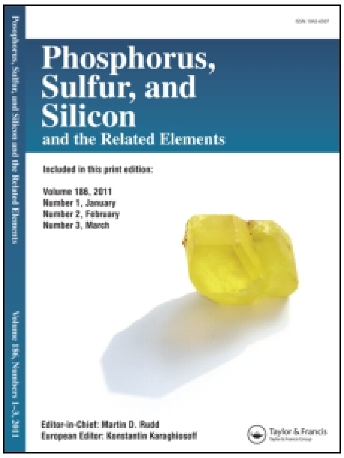

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Generation and Trapping of *o*-Thioquinones on Solid Support: Synthesis of Hydroxylated 4-Thiaflavans

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Generation and Trapping of *o*-Thioquinones on Solid Support: Synthesis of Hydroxylated 4-Thiaflavans

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The generation and trapping of o-thioquinones was successfully applied to the synthesis of hydroxy-4-thiaflavans on solid support using commercially available carboxy and aminomethylated polystyrene resins. These valuable cycloadducts are obtained as pure compounds without any intermediate purification, in better overall yields than the solution phase procedure.

Keywords Antioxidants; phthalimidesulfenyl chloride; solid phase synthesis; 4-thiaflavans; *o*-thioquinones

INTRODUCTION

Mono-*o*-thioquinones appeared in the literature for the first time in the 1971,[1] and for many years they did not find any practical synthetic application, mainly because of the harsh reaction conditions required for their generation.[2] The situation changed when an effective methodology for their formation, under very mild reaction conditions, was discovered in our group.[3] The key starting materials for the generation of *o*-thioquinones are the corresponding *o*-hydroxy-*N*-thiophthalimides, in turn obtained in good yields, as indefinitely stable crystalline compounds, by reacting electron-rich phenols with the phthalimidesulfenyl

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Dedicated to Professor Marian Mikołajczyk, CBMiM PAN in Łódź, Poland, on the occasion of his 70th birthday.

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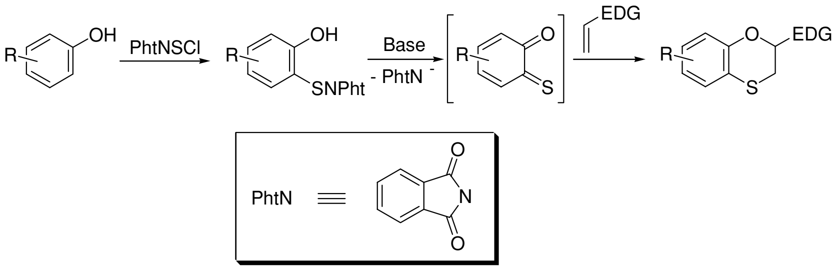
chloride **1** (PhtNSCl, Pht = Phthaloyl).[3] The reaction of *o*-hydroxy-*N*-thiophthalimides with weak bases, such as triethylamine, causes deprotonation of the hydroxy group followed by elimination of the phthalimide anion and formation of the *o*-thioquinone species. Once generated, these short-lived reactive intermediates can be trapped as dienophiles,[4] across the carbon-sulfur double bond, or, more conveniently, as heterodienes in an inverse electron-demand hetero Diels–Alder reaction, with a large number of electron-rich alkenes acting as dienophiles, providing benzoxathiin cycloadducts.[3,5] In all cases tested, this [4+2] cycloaddition afforded a single regioisomeric 1,4-benzoxathiin, deriving from the interaction of the oxygen of the thione with the more electron-rich carbon of the alkene (Scheme 1).



SCHEME 1 General procedure for the solution phase generation and trapping of *o*-thioquinones.

Using styrenes as dienophiles, the above reaction affords cycloadducts with the 4-thiaflavan skeleton that showed very promising biological activities.[6,7] In particular, when properly substituted with hydroxy groups, these heterocyclic derivatives are able to mimic the antiradical activity of either flavonoids, bearing a catechol group on the **B** ring like catechin, and/or tocopherols, like α-tocopherol or Vitamin E, due to the presence of the hydroxy-thiachromane moiety (**A** and **C** fused rings, Figure 1).

As a matter of fact, these 4-thiaflavans showed effective in vitro protection against DNA oxidative damage caused by either hydroperoxides or hydroxyl radicals obtained by Fenton chemistry.[8] Consequently, they possess what we call a "multidefence"[9] antioxidant activity, combining the abilities of the two more important families of natural antioxidants.

