** (39 mg, 0.13 mmol) and picolyl chloride hydrochloride (**10**)(60 mg, 0.37 mmol) in dry DMF (5 mL) was bubbled nitrogen for 5 min and Et_3N (65 mg, 0.65 mmol) added via a syringe. The mixture was kept under a positive pressure of nitrogen for 24 h, saturated aqueous NH_4Cl (50 mL) was added, and the mixture was extracted with

dichloromethane (5 × 15 mL). The combined organic phase dried over Na_2SO_4 and evaporated to dryness to give a crude which was purified by flash chromatography (eluent: petroleum ether:ethyl acetate/2:3) to give (*M*)-**14** (49 mg, 76%) as a yellow solid: mp 157−159 °C. $[\alpha]^{20}_D = -35$ (*c* 0.165, $CHCl_3$). ^{1}H δ: 8.53 (ddd, 2H, *J* = 5.2, 1.8, 0.8 Hz, *H*α Py); 7.58 (dt, 2H, *J* = 7.6 and 1.8 Hz, *H*γ Py); 7.42 (d, 2H, *J* = 8.8 Hz); 7.17−7.06 (m, 4H, *H*β e *H*β′ Py); 6.49 (d, 2H, *J* = 8.8 Hz); 4.06 (s, 4H); 3.71 (s, 6H). ^{13}C δ: 160.1 (s); 157.2 (s); 156.9 (s); 147.9 (d); 138.0 (d); 136.7 (d); 123.7 (d); 122.5 (d); 11.2 (s); 110.6 (s); 103.4 (d); 56.0 (q); 42.3 (t). Mass *m*/*z* (rel int, %): 492 ($M^{+\bullet}$,2); 460 (1); 428 (4); 368 (20); 124 (24); 93 (100). Anal. Calcd for $C_{26}H_{24}N_2O_4S_2$: C, 63.39; H, 4.91; N, 5.69. Found: C, 63.56; H, 4.77; N, 5.55.

(*M*)-6-({2-Hydroxy-3-[2-hydroxy-6-methoxy-3-(2-pyridylmethylthio)phenyl]-4-methoxyphenyl}disulfanyl)-2-[2-hydroxy-6-methoxy-3-(2-pyridylmethylthio)phenyl]-3-methoxyphenol (15). To a solution of thiol (*M*)-**4** (33 mg, 0.11 mmol) and picolyl chloride hydrochloride **10** (36 mg, 0.22 mmol) in dry THF (11 mL) was added Et_3N (22 mg, 0.22 mmol) via a syringe. The mixture was kept under a positive pressure of nitrogen for 22 h, saturated aqueous NH_4Cl (40 mL) was added, and the mixture was extracted with dichloromethane (4 × 20 mL). The combined organic phase was dried over Na_2SO_4 and evaporated to dryness to give a crude which was purified by flash chromatography (eluent: petroleum ether: ethyl acetate/1:3) followed by preparative TLC (eluent dichloromethane:methanol/40:1) to give disulfide (*M*,*M*)-**5** (4 mg, 11%), sulfide (*M*)-**14** (10 mg, 19%), and compound (*M*,*M*)-**15** (11 mg, 24%) as a yellow solid: mp 198−200 $[\alpha]^{20}_D = -48$ (*c* 0.45, $CHCl_3$); ^{1}H δ: 8.53 (d, 2H, *J* = 5.0 Hz, Hα Py); 7.58 (dt, 2H, *J* = 7.6 and 1.8 Hz, H*γ* Py); 7.46 (d, 2H, *J* = 8.8 Hz); 7.39 (d, 2H, *J* = 8.8 Hz); 7.15−7.04 (m, 4H, H*β* and H*β*′ Py); 6.47 (d, 2H, *J* = 8.8 Hz); 4.03 (s, 4H); 3.68 (s, 6H); 3.67 (s, 6H). Mass (ESI) *m*/*z*: (801, MH^+). Anal. Calcd for $C_{40}H_{36}N_2O_8S_4$: C, 59.98; H, 4.53; N, 3.50. Found: C, 60.17; H, 4.38; N, 3.44.

