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Synthesis of Flavones via Application of the Nitrile Oxide and the Stille Reactions

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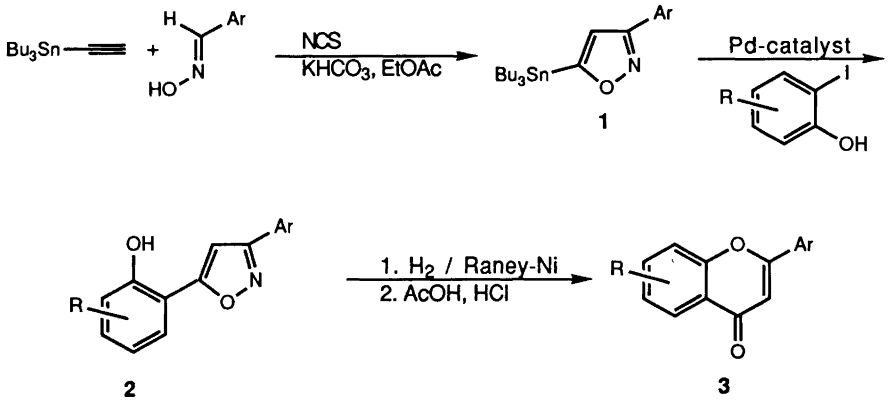
Hydroxylated and methoxylated benzaldehyde oximes have been chlorinated, dehydrohalogenated and cycloadded to tributylstannylacetylene to give 3-aryl-5-tributylstannylisoxazoles in good to excellent yields. The palladium-catalyzed coupling reaction, the so-called Stille reaction, of hindered and electron-rich 2-iodophenols and a 2-iodo-1,4-benzoquinone with 3-aryl-5-tributylstannylisoxazoles gave 3-aryl-5-(2-hydroxyaryl)isoxazoles in moderate to excellent yields. The coupling reaction was studied under various conditions and with various Pd(II) and Pd(0) complexes. Reduction of the 3,5-diarylisoxazoles with H_2/Raney-Ni, hydrolysis and acid-catalyzed cyclisation gave flavones. The synthesis of 2-iodo-3,5-dimethoxy-1,4-benzoquinone is described.

Much attention has been paid to naturally occurring flavones because of their pharmaceutical and ecological effects. Special interest has been focused on highly hydroxylated or methoxylated flavones during the last decade since they have been proved to be anticarcinogenic[1] and to inhibit HIV-reverse-transcriptase.[2] Several flavone syntheses have been described but only few efficient general syntheses of highly hydroxylated derivatives are known.[3]

In previous papers[4] we have described new synthetic routes to flavones, flavanones, isoflavanones, chalcones and quinolones. The syntheses involved isoxazolines or isoxazoles as key intermediates. However, these procedures required hydroxylated styrenes or phenylacetylenes, which are unstable and difficult to prepare.

Recently we applied the Stille reaction which avoided this limitation and also allowed for the use of highly oxygenated derivatives.[5] This procedure started with a 1,3-dipolar cycloaddition of an aromatic nitrile oxide to tributylstannylacetylene to give 3-aryl-5-tributylstannylisoxazole **1**. Tributylstannylisoxazoles were coupled with 2-iodophenols to give 3-aryl-5-(2-hydroxyaryl)-isoxazoles **2**. Reduction and subsequent acid-catalysed cyclisation in acetic acid gave the corresponding flavones **3** (Scheme 1).

These reactions have been extended to other phenols. The effect of various Pd catalysts were investigated in order to optimize the yields. The coupling between 2-iodo-3,5-dimethoxy-1,4-benzoquinone **4** to 5-tributylstannyl-3-(3,4,5-trimethoxyphenyl)isoxazole **1d** gave



Scheme 1.

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selectively 5-(3,6-dihydroxy-2,4-dimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)isoxazole **2i** or 3,5-dimethoxy-2-[3-(3,4,5-trimethoxyphenyl)isoxazol-5-yl]-1,4-benzoquinone **5** depending on the catalyst system. Reduction and acid-catalysed cyclisation of **2i** furnished 6-hydroxy-3′,4′,5′,5,7-pentamethoxyflavone **3i**.