RESULTS AND DISCUSSION

Our original synthetic procedure is currently well established in solution phase.[7b] For example using resorcinol (**2**) or 2,6-

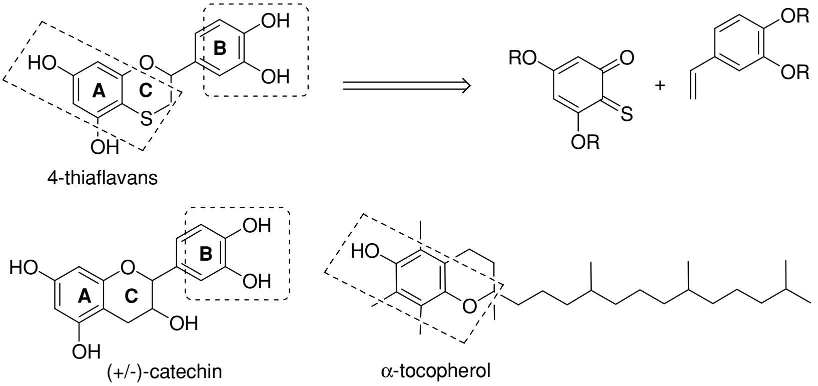
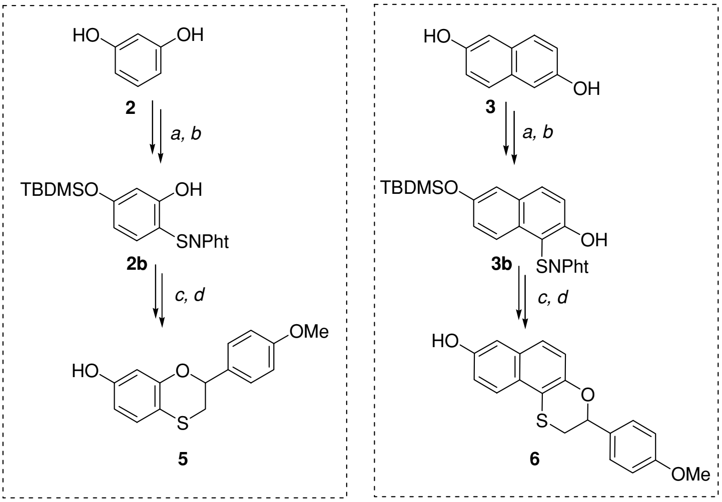


FIGURE 1 Structural similarities of hydroxy-4-thiaflavans with (+/−)-catechin and α-tocopherol.

dihydroxynaphthalene (**3**) as starting model phenols and 4-methoxystyrene (**4**) as model dienophile, four steps, each entailing a flash chromatography purification (see experimental section), are necessary to isolate benzoxathiins **5** and **6** with overall yields ranging from 25% to 40% as depicted in Scheme 2.



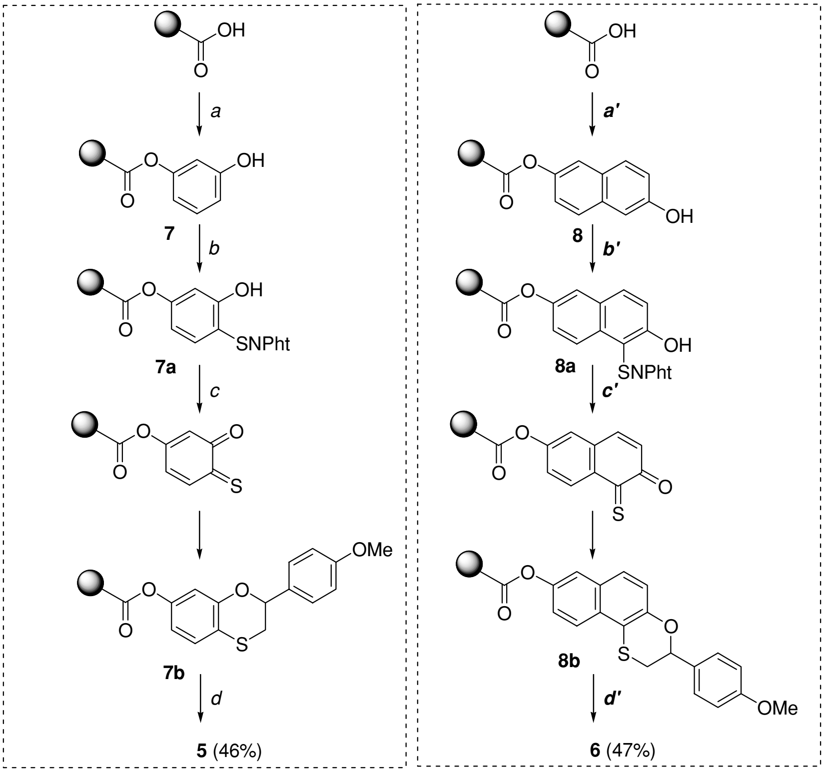
Reagents and condition: *a*) TBDMSCl, dry DMF, Imidazole, Flash Chromatography; **2a**, **3a**
b) PhtNSCl (**1**), $CHCl_3$, rt, 1.5h, Flash Chromatography; **2b**, **3b**
c) 4-methoxystyrene (**4**), $CHCl_3$, 60 °C, 23h, Flash Chromatography; **2c**, **3c**
d) TBAF·$3H_2O$, THF, 0 °C, 0.5h, Flash Chromatography; **5, 6**