Methyl 2-(2-Hydroxy-3-{2-hydroxy-3-[(2-hydroxy-3-{2-hydroxy-6-methoxy-3-[(methoxycarbonyl)methylthio]-phenyl}-4-methoxyphenyl)disulfanyl]-6-methoxyphenyl}-4-methoxyphenylthio)acetate (16). To a solution of thiol **4** (22 mg, 0.07 mmol) in dry THF (7 mL) were added bromo derivative **9** (14 mg, 0.08 mmol) and Et_3N (14 mg, 0.14 mmol) via a syringe. The mixture was kept under a positive pressure of nitrogen for 1 h, saturated aqueous NH_4Cl (40 mL) was added, and the mixture extracted with diethyl ether (4 × 15 mL). The combined organic phase dried over Na_2SO_4 and evaporated to dryness to give a crude which was purified with two consecutives separations by flash chromatography (eluent: dichloromethane:methanol/50:1 and petroleum ether: ethyl acetate/2:1) to give compound **13** (16 mg, 49%) and derivative **16** (12 mg, 44%) as a yellow solid. mp 230−232 °C. ^{1}H δ: 7.54 (d, 2H, *J* = 8.8 Hz); 7.35 (d, 2H, *J* = 8.8 Hz); 7.20 (s, 2H, OH); 6.54 (d, 2H, *J* = 8.8 Hz); 6.51 (d, 2H, *J* = 8.8 Hz); 6.25 (s, 2H, OH); 4.15 (q, 4H, *J* = 7.2 Hz); 3.74 (s, 6H); 3.71 (s, 3H); 3.67 (s, 3H); 3.46 (s, 4H); 1.22 (t, 6H, *J* = 7.2 Hz). ^{13}C δ: 170.7 (s); 161.1 (s); 160.3 (s); 156.3 (s); 155.6 (s); 136.9 (d); 136.8 (d); 112.8 (2s); 110.1 (s); 109.5 (s); 104.0 (2d); 61.9 (t); 56.0 (q); 53.4 (q); 39.3 (t); 14.0 (q). Mass (ESI) *m*/*z*: (791, MH^+). Anal. Calcd for $C_{36}H_{38}O_{12}S_4$: C, 54.67; H, 4.84. Found: C, 54.50; H, 5.07.

(*P*)-Methyl-(2*R*)-3-[3-(3-{(2*R*)-2-[(*tert*-butoxy)carbonylamino]-2-(methoxycarbonyl)ethylthio}-2-hydroxy-6-methoxyphenyl)-2-hydroxy-4-methoxyphenylthio]-2-[(*tert*-butoxy)carbonylamino]propanoate (18). Nitrogen was bubbled for 5 min into a solution of (*P*)-**4** (32 mg, 0.10 mmol) and amino acid **17** (79 mgr, 0.20 mmol) in dry DMF (5 mL), Et_3N (20 mg, 0,20 mmol) was added via a syringe, and the mixture was kept at room temperature for 5 h. The previous described workup and flash chromatography (eluent: petroleum ether:ethyl acetate/3:2) gave derivative (*P*,*R*,*R*)-**18** (43 mg, 60%) as a pale yellow glassy solid, mp 72−75 °C. $[\alpha]^{20}_D = +80.8$ (*c* 0.25, $CHCl_3$). ^{1}H δ: 7.48 (d, 2H, *J* = 8.8 Hz); 6.62 (bs, 2H, OH); 6.55 (d, 2H, *J* = 8.8 Hz); 5.47−5.43 (m, 2H, *NH*); 4.52−4.46 (m, 2H); 3.74 (s, 3H); 3.57 (s, 6H); 3.18 (ad, 4H, *J* = 4.8 Hz); 1.43 (s, 18H). ^{13}C δ: 171.1 (s); 159.7 (s); 155.7 (s); 155.1 (s); 136.6 (d); 129.9 (s); 109.9 (s); 103.9 (d); 80.2 (s); 56.0 (q); 53.1 (d); 52.5 (q); 38.8 (t); 28.3 (q). Anal. Calcd for $C_{32}H_{44}N_2O_{12}S_2$: C, 53.92; H, 6.22; N, 3.93. Found: C, 54.13; H, 6.45; N, 3.77.