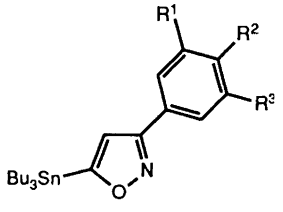
Results and discussion

Synthesis of 3-aryl-5-tributylstannylisoxazoles. The nitrile oxides were generated by chlorination of the corresponding benzaldehyde oximes with *N*-chlorosuccinimide in the presence of potassium hydrogen carbonate and traces of water. The chlorination, dehydrochlorination and cycloaddition were performed as a one-pot reaction.[6] The yields are listed in Table 1.

Chlorination at the aromatic ring did not occur in salicylaldehyde oxime, 4-hydroxybenzaldehyde oxime, 3,4-methylenedioxybenzaldehyde oxime, 3,4-dimethoxybenzaldehyde oxime (veratraldoxime) or 3,4,5-trimethoxybenzaldehyde oxime. *O*-Silylated 2,4-dihydroxybenzaldehyde oxime selectively gave the hydroximoyl chloride, whereas the unprotected oxime gave almost complete chlorination at the aromatic ring.[4b] The 3-aryl-5-tributylstannylisoxazoles decomposed slowly at room temperature.

Synthesis of iodophenols and 2-iodo-3,5-dimethoxy-1,4-benzoquinone **4**. The syntheses of 2-iodoresorcinol, 4-iodoresorcinol, 2-iodo-5-methoxyresorcinol, iodophloroglucinol, diiodophloroglucinol and triiodophloroglucinol have been described previously.[7] The synthesis of 5,6,7-trihydroxy- or -trimethoxy-substituted flavones required the availability of 3,4,5-trihydroxy- or -trimethoxy-substituted 2-iodophenols. All attempts to iodinate 3,4,5-trimethoxyphenol failed. Instead we found that 3,4,5-trimethoxyphenol, on treatment with an excess of iodine in H_2O–THF, was quantitatively oxidized to 2,6-dimethoxy-1,4-benzoquinone. Iodination of 2,6-dimethoxy-1,4-benzoquinone with 1.75 mol of ICl (iodine monochloride) in dry CH_2Cl_2 gave a mixture of 2-iodo-3,5-dimethoxy-1,4-benzoquinone, 2,6-diiodo-3,5-dimethoxy-1,4-benzoquinone and starting material in a 7.5:1.5:1.0 ratio as measured by ^1H NMR spectroscopy of the crude product. The excess of ICl was removed by addition of cyclohexene. Pure 2-iodo-3,5-dimethoxy-1,4-benzoquinone **4** was isolated by column chromatography over silica gel. The iodoquinone is unstable and decomposed partially during the chromatographic separation, which was the main reason that only 43% was isolated. It was not possible to oxidize and iodinate 3,4,5-trimethoxyphenol to **4** in a one-pot reaction with ICl. 2-Iodoquinones, as well as 2-iodophenols, can be used in the Stille coupling with organostannanes.

Table 1. Synthesis of 3-aryl-5-tributylstannylisoxazoles from the corresponding benzaldehyde oximes and tributylstannylacetylene.



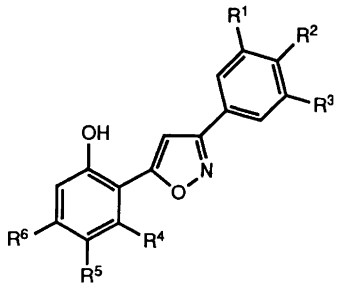
1

Compound	R^1	R^2	R^3	Yield (%)
1a	H	H	H	86
1b	H	OH	H	92
1c	OMe	OMe	H	74
1d	OMe	OMe	OMe	96