SCHEME 2 Solution phase synthesis of 4-thiaflavans **5** and **6**.

This approach is, at least, competitive, regarding number of steps and overall yields, with the other procedures available for the synthesis of benzoxathiins[10]; nevertheless, we decided to study a further improvement considering the possibility to apply it on solid phase. This would allow an oversimplification of the whole process and, reasonably, permit avoidance of some of the tedious and poor eco-friendly intermediate chromatographic purification procedures.

We have recently demonstrated that α-acylthiones, obtained from a similar application of the chemistry of phthalimidesulfenyl chloride to β-dicarbonyls, can be successfully accomplished from solid supported β-ketoesters.[11] Thus we decided to explore the possibility of linking a phenol moiety on solid support to be used as the scaffold for the generation of *o*-thioquinones and for the assembling of the 4-thiaflavan skeleton on the resin.

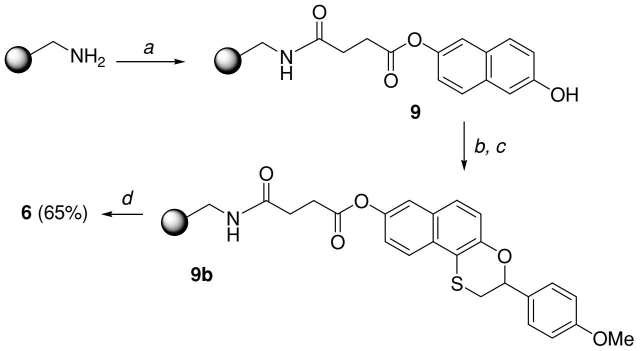
Phenols are involved in several solid-phase organic reactions, and they can be immobilized on resins through a variety of synthetic strategies, including the mono-functionalization of symmetrical derivatives such as resorcinol (**2**) or 2,6-dihydroxynaphthalene (**3**).[12] Despite the fact that silyl modified resins have been described in the literature,[13] their use for either the protection or the linkage of the phenols to the solid support was not feasible and practical enough for the required improvement of the methodology depicted in Scheme 1. Thus we decided to use easily available carboxylic pending Merrifield resins and to introduce **2** and **3** through an ester link to give supported monohydroxyesters **7** and **8**, respectively (Scheme 3). Clearly the transformation of one of the O—H groups into an O-C(O)R residue causes a depletion of the electron-rich character of the phenolic ring, hence of its ability to react with **1** in a S_EAr.[14] Nevertheless, the availability of carboxylic modified resins, as well as simple methodologies for esterification and hydrolysis, prompted us to evaluate this possibility. As depicted in Scheme 3, the esterification step can be carried out either via the formation of a solid supported acyl chloride[15] or by activating the carboxylic acid with DCC (paths *a* and *a'* respectively).[16] Working on solid phase, it was possible to completely avoid the reaction of both the hydroxy groups, i.e., one of the drawbacks of the solution phase methodology (Scheme 2, step *a*). In both cases we verify the formation of the required mono-hydroxyesters **7** and **8** by FTIR of the resin after washing and drying (see the Experimental section). FTIR analysis was used for problem-solving also to verify the occurrence of the S_EAr of supported phenols with **1** (i.e., the formation of phthalimides **7a** and **8a**) and of the [4+2] cycloaddition, giving rise to supported benzoxathiins **7b** and **8b**. In fact, the introduction and the elimination of the phthaloyl group can be easily monitored by FTIR due to the characteristic imidic C=O stretching multiple bands. The actual formation of 4-thiaflavans on solid phase was demonstrated by saponification with LiOH in THF that allowed the isolation of derivatives **5** and **6** in 46% and 47% overall yield, respectively, as pure compounds without any purification procedure as depicted in Scheme 3.