2-Ethoxy-8-(2-ethoxy-7-methoxy(2*H*,3*H*-benzo[*e*]1,4-oxathiin-8-yl))-7-methoxy-2*H*,3*H*-benzo[*e*]1,4-oxathiane (20). To a suspension of thiophthalimide **3** (100 mg, 0.17 mmol) in dry chloroform (10 mL) were added ethyl vinyl (**19**) (37 mg, 0.51 mmol) and triethylamine (51 mg, 0.51 mmol), and the mixture was kept for 40 h at 60 °C. The crude obtained after evaporation of the solvent was purified by flash silica gel chromatography (eluent: dichloromethane) to give compound **20** as the single **A** isomer and an unseparable mixture of **B** and **C** isomers (52 mg, 68% overall). **Major** (**A**). Mp 169−170 °C. ^{1}H 7.03 (d, 2H, *J* = 8.0 Hz); 6.57 (d, 2H, *J* = 8.0 Hz); 5.18 (X part of an ABX system, dd, 2H, *J* = 5.8 and 2.6 Hz); 3.68 (s, 6H); 3.68−3.35 (m, 4H); 3.05 (A part of an ABX system, 2H, J_{AB} = 12.5 Hz); 2.94 (B part of an ABX system 2H, J_{AB} = 12.5 Hz); 1.06 (t, 6H, *J* = 7.4 Hz). ^{13}C δ: 155.9 (s); 148.8 (s); 126.1 (d); 113.8 (s); 109.4 (s); 105.3 (d); 96.3 (d); 64.0 (t); 56.1 (q); 29.3 (t); 14.9 (q). Mass: *m*/*z* (rel int, %): 450 ($M^{+\bullet}$, 100); 422 (15); 404 (29). Anal. Calcd for $C_{22}H_{26}O_6S_2$: C, 58.64; H, 5.82. Found: C 58.49; H, 5.96.

^{1}H NMR Data for Mixture of Isomers B + C: δ 7.04 (d, 2H, *J* = 8.8 Hz); 6.58 (d, 2H, *J* = 8.8 Hz); 5.24−5.12 (m, 2H); 3.71−3.40 (m, 4H); 3.66 (s, 6H); 3.09−2.93 (m, 4H); 1.13−1.05 (m, 6H) δ.

Typical Procedure for the Synthesis of Cycloadducts 29−32. To a 10 mg/mL suspension of thiophthalimide **3** in dry chloroform (a clear solution for (*M*)-**3**) were added bis-vinyl ethers **25**−**28** (1 equiv) and triethylamine (3 equiv) and the mixtures kept for 24 h at 60 °C. The crude obtained after evaporation of the solvent was purified by flash silica gel chromatography to give the corresponding cycloadducts **29**−**32**, see Scheme 6.

3,20-Dimethoxy-10,13,22,23-tetraoxa-7,16-dithiahexacyclo[12.6.2.2⟨2,6⟩.0⟨2,24⟩.0⟨9,23⟩.0⟨17,21⟩]tetracosa-1(21),2,4,6(24),17,19-hexaene (29): from *M*-**3** (70 mg, 0.12 mmol) and ethylene glycol divinyl ether **25** (14 mg, 0.12 mmol). After 24 h at 60 °C, flash chromatography gave cycloadduct **25** (47 mg, 95% overall) as mixture of two diastereoisomers (eluent: dichloromethane). **Major** (*M*, *S*, *S*-**29**). Mp 184−186 °C. $[\alpha]^{20}_D = -147.6$ (*c* 0.38, $CHCl_3$). ^{1}H δ: 7.07 (d, 2H, *J* = 8.8 Hz); 6.65 (d, 2H, *J* = 8.8 Hz); 5.28 (t, 2H, *J* = 3.0 Hz); 4.10−3.94 (m, 2H); 3.70 (s, 6H); 3.70−3.55 (m, 2H); 3.24 (dd, 2H, *J* = 13.2 and 3.0 Hz); 2.89 (dd, 2H, *J* = 13.2 and = 3.0 Hz). ^{13}C δ: 156.5 (s); 146.7 (s); 126.7 (d); 114.5 (s); 109.9 (s); 106.1 (d); 93.6 (d); 68.3 (t); 56.4 (q); 28.8 (t). Mass *m*/*z* (rel int, %): 420 ($M^{+\bullet}$, 100); 375 (5). Anal. Calcd for $C_{20}H_{20}O_6S_2$: C, 57.13; H, 4.79. Found: C, 57.46; H, 5.00. **Minor** (*M*, *S*, *R*-**29**). Mp 98−100 °C. $[\alpha]^{20}_D = -94.4$ (*c* 0.25, $CHCl_3$). ^{1}H δ: 7.07 (d, 2H, *J* = 8.6 Hz); 6.66 (d, 1H, *J* = 8.6 Hz); 6.64 (d, 1H, *J* = 8.6 Hz); 5.49 (t, 1H, *J* = 2.0 Hz); 5.41 (dd, 1H, *J* = 8.4 and 1.6 Hz); 4.14−3.88 (m, 4H); 3.70 (s, 6H); 3.28 (dd, 1H, *J* = 11.2 and 8.4 Hz); 3.10−2.89 (m, 3H). ^{13}C δ: 156.5 (s); 155.7 (s); 127.6 (d); 125.1 (d); 111.7 (s); 108.4 (s); 106.9 (d); 105.7 (d); 94.7 (d); 94.4 (d); 65.0 (t); 61.6 (t); 56.3 (q); 29.4 (t); 28.5 (t).