Stille coupling between 3-tributylstannylisoxazoles and 2-iodophenols or 2-iodo-3,5-dimethoxy-1,4-benzoquinone. Sakamoto *et al.*[8] described the coupling between 2-(methoxymethoxy)iodobenzene and 3-methyl-5-tributylstannylisoxazole with $PdCl_2(PPh_3)_2$ as the catalyst in refluxing dioxane to give 5-[2-(methoxymethoxy)-phenyl]-3-methylisoxazole in 68% yield. Under similar conditions we were able to couple the unprotected 2-iodophenol with 3-aryl-5-tributylstannylisoxazoles in 50% yields. This method was also applied to other iodophenols (Table 2, conditions A). Dioxane and ethylene glycol dimethyl ether were suitable solvents, whereas THF, DMF and HMPT[9] gave poor results. The presence of triphenylphosphine as a ligand in the Pd^{II} catalyst had no significant effect. Slightly increased dimerisation of the organostannane was occasionally observed. Benzyl(chloro)bis(triphenylphosphine) palladium^{II} gave slightly lower yields than $PdCl_2$. Application of the conventional $Pd^0(PPh_3)_4$ catalyst gave poor results. A report by Farina and Krishnan[10] led us to test $Pd(AsPh_3)_4$, generated *in situ* from tris(dibenzylideneacetone)dipalladium (Pd_2dba_3) and 4 mol of $AsPh_3$. With this catalyst the coupling proceeded even at room temperature but the best yields were obtained at 50°C. At higher temperatures precipitation of black material indicated decomposition of the catalyst. Iodobenzenes containing two *ortho*-hydroxy groups reacted poorly under conditions B, whereas *ortho*-monosubstituted iodobenzenes gave good yields, under the same conditions, presumably depending on steric rather than on electronic factors, as indicated from the results from the coupling with 2-iodoresorcinol and 4-iodoresorcinol (Table 2, conditions B). A milky suspension was produced when $SbPh_3$ was mixed with Pd_2dba_3 in dioxane.[10] In spite of the low solubility of $Pd(SbPh_3)_4$ a fair yield of **2g** was obtained even at room temperature for the coupling between 4-iodoresorcinol and **1d**. However, because of its low stability lower yields were obtained with this catalyst, than with $Pd(AsPh_3)_4$.

As a consequence of their biosynthetic origin via the polyketide pathway, most naturally occurring flavones contain hydroxy groups in the 5 and 7 positions of the *A*

Table 2. Palladium-catalysed coupling between *o*-hydroxyiodoaromatics and 3-aryl-5-tributylstannylisoxazoles.



2

Compound	R^1	R^2	R^3	R^4	R^5	R^6	Condition[a]	Yield (%)
2a	H	OH	H	H	H	H	A	50
							B	95
2b	H	OH	H	H	H	OH	A	43
							B	78
2c	H	OH	H	OH	H	H	A	42
							B	<5
2d	H	OH	H	OH	H	OH	A	35
							B	<5
2e	H	OH	H	OH	H	OMe	A	44
							B	<5
2f	OMe	OMe	OMe	H	H	H	B	81
2g	OMe	OMe	OMe	H	H	OH	B	67
2h	OMe	OMe	OMe	OH	H	OH	A	43
2i	OMe	OMe	OMe	OMe	OH	OMe	C	80

[a] Conditions: A, 5% $PdCl_2$, 101 °C; B, 2.5% Pd_2dba_3 and 20% $AsPh_3$, 50 °C; C, 10% $Pd(PPh_3)_4$, 101 °C. Solvent: dioxane.