Reagents and condition: *a*) *i*) $SOCl_2$, PhMe 60 °C 2h, *ii*) resorcinol (**2**), DMAP, Py, CH_2Cl_2, rt, 24; **7**
a') 2,6-Dihydroxynaphthalene (**3**), DCC, DMAP, CH_2Cl_2, rt, 24h; **8**
b, ***b'***) PhtNSCl (**1**), $CHCl_3$, rt, 24h; **7a**, **8a**
c, ***c'***) 4-methoxystyrene (**4**), Et_3N, $CHCl_3$, 60 °C, 24h; **7b**, **8b**
d, ***d'***) LiOH, THF, rt, 3h; **5**, **6**: NO Flash Chromatography!

SCHEME 3 Solid phase synthesis of 4-thiaflavans **5** and **6**.

The above result deserves some additional comment. We have indeed verified that the S_EAr with the phthalimidesulfenyl chloride (**1**) is an efficient process also on solid supported mono-hydroxyester. As expected it requires longer reaction times (1.5 h vs. 24 h; see Schemes 2



Reagents and condition: *a*) *i*) Succinic Anhydride, Py, rt, 24h;
ii) 2,6-Dihydroxynaphthalene (**3**), DCC, DMAP, DMF/CH_2Cl_2, rt, 24h; **9**
b) PhtNSCl (**1**), $CHCl_3$, rt, 24h; **9a**
c) 4-methoxystyrene (**4**), Et_3N, $CHCl_3$, 60 °C, 24h; **9b**
d) LiOH, THF, rt, 3h; **6**: NO Flash Chromatography!

SCHEME 4 Improved solid phase synthesis of 4-thiaflavan **6**.

and 3), but it occurs with the same regiospecificity observed in solution phase.

On the other hand, the generation and trapping of *o*-thioquinones works very well on solid phase under the same reaction conditions used in solution phase, allowing the isolation of valuable 4-thiaflavans without flash chromatography purification and with better overall yields. This relevant result indicates that the sulfenylation and the cycloaddition reactions occurred in an almost quantitative yield on the solid supported phenols. In any other events the 4-thiaflavan cycloadducts would have been contaminated with the by-products deriving from the basic hydrolysis of residual solid supported phenols and *o*-hydroxy-*N*-thiophthalimides.

Before verifying the applicability of this new procedure for the preparation of a wide pool[17] of hydroxy-4-thiaflavans, we reasoned that, perhaps, using an appropriate linker to increase the distance between the resin and the phenol could produce a further improvement of the methodology. Indeed, by reacting a commercially available aminomethylated polystyrene resin with succinic anhydride, we prepared a solid support bearing a more sterically available carboxylic acid.[18] To our satisfaction, using this modified resin and following the previously reported synthetic sequence, 4-thiaflavan **6** was isolated in 65% overall yield after a simple acidic work-up of the resin washing solvents, without any chromatographic purification, since, as expected, the amidic bond revealed to be stable under the basic conditions used for the releasing of the cycloadduct from the resin (Scheme 4).

CONCLUSION

Biologically valuable 4-thiaflavans can be efficiently obtained by hetero Diels–Alder reaction of solid supported *o*-thioquinones. The whole process optimized on solid phase gave, at least with the two model phenols chosen, better overall yields and higher simplicity than the procedure in solution. The applicability of this methodology for the preparation of a pool[17] of biologically active 4-thiaflavans is under study.