3,23-Dimethoxy-10,13,16,25,26-pentaoxa-7,19-dithiahexacyclo[15.6.2.2⟨2,6⟩.0⟨2,27⟩.0⟨9,26⟩.0⟨20,24⟩]heptacosa-1(24),2,4,6(27),20,22-hexaene (30): from **3** (60 mg, 0.10 mmol) and diethylene glycol divinyl ether **26** (16 mg, 0.10 mmol). After 24 h at 60 °C, flash chromatography gave cycloadduct **30** (23 mg, 50% overall) as mixture of two diastereoisomers (eluent: dichloromethane/methanol:60/1). **Major**. Pale yellow solid, mp 162−164 °C. ^{1}H δ: 7.08 (d, 2H arom, *J* = 8.6 Hz); 6.60 (d, 2H, *J* = 8.6 Hz); 5.32 (dd, 2H, *J* = 4.8 and 2.6 Hz); 3.96−3.84 (m, 2H); 3.68 (s, 6H); 3.71−3.48 (m, 6H); 3.11 (dd, 2H, *J* = 13.2 and 2.8 Hz); 2.88 (dd, 2H, *J* = 13.2 and 4.8 Hz). ^{13}C δ: 156.5 (s); 147.7 (s); 127.0 (d); 113.7 (s); 109.7 (s); 105.5 (d); 95.1 (d); 69.2 (t); 68.4 (t); 56.4 (q); 29.4 (t). Mass *m*/*z* (rel int, %): 464 ($M^{+\bullet}$, 79); 375 (4); 84 (100). Anal. Calcd for $C_{22}H_{24}O_7S_2$: C, 56.88; H, 5.21. Found: C, 56.92; H, 5.17. **Minor**. Mp 172−173 °C. ^{1}H δ: 7.03 (d, 2H, *J* = 8.4 Hz); 6.61 (d, 1H, *J* = 8.4 Hz); 6.60 (d, 1H arom, *J* = 8.4 Hz); 5.50 (dd, 1H, *J* = 8.2 and 1.8 Hz); 5.29 (t, 1H, *J* = 2.0 Hz); 3.71 (s,

3H); 3.68 (s, 3H); 3.85−3.45 (m, 8H); 3.45−2.65 (m, 4H). ^{13}C δ: 156.4 (s); 156.1 8s); 149.1 (s); 146.6 (s); 126.6 (d); 125.4 (d); 114.1 (s); 113.7 (s); 109.2 (s); 108.8 (s); 106.1 (d); 105.8 (d); 96.5 (d); 91.6 (d); 71.9 (t); 69.4 (t); 67.2 (t); 64.5 (t); 56.6 (q); 56.4 (q); 29.4 (t); 28.9 (t).