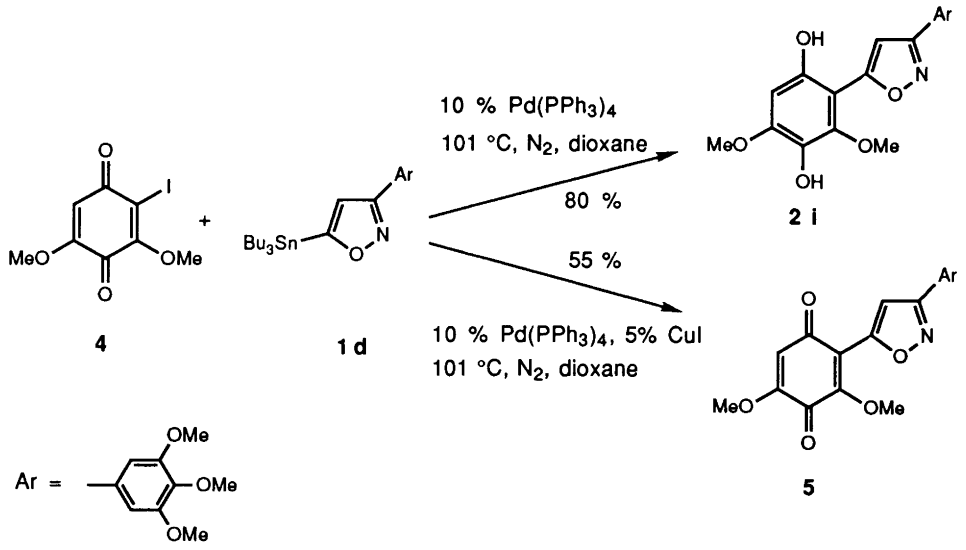
ring. We therefore made efforts to optimize the yields of the coupling with iodophloroglucinol. Iodophloroglucinol was thermally unstable and decomposed in the presence of acid, which decreased the yields of the coupling products. A large excess of iodophloroglucinol increased the crude yield considerably as indicated by the ^1H NMR spectra, but caused serious separation problems.

Bromophloroglucinol was more stable than iodophloroglucinol, but also less reactive, which under conditions A gave rise to competing dimerisation and destannylation of the 5-tributylstannylisoxazole, leading to lower yields.

When triiodophloroglucinol was substituted for iodophloroglucinol in the coupling with **1b**, a mixture of diiodo-**2d**, monoiodo-**2d**, and **2d** was obtained. Reduction of the crude product followed by cyclisation in AcOH–HCl gave the corresponding flavone (apigenin) **3d** in 30% overall yield.

In contrast with the iodophenols, 2-iodo-3,5-dimethoxy-1,4-benzoquinone **4** gave a better yield in the coupling reaction with tributylstannylisoxazoles with $Pd(PPh_3)_4$ than with $Pd(AsPh_3)_4$ as the catalyst. Using 10% $Pd(PPh_3)_4$ and 5% CuI as the catalyst[11] isoxazolylquinone **5** containing minor impurities was isolated in 55% yield. To our surprise the isoxazolylhydroquinone **2i** was obtained in a yield of 80% using 10% $Pd(PPh_3)_4$ without CuI as a co-catalyst (Scheme 2). We cannot explain why the quinone was reduced during the cross-coupling. However, presence of CuI could catalyse the oxidation of hydroquinone to quinone by molecular oxygen in the solvent.

Reduction and cyclisation. The 3-aryl-5-(2-hydroxyaryl)isoxazoles were converted into the corresponding 1,3-diketones in the usual manner,[4,5] by hydrogenation over Raney-nickel in aqueous ethanol in the presence of boric acid. Owing to their poor solubility in ethanol–water, some of the 3,5-diarylisoxazoles were dissolved in dioxane–ethanol–water. The ^1H NMR spectra of the crude products revealed that partial cyclisation to the flavones had taken place. An excess of H_2 was necessary to reduce iodine of diiodo-**2d** and monoiodo-**2d**. The 1,3-diketones were subjected to cyclodehydration in acetic acid and a catalytic amount of HCl at 100 °C for 1.5 h. Flavones **3a–h**, were obtained in 27–80% yields from the corresponding isoxazoles (Table 3). Our melting

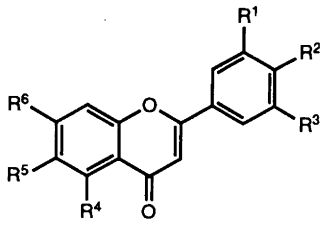


Scheme 2.

point for 4′,5-dihydroxyflavone **3c** (255–258°C) differed from the literature data (237–240°C).[3a,12]

During the reduction and cyclodehydration partial demethylation of **5** took place, which gave rise to a mixture of flavones. From this mixture 6-hydroxy-3′,4′,5′,5,7-pentamethoxyflavone **3i** was isolated in 10% yield by TLC. No demethylation was observed when hydroquinone **2i** was reduced and cyclodehydrated and the corresponding flavone could be isolated in 40% yield. The demethylation of the *A*-ring methoxy groups is described in a recent report.[13]

Table 3. Reductive ring-opening and cyclodehydration of 3,5-diarylisoxazoles.