EXPERIMENTAL

General

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 200 spectrometer at 200 and 50 MHz, respectively, in $CDCl_3$ using residual $CHCl_3$ at $\delta_H = 7.26$ ppm and the central line of $CDCl_3$ at $\delta_C = 77.0$ ppm as references. FTIR spectra were recorded on a Perkin-Elmer 1600. Toluene, THF, CH_3Cl, DCM, DMF, and TEA were dried following standard procedures. All commercial reagents were used without further purification as obtained from freshly opened containers. Phthalimidesulfenyl chloride (**1**) was prepared as reported elsewhere.[19]

Solution Phase Synthesis[7b]

General Procedure for the Mono-silylation Reaction (Step a in Scheme 2)

To a solution of phenol and IMI (1 eq.) in anhydrous DMF, a solution of TBDMSCl (0.5 eq.) in anhydrous DMF was added dropwise. The reaction mixture was stirred at room temperature under argon atmosphere and monitored by TLC until the disappearance of the starting phenol. The crude reaction mixture was diluted with petroleum ether, and washed with saturated NH_4Cl and water. The organic phase was dried over anhydrous $NaSO_4$ and evaporated to dryness. Purification of the residue by flash chromatography on silica gel afforded the required products.

3-(tert-Butyl-dimethyl-silyloxy)-phenol (2a)

The compound was obtained as colorless oil by flash chromatography on silica gel with dichloromethane:methanol 50:1 as eluent, 61% yield.

^{1}H NMR: $\delta = 0.20$ (s, 6H), 0.99 (s, 9H), 5.46 (bs, 1H), 6.37–6.38 (m, 1H), 4.43–6.44 (m, 1H), 4.43–6.47 (m, 2H), 7.07 (t, $J = 8.2$ Hz, 1H). ^{13}C NMR: $\delta = -4.6$, 18.1, 25.6, 107.7, 108.7, 112.5, 129.9, 156.5, 156.7.

6-(tert-Butyl-dimethyl-silyloxy)-naphthalen-2-ol (3a)

The compound was obtained as a colorless oil by flash chromatography on silica gel with dichloromethane:methanol 50:1 as eluent, 74% yield. ^{1}H NMR: $\delta = 0.25$ (s, 6H), 1.03 (s, 9H), 7.02–7.16 (m, 4H), 7.52–7.62 (m, 2H). ^{13}C-NMR: $\delta = -4.3$, 18.3, 27.8, 109.5, 115.0, 117.9, 122.7, 127.5, 128.4, 129.8, 130.1, 151.6, 151.7.

General Procedure for the Sulfenylation Reaction (Step b in Scheme 2)

A solution of phthalimidesulfenyl chloride **1** (1 eq.) in dry chloroform was added to a solution of the mono-silylated phenol in chloroform kept at 0°C. The reaction mixture was heated to room temperature and stirred until complete disappearance of the starting product monitored by TLC (1.5 h). The crude mixture was diluted with ethyl acetate, and washed with saturated $NaHCO_3$ and water. The organic phase was dried over anhydrous $NaSO_4$ and evaporated to dryness. Purification of the residue by flash chromatography on silica gel afforded the required product.

2-[4-(tert-Butyl-dimethyl-silyloxy)-2-hydroxy-phenylsulfanyl]-isoindole-1,3-dione (2b)

The compound was isolated after work-up as a white solid not requiring further purification, mp 180–183°C, 96% yield. ^{1}H NMR $\delta = 0.19$ (s, 6H), 0.94 (s, 9H), 6.35 (dd, $J = 8.4$, 2.4 Hz, 1H), 6.47 (d, $J = 2.4$ Hz, 1H), 7.70 (d, $J = 8.4$ Hz, 1H), 7.75–7.92 (m, 4H), 8.30 (s, 1H). ^{13}C-NMR: $\delta = -4.5$, 18.1, 25.4, 107.7, 110.8, 113.2, 124.1, 131.8, 134.7, 139.4, 160.4, 161.6, 168.5.

2-[6-(tert-Butyl-dimethyl-silyloxy)-2-hydroxy-naphthalen-1-sulfanyl]-isoindole-1,3-dione (3b)

The compound was obtained as a white solid by flash chromatography on silica gel using dichloromethane as eluent, mp 182–186°C, 44% yield. ^{1}H NMR: $\delta = 0.23$ (s, 6H), 1.01 (s, 9H), 7.10 (d, 1H,$J = 2.2$ Hz), 7.21 (d, 1H,$J = 8.8$ Hz), 7.24–7.32 (m, 1H), 7.68–7.79 (m, 3H), 7.83–7.92 (m, 2H), 9.04 (d, 1H,$J = 8.8$ Hz), 9.06 (s, 1H).