3,26-Dimethoxy-10,13,16,19,28,29-hexaoxa-7,22-dithiahexacyclo[18.6.2.2⟨2,6⟩.0⟨2,30⟩.0⟨9,29⟩.0⟨23,27⟩]-triaconta-1(27),2,4,6(30),23,25-hexaene (31): from **3** (60 mg, 0.10 mmol) and triethylene glycol divinyl ether **27** (20 mg, 0.10 mmol). After 24 h at 60 °C, flash chromatography gave cycloadduct **31** (27 mg, 52% overall) as mixture of two diastereoisomers (eluent: petroleum ether/dichloromethane: 10/1). **Major**. Pale yellow solid, mp 143−145 °C. ^{1}H δ: 7.04 (d, 2H, J = 8.8 Hz); 6.59 (d, 2H, J = 8.8 Hz); 5.21 (dd, 2H, J = 5.4 and 2.1 Hz); 3.80−3.30 (m, 12H); 3.67 (s, 6H); 3.11 (dd, 2H, J = 12.4 and 2.1 Hz); 2.99 (dd, 2H, J = 12.4 and 5.4 Hz). ^{13}C δ: 155.7 (s); 148.1 (s); 126.0 (d); 113.9 (s); 109.7 (s); 105.5 (d); 96.1 (d); 69.0 (t); 68.8 (t); 68.7 (t); 56.1 (q); 29.2 (t). Mass m/z (rel int, %): 508 ($M^{+\bullet}$, 100); 463 (2). Anal. Calcd for $C_{24}H_{28}O_8S_2$: C, 56.68; H, 5.55. Found: C, 56.36; H, 5.77. **Minor**. Mp 167−169 °C ^{1}H δ: 7.09 (d, 1H, J = 8.4 Hz); 7.03 (d, 1H, J = 8.4 Hz); 6.60 (d, 1H arom, J = 8.4 Hz); 6.58 (d, 1H, J = 8.4 Hz); 5.97 (dd, 1H, J = 5.4 and 3.0 Hz); 5.29 (t, 1H, J = 1.8 Hz); 4.18 − 4.07 (m, 1H); 3.69 (s, 3H); 3.65 (s, 3H); 3.86 − 3.28 (m, 11H); 3.16 (dd, 1H, J = 12.8 and 1.8 Hz); 3.07 (dd, 1H, J = 12.9 and 3.0 Hz); 2.93−2.84 (m, 2H). ^{13}C δ: 156.6 (s); 156.0 (s); 148.5 (s); 147.2 (s); 126.8 (d); 126.6 (d); 114.0 (s); 113.9 (s); 110.0 (s); 109.1 (s); 105.5 (d); 105.2 (d); 94.5 (d); 92.9 (d); 71.1 (t); 70.8 (t); 69.8 (t); 69.5 (t); 68.8 (t); 64.2 (t); 56.3 (q); 56.1 (q); 29.7 (t); 28.9 (t) .

3,29-Dimethoxy-10,13,16,19,22,31,32-heptaoxa-7,25-dithiahexacyclo[21.6.2.2⟨2,6⟩.0⟨2,33⟩.0⟨9,32⟩.0⟨26,30⟩]-tritriaconta-1(30),2,4,6(33),26,28-hexaene (32): from **3** (102 mg, 0.17 mmol) and tetraethylene glycol divinyl ether **28** (42 mg, 0.17 mmol). After 24 h at 60 °C, flash chromatography gave cycloadduct **32** (43 mg, 46% overall) as mixture of two diastereoisomers (eluent: dichloromethane/methanol:40/1). **Major**. Pale yellow solid, mp 135−138 °C. ^{1}H δ: 7.04 (d, 2H, J = 8.4 Hz); 6.59 (d, 2H, J = 8.4 Hz); 5.19 (dd, 2H, J = 5.4 and 2.6 Hz); 3.74−3.29 (m, 16H); 3.69 (s, 6H); 3.11 (dd, 2H, J = 12.8 and 2.6 Hz); 2.90 (dd, 2H, J = 12.8 and 5.4 Hz). ^{13}C δ: 156.2 (s); 148.1 (s); 126.3 (d); 114.1 (s); 110.2 (s); 105.6 (d); 96.4 (d); 70.6 (t); 70.4 (t); 69.9 (t); 68.3 (t); 56.3 (q); 29.3 (t). Mass m/z (rel int, %): 552 ($M^{+\bullet}$, 100). Anal. Calcd for $C_{26}H_{32}O_9S_2$: C, 56.50; H, 5.84. Found: C, 56.72; H, 5.63. **Minor**. Mp 139 °C. ^{1}H δ: 7.04 (d, 1H arom, J = 8.6 Hz); 7.02 (d, 1H, J = 8.6 Hz); 6.60 (d, 1H, J = 8.6 Hz); 6.59 (d, 1H, J = 8.6 Hz); 5.84 (dd, 1H, J = 5.6 and 2.6 Hz); 5.24 (dd, 1H, J = 3.2 and 2.2 Hz); 3.68 (s, 3H); 3.66 (s, 3H); 4.00−3.45 (m, 16H); 3.21−2.85 (m, 4H). ^{13}C δ: 156.0 (s); 155.7 (s); 148.6 (s); 147.7 (s); 126.5 (d); 126.0 (d); 114.2 (s); 113.7 (s); 109.7 (s); 109.1 (s); 105.5 (d); 105.3 (d); 96.8 (d); 96.1 (d); 71.5 (t); 70.6 (t); 70.10 (t); 70.06 (t); 69.5 (t); 69.4 (t); 67.5 (t); 67.4 (t); 56.3 (q); 55.9 (q); 29.1 (t); 28.9 (t).

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