3

Compound	R^1	R^2	R^3	R^4	R^5	R^6	Yield (%)
3a	H	OH	H	H	H	H	60
3b	H	OH	H	H	H	OH	62
3c	H	OH	H	OH	H	H	66
3d	H	OH	H	OH	H	OH	65
3e	H	OH	H	OH	H	OMe	62
3f	OMe	OMe	OMe	H	H	H	80
3g	OMe	OMe	OMe	H	H	OH	81
3h	OMe	OMe	OMe	OH	H	OH	27
3i	OMe	OMe	OMe	OMe	OH	OMe	40

Experimental

^{1}H NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer. Mass spectra were recorded on a V.G. Micro-Mass 7070F spectrometer operating at 70 eV with a direct inlet.

Materials. The iodophenols,[7] tributylstannylacetylene,[14] dipalladium trisdibenzylideneacetone[15] and benzyl(chloro)bis(triphenylphosphine)palladium[16] were synthesized according to the known procedures. Iodophloroglucinol and 3-aryl-5-tributylstannylisoxazoles **1a–d** were stored below −5°C. Dioxane was distilled over sodium and benzophenone before use.

3-Aryl-5-tributylstannylisoxazole derivatives **1a–d**. The arenecarbaldehyde oxime (15 mmol) was dissolved in ethyl acetate (10 ml). Potassium hydrogen carbonate (3 g), one drop of water, tributylstannylacetylene (3.15 g, 10 mmol) and *N*-chlorosuccinimide (2.0 g, 15 mmol) were consecutively added to the solution. The mixture was stirred at room temperature for 20 h. The suspension was filtered through a layer of Celite and the solvent was evaporated off *in vacuo*. The crude product was purified on a silica gel column with diethyl ether–petroleum ether to give the pure 3-aryl-5-tributylstannylisoxazoles as yellow syrups.

3-Phenyl-5-tributylstannylisoxazole **1a**. Yield = 3.7 g (85%). The ^{1}H NMR spectral data agree with literature data.[8]

3-(4-Hydroxyphenyl)-5-tributylstannylisoxazole **1b**. Yield = 4.15 g (92%). The ^{1}H NMR spectra data are described elsewhere.[5]

3-(3,4-Dimethoxyphenyl)-5-tributylstannylisoxazole **1c**. The synthesis of compound **1c** was scaled down by a

factor of five from the above-described procedure. Yield = 730 mg (74%). ^{1}H NMR ($CDCl_3$): δ 0.87 (9 H, t, *J* 7.0 Hz), 1.1–1.8 (18 H, m), 3.89 (3 H, s), 3.92 (3 H, s), 6.61 (1 H, s), 6.90 (1 H, d, *J* 8.3 Hz), 7.31 (1 H, dd, *J* 8.3 and 2.0 Hz), 7.44 (1 H, d, *J* 2.0 Hz).

5-Tributylstannyl-3-(3,4,5-trimethoxyphenyl)isoxazole **1d**. Yield = 5.03 g (96%). ^{1}H NMR ($CDCl_3$): δ 0.88 (9 H, t, *J* 7.0 Hz), 1.2–1.7 (18 H, m), 3.86 (3 H, s), 3.90 (6 H, s), 6.60 (1 H, s), 7.04 (2 H, s).

Stille coupling. Conditions A

3,5-Diarylisoxazole (**2a–e, h**). Aryl iodide (1.3 mmol), 3-aryl-5-tributylstannylisoxazole (1 mmol) and $PdCl_2$ (8.9 mg, 0.05 mmol) were refluxed in dry dioxane under an N_2 atmosphere for 5 h. The reaction mixture was cooled to room temperature and filtered through a 20 mm layer of silica gel and the solvent was evaporated off. The crude product was purified by flash chromatography on silica gel (diethyl ether).