General Procedure for the Cycloaddition Reaction (Step c in Scheme 2)

To a solution of the *o*-hydroxy-*N*-thiophthalimide derivatives in dry CH_3Cl (roughly 0.1 M), *p*-methoxystyrene (**4**) (1.5 eq.) and Et_3N (1 eq.) were added in sequence, and the reaction mixture was heated at 60°C and monitored, either by ^1H NMR or TLC, until the disappearance of the starting thiophthalimide (23 h). Evaporation of the solvent and flash chromatography on silica gel allowed the isolation of the silylated cycloadducts.

7-(tert-Butyl-dimethyl-silanyloxy)-2,3-dihydro-2-(4-methoxy-phenyl)-1,4-benzoxathiin (2c)

The compound was obtained as a colorless oil by flash chromatography on silica gel using petroleum ether:dichloromethane 3:1 as eluent, 63% yield. ^1H NMR: $\delta = 0.20$ (s, 6H), 0.99 (s, 9H), 3.02 (dd, $J = 13.2$, 1.8 Hz, 1H), 3.25 (dd, $J = 13.2$, 9.6 Hz, 1H), 3.84 (s, 3H), 5.15 (dd, $J =$ 9.6, 1.8 Hz, 1H), 6.44–6.49 (m, 2H), 6.93–6.98 (m, 3H), 7.34–7.36 (m, 2H). ^{13}C NMR: $\delta = -4.5$, 18.1, 25.6, 31.6, 55.3, 76.6, 108.7, 110.4, 114.0, 114.3, 127.3, 127.5, 132.5, 152.9, 153.8, 159.7.

8-(tert-Butyl-dimethyl-silyloxy)-2,3-dihydro-3-(4-methoxy-phenyl)-naphth[2,1-b][1,4]-oxathiin (3c)

The compound was obtained as a white solid by flash chromatography on silica gel using petroleum ether:ethyl acetate 10:1 as eluent, mp 113–115°C, 75% yield. ^1H NMR: $\delta = 0.25$ (s, 6H), 1.03 (s, 9H), 3.21 (dd, $J = 14.0$, 2.6 Hz, 1H), 3.64 (dd, $J = 14.0$, 9.2 Hz, 1H), 3.84 (s, 3H), 5.23 (dd, $J = 9.2$, 2.6 Hz, 1H), 6.94–6.98 (m, 3H), 7.06–7.15 (m, 2H), 7.37–7.43 (m, 3H), 7.79 (d, $J = 8.6$ Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = -4.4$, 18.2, 25.7, 31.5, 55.2, 76.1, 110.3, 114.1, 115.8, 120.3, 122.0, 123.9, 124.5, 127.3, 130.5, 132.5, 148.7, 152.2, 159.7.

General Procedure for the Desilylation Reaction (Step d in Scheme 2)

To a solution of the silylated cycloadducts in dry THF (0.04 M) kept at 0°C, a solution of $TBAF \cdot 3H_2O$ in THF (1eq.) was added, and the reaction mixture monitored by TLC until the disappearance of the reagents (0.5 h). The crude mixture was diluted with ethyl acetate, and washed with saturated NH_4Cl and water. The organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness. Purification of the residue by flash chromatography on silica gel afforded the required 4-thiaflavans **5** and **6**.

2,3-Dihydro-2-(4-metoxy-phenyl)-1,4-benzoxathiin-7-ol (5)

The compound was obtained as a colorless glassy solid by flash chromatography on silica gel with dichloromethane:ethyl acetate 20:1 as eluent, 96% yield. ^{1}H NMR: $\delta = 3.06–3.23$ (m, 2H), 3.79 (s, 3H), 5.13 (dd, $J = 9.0, 2.4$ Hz, 1H), 6.42 (d, $J = 2.5$ Hz, 1H), 6.46 (dd, $J = 8.5, 2.5$ Hz, 1H), 6.89 (d, $J = 8.5$ Hz, 1H), 6.93–6.97 (m, 3H), 7.36–7.39 (m, 2H), 8.32 (br s, 1H). ^{13}C NMR: $\delta = 31.8$, 55.5, 77.5, 106.2, 107.5, 110.5, 114.6, 128.3, 128.5, 133.5, 154.0, 156.5, 160.5. Anal: Calcd for $C_{15}H_{14}O_3S$: C, 65.67, H, 5.14. Found C, 65.81; H, 5.05%.