Conditions B

3,5-Diarylisoxazole **2a–g**. Aryl iodide (1 mmol), Pd_2dba_3 (22.7 mg, 0.05 equiv. of Pd) and $AsPh_3$ (61.2 mg, 0.2 equiv.) in dry dioxane (5 ml) were stirred for 15 min at 20°C under nitrogen. 3-Aryl-5-tributylstannylisoxazole (1.3 mmol) in dry dioxane (1 ml) was added to the solution through a septum via syringe and the temperature was raised to 50°C. After 48 h the reaction mixture was filtered through a 20 mm layer of silica gel and the solvent was evaporated off. The crude products were refluxed for 30 min in CH_2Cl_2. The suspension was stored at −5°C for 3 h. The precipitate was filtered off and washed with CH_2Cl_2 to give the isoxazoles **2a**, **b**, **f**, **g**. Isoxazoles **2c**, **d**, **e** could be isolated in low yields after purification by flash chromatography on silica gel (diethyl ether).

3-(4-Hydroxyphenyl)-5-(2-hydroxyphenyl)isoxazole **2a**. Yield = 240 mg (95%). An analytically pure sample was obtained after recrystallization from acetonitrile. M.p. 269–270°C. MS: *m/z* = 253 (M^+). ^{1}H NMR (CD_3OD–$CDCl_3$ 1:3): δ 6.85–6.98 (4 H, m), 7.16 (1 H, s), 7.25 (1 H, td, *J* 8.0 and 2 Hz), 7.69 (2 H, d, *J* 8.7 Hz), 7.86 (1 H, dd, *J* 8.0 and 2 Hz).

5-(2,4-Dihydroxyphenyl)-3-(4-hydroxyphenyl)isoxazole **2b**. Yield = 210 mg (78%). An analytically pure sample was obtained after recrystallization from acetonitrile. M.p. 275–278°C. MS: *m/z* = 269 (M^+). ^{1}H NMR (CD_3OD–$CDCl_3$ 1:3): δ 6.38 (1 H, dd, *J* 8.5 and 2.0 Hz), 6.48 (1 H, d, *J* 2.1 Hz), 6.87 (2 H, d, *J* 8.7 Hz), 6.97 (1 H, s), 7.58 (1 H, d, *J* 8.5 Hz), 7.70 (2 H, d, *J* 8.7 Hz).

5-(2,6-Dihydroxyphenyl)-3-(4-hydroxyphenyl)isoxazole **2c**. Yield = 112 mg (42%). An analytically pure sample was obtained after recrystallization from tetrahydrofuran–petroleum ether. M.p. 255–258°C.[3a,12] MS: *m/z* = 269 (M^+). ^{1}H NMR (CD_3OD): δ 6.47 (2 H, d, *J* 8.2 Hz), 6.88 (2 H, d, *J* 8.7 Hz), 7.06 (2 H, s), 7.08 (1 H, t, *J* 8.2 Hz), 7.67 (2 H, d, *J* 8.7 Hz).

3-(4-Hydroxyphenyl)-5-(2,4,6-trihydroxyphenyl)-isoxazole **2d**. Yield = 100 mg (35%). An analytically pure sample was obtained after recrystallization from ethyl acetate–petroleum ether. M.p. 289–291°C. MS: *m/z* = 285 (M^+). The ^{1}H NMR spectral data are described elsewhere.[5]

5-(2,6-Dihydroxy-4-methoxyphenyl)-3-(4-hydroxyphenyl)-isoxazole **2e**. Yield = 132 mg (44%). An analytically pure sample was obtained after recrystallization from acetonitrile. M.p. 237–239°C. MS: *m/z* = 299 (M^+). ^{1}H NMR (CD_3OD): δ 3.75 (3 H, s), 6.05 (2 H, s), 6.86 (2 H, d, *J* 8.7 Hz), 6.87 (1 H, s), 7.68 (2 H, d, *J* 8.7 Hz).