2,3-Dihydro-3-(4-metoxy-phenyl)-naphth[2,1-b][1,4] oxathiin-8-ol (6)

The compound was obtained as a white solid by flash chromatography on silica gel using dichloromethane:ethyl acetate 20:1 as eluent, mp 160–163°C, 32% yield.^{1}H NMR: $\delta = 3.34–3.35$ (m, 2H), 3.82 (s, 3H), 5.22 (dd, $J = 6.8, 4.4$ Hz, 1H), 6.97–7.03 (m, 3H), 7.15–7.18 (m, 2H), 7.40–7.48 (m, 3H), 7.71–7.73 (m, 1H), 8.53 (br s, 1H). ^{13}C NMR: $\delta =$ 31.6, 55.6, 76.8, 111.0, 111.3, 114.7, 119.1, 121.1, 124.6, 124.9, 126.4, 128.4, 131.8, 133.6, 149.0, 155.0, 160.7. Anal: Calcd for $C_{19}H_{16}O_3S$: C, 70.35; H, 4.97. Found C, 70.55; H, 5.12%.

Solid Phase Synthesis

Carboxy polystyrene resin was purchased from Novabiochem as a 1% cross-linked divinylbenzene-styrene copolymer of 100–200 mesh with a loading of 1.4 mmol/g. Aminomethylated polystyrene resin was purchased from Novabiochem as a copolymer of 100–200 mesh with a loading of 1.2 mmol/g. Solid phase reactions were carried out in securely sealed vials and the resin suspensions transferred by plastic pipettes. Solid phase work-up was carried out by means of the plastic syringe technique. Flat-bottom PE syringes were equipped with sintered Teflon filters, Teflon tubing, and valves, which allow suction to be applied to the syringe from below. The resins were washed with the solvent used for the reaction and sequentially with DCM, MeOH, diethyl ether, and again DCM, and the shrunken beads were dried under vacuum over KOH before further transformations and analyses.

The purity of final cycloadducts **5** and **6** was verified by comparison with an authentic sample obtained by solution phase synthesis.

2,3-Dihydro-2-(4-metoxy-phenyl)-1,4-benzoxathiin-7-ol (5) (Step a in Scheme 3)

i) Commercial carboxy polystyrene resin (500 mg, loading 1.4 mmol/g, 0.7 mmol) was swelled in dry toluene (3 mL) for 30 min, then $SOCl_2$ (300 μL, 3.5 mmol) was added, and the mixture was heated at 60°C for 2 h to afford the solid supported acyl chloride. IR (KBr): $\nu = 1768 + 1734$ (C=O stretch), 870 (C-Cl stretch) cm^{-1}. *ii*) The acyl chloride resin (0.7 mmol) was swelled in dry CH_2Cl_2 (10 mL). After 30 min at room temperature resorcinol (231 mg, 2.1 mmol), DMAP (15 mg, 0.12 mmol) and Py (113 μL, 1.4 mmol) were added in sequence and the mixture swelled for 24 h at room temperature to afford the solid supported mono-hydroxyester **7**. IR (KBr): $\nu = 3428$ (OH stretch),1734 (C=O stretch) cm^{-1}.

Step b in Scheme 3

The phenol resin **7** (0.7 mmol) was swelled in $CHCl_3$ (6 mL). After 30 min at room temperature, PhtNSCl **1** (450 mg, 2.1 mmol) was added and the mixture swelled for 24 h at room temperature to afford the solid supported *o*-hydroxy-*N*-thiophthalimide **7a**. IR (KBr): $\nu = 3373$ (OH stretch), $1779 + 1734 + 1701$ (PhtN, C=O stretch) cm^{-1}.

Step c in Scheme 3

The *o*-hydroxythiophthalimide resin **7a** (0.7 mmol) was swelled in $CHCl_3$ (4 mL). After 30 min at room temperature, 4-methoxystyrene (**4**) (281 mg, 2.1 mmol) and TEA (212 mg, 2.1 mmol) were added in sequence and the mixture was heating at 60°C for 24 h to afford the solid supported 4-thiaflavan **7b**. IR (KBr): $\nu = 1737$ (C=O stretch) cm^{-1}.

Step d in Scheme 3

The 4-thiaflavan functionalized resin **7b** (0.7 mmol) was swelled in THF (5 mL). After 30 min at room temperature, a solution of LiOH (51 mg, 2.1 mmol) in H_2O (2 mL) was added, and the mixture swelled for 3 h at room temperature. The resin was filtered and washed with CH_2Cl_2 (3×15 mL), the collected organic phase washed with saturated NH_4Cl (2×30 mL), H_2O (50 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the cycloadduct **5** as pure compound, overall yield 46%.

2,3-Dihydro-3-(4-metoxy-phenyl)naphth[2,1-b][1,4]oxathiin-8-ol (6)

Commercially available carboxy polystyrene resin (400 mg, loading 1.4 mmol/g, 0.56 mmol) was swelled in dry DCM (3 mL). After 30 min at room temperature DCC (346 mg, 1.68 mmol), DMAP (205 mg, 1.68 mmol) and 2,6-dihydroxynaphthalene (269 mg, 1.68 mmol) were added in sequence and the mixture swelled for 24 h at room temperature to afford the solid supported mono-hydroxyester **8**. IR (KBr): $\nu = 3443$ (OH stretch), 1737 (C=O stretch) cm^{-1}.

Steps b′, c′) and d′) in Scheme 3

Solid supported *o*-hydroxy-*N*-thiophthalimide **8a**. IR (KBr): $\nu = 3444$ (OH stretch), 1781 + 1736 + 1701 (PhtN, C=O stretch) cm^{-1}. Solid supported 4-thiaflavan **8b**. IR (KBr): $\nu = 1736$ (C=O stretch) cm^{-1}. After washing and work-up, 4-thiaflavan **6** was isolated as pure compound in 47% overall yield.

Optimized Synthesis of 2,3-Dihydro-3-(4-metoxy-phenyl)naphth[2,1-*b*][1,4]oxathiin-8-ol (*6*)

Step a in Scheme 4

i) Commercially available aminomethylated polystyrene resin (3.0 g, loading 1.2 mmol/g, 3.6 mmol) was pre-swelled in dry Py (35 mL). A solution of succinic anhydride (1.08 g, 10.8 mmol) in dry Py (12 mL) was added to this suspension, and the mixture was swelled for 24 h at room temperature. The resin was filtered, washed with Py, DMF, DCM, and EtOH (3 × 20 mL each), and then dried under reduced pressure over KOH pellets. This procedure was repeated again to afford the desired succinic acid mono-amide pending resin. IR (KBr): $\nu = 3500\text{–}2500$ (C(O)O-H + C(O)N-H stretch), 1718 + 1654 (C=O stretch) cm^{-1}. *ii*) The succinic acid resin (926 mg, loading 1.08 mmol/g, 1 mmol) was swelled in dry DMF:DCM (4:1, 15 mL). After 1 h at room temperature, DCC (620 mg, 3 mmol), DMAP (430 mg, 3.5 mmol), and 2,6-dihydroxynaphthalene (**3**) (480 mg, 3 mmol) were added in sequence and the mixture swelled for 24 h at room temperature. After classical washing, the mono-hydroxyester resin **9** was dried in vacuum. IR (KBr): $\nu = 3313$ (O-H stretch), 1757 + 1654 (C=O stretch) cm^{-1}.

Step b in Scheme 4

The phenol resin **9** (1 mmol) was swelled in $CHCl_3$ (10 mL). After 1 h, PhtNSCl **1** (639 mg, 3 mmol) was added, and the mixture swelled for 24 h at room temperature to afford the solid supported *o*-hydroxy-*N*-thiophthalimide **9a**. IR (KBr): $\nu = 3400$ (OH stretch), 1781 + 1737 + 1703 (PhtN, C=O stretch) cm^{-1}.

Step c in Scheme 4

The *o*-hydroxy-*N*-thiophthalimide resin **9a** (1 mmol) was swelled in $CHCl_3$ (4 mL). After 30 min at room temperature, styrene **4** (402 mg, 3 mmol) and TEA (301 mg, 3 mmol) were added in sequence, and the mixture was heated at 60°C for 24 h to afford the solid supported 4-thiaflavan **9b**. IR (KBr): $\nu = 1731 + 1675$ (C=O stretch) cm^{-1}.

Step d in Scheme 4

The 4-thiaflavan functionalized resin **9b** (1 mmol) was swelled in THF (5 mL). After 30 min at room temperature, a solution of LiOH (72 mg, 3 mmol) in H_2O (2 mL) was added, and the mixture was swelled for 3 h at room temperature. The resin was filtered and washed with CH_2Cl_2 (3 × 15 mL), the collected organic phases washed with saturated NH_4Cl (2 × 30 mL) and H_2O (50 mL), and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure gave the cycloadduct **6** as pure compound in 65% overall yield.

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