5-(2-Hydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)isoxazole **2f**. Yield = 265 mg (81%). An analytically pure sample was obtained after recrystallization from acetone. M.p. 235–238°C. MS: *m/z* = 328 ($M^+ + 1$). ^{1}H NMR (CD_3OD–$CDCl_3$ 1:3): δ 3.85 (3 H, s), 3.95 (6 H, s), 6.89–6.99 (2 H, m), 7.09 (2 H, s), 7.17 (1 H, s), 7.26 (1 H, td, *J* 7.8 and 2 Hz), 7.88 (1 H, dd, *J* 8.1 and 2 Hz).

5-(2,4-Dihydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)-isoxazole **2g**. Yield = 231 mg (67%). An analytically pure sample was obtained after recrystallization from tetrahydrofuran–petroleum ether. M.p. 275–277°C. MS: *m/z* = 343 (M^+). ^{1}H NMR (CD_3OD–$CDCl_3$ 1:3): δ 3.85 (3 H, s), 3.93 (6 H, s), 6.40–6.48 (2 H, m), 7.02 (1 H, s), 7.09 (2 H, s), 7.71 (1 H, d, *J* 9.5 Hz).

5-(2,4,6-Trihydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)-isoxazole **2h**. Yield = 154 mg (43%). An analytically pure sample was obtained after recrystallization from methanol–water. M.p. 229–232°C. MS: *m/z* = 359 (M^+). ^{1}H NMR (CD_3OD): δ 3.80 (3 H, s), 3.90 (6 H, s), 5.97 (2 H, s), 6.92 (1 H, s), 7.14 (2 H, s).

Conditions C

5-(3,6-Dihydroxy-2,4-dimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)isoxazole **2i**. A mixture of iodoquinone **4** (294 mg, 1 mmol) and $Pd(PPh_3)_4$ (115.5 mg, 0.1 mmol) was stirred in dry dioxane (10 ml) for 15 min at 20°C under nitrogen. The stannylisoxazole **1d** (681 mg, 1.3 mmol) dissolved in dioxane (1 ml) was added through a septum via syringe. The flask was heated in an oil bath at 110°C with stirring for 2.5 h. The reaction mixture was cooled to room temperature and filtered through a 20 mm layer of silica gel, and the solvent was evaporated off. Purification by flash chromatography on silica gel (diethyl ether) gave **2i** (322 mg, 80%). An analytically pure sample was obtained after recrystallization from methanol to give white crystals. M.p. 207–209°C. MS: *m/z* = 404 ($M^+ + 1$). ^{1}H NMR (CD_3OD–$CDCl_3$ 1:3): δ

3.80 (3 H, s), 3.86 (3 H, s), 3.87 (3 H, s), 3.93 (6 H, s), 6.38 (1 H, s), 6.92 (1 H, s), 7.10 (2 H, s).

3,5-Dimethoxy-2-[3-(3,4,5-trimethoxyphenyl)isoxazol-5-yl]-1,4-benzoquinone **5**. A mixture of iodoquinone **4** (294 mg, 1 mmol), $Pd(PPh_3)_4$ (115.5 mg, 0.1 mmol) and CuI (9.5 mg, 0.05 mmol) was stirred in dry dioxane (10 ml) for 15 min at 20°C under an N_2 atmosphere. The stannylisoxazole **1d** (681 mg, 1.3 mmol) dissolved in dioxane (1 ml) was added through a septum via syringe. The flask was heated in an oil bath at 110°C with stirring for 5 h. The mixture was worked up as described above. Purification yielded **5** (222 mg, 55%) containing minor impurities. An analytically pure sample was obtained after recrystallization from methanol to give red crystals. M.p. 180–183°C. MS: $m/z = 401$ (M^+). ^{1}H NMR ($CDCl_3$): δ 3.83–3.98 (12 H, m), 4.15 (3 H, s), 5.98 (1 H, s), 7.08 (2 H, s), 7.14 (1 H, s).

General procedure for the reduction and cyclodehydration

Flavones **3a–h**. The 3,5-diarylisoxazole (0.5 mmol) was catalytically reduced over Raney-nickel in a water–ethanol or a water–ethanol–dioxane solution under an H_2 atmosphere (1 atm). After 45 to 75 min 1 equivalent of H_2 had been absorbed. The suspension was filtered through a layer of Celite, and the solvent was evaporated off. The residue was stirred at 100°C in 3 ml glacial acetic acid containing 1 drop of concentrated HCl for 1.5 h. The mixture was allowed to cool to room temperature and 20 ml of cold water was slowly added. The precipitated flavone was filtered off, washed with water and dried.

4'-Hydroxyflavone **3a**. Yield = 72 mg (60%). An analytically pure sample was obtained after recrystallization from acetone–petroleum ether. M.p. 270–271°C. MS: $m/z = 238$ (M^+). ^{1}H NMR (CD_3OD–$CDCl_3$ 1:3): δ 6.70 (1 H, s), 6.91 (2 H, d, *J* 9.0 Hz), 7.39 (1 H, td, *J* 7.8 and 1.2 Hz), 7.56 (1 H, dd, *J* 8.1 and 1.2 Hz), 7.69 (1 H, td, *J* 8.1 and 1.6 Hz), 7.81 (2 H, d, *J* 9.0 Hz), 8.11 (1 H, dd, *J* 8.0 and 1.6 Hz).

4',7-Dihydroxyflavone **3b**. Yield = 79 mg (62%). An analytically pure sample was obtained after recrystallization from methanol–toluene. M.p. 314–316°C. MS: $m/z = 254$ (M^+). ^{1}H NMR (CD_3OD–$CDCl_3$ 1:3): δ 6.60 (1 H, s), 6.84–6.94 (4 H, m), 7.78 (2 H, d, *J* 9.1 Hz), 7.94 (1 H, d, *J* 8.7 Hz).

4',5-Dihydroxyflavone **3c**. Yield = 84 mg (66%). An analytically pure sample was obtained after recrystallization from methanol–water. M.p. 255–258°C. MS: $m/z = 254$ (M^+). ^{1}H NMR (CD_3OD–$CDCl_3$ 1:1): δ 6.68 (1 H, s), 6.75 (1 H, dd, *J* 8.3 and 1.0 Hz), 6.93 (2 H, d, *J* 9.4 Hz), 7.05 (1 H, dd, *J* 8.3 and 1.0 Hz), 7.57 (2 H, t, *J* 8.3 Hz), 7.86 (2 H, d, *J* 9.4 Hz)

4',5,7-Trihydroxyflavone **3d**. Yield = 88 mg (65%). An analytically pure sample was obtained after recrystallization from ethanol. M.p. 348–350°C. MS: $m/z = 270$ (M^+). The ^{1}H NMR spectral data are described elsewhere.[5]

4',5-Dihydroxy-7-methoxyflavone **3e**. Yield = 88 mg (62%). An analytically pure sample was obtained after recrystallization from methanol. M.p. 285–287°C. MS: $m/z = 284$ (M^+). ^{1}H NMR (CD_3OD–$CDCl_3$ 1:1): δ 3.85 (3 H, s), 6.30 (1 H, d, *J* 2.0 Hz), 6.50 (1 H, d, *J* 2.0 Hz), 6.53 (1 H, s), 6.90 (2 H, d, *J* 9.0 Hz), 7.77 (2 H, d, *J* 9.0 Hz).

3',4',5'-Trimethoxyflavone **3f**. Yield = 125 mg (80%). An analytically pure sample was obtained after recrystallization from methanol. M.p. 174–176°C. MS: $m/z = 312$ (M^+). ^{1}H NMR (CD_3OD): δ 3.87 (3 H, s), 3.93 (6 H, s), 6.75 (1 H, s), 7.13 (2 H, s), 7.41 (1 H, td, *J* 8.0 and 1.0 Hz), 7.58 (1 H, dd, *J* 8.0 and 1.0 Hz), 7.71 (1 H, td, *J* 8.0 and 2 Hz), 8.14 (1 H, dd, *J* 8.0 and 2.0 Hz).

7-Hydroxy-3',4',5'-trimethoxyflavone **3g**. Yield = 133 mg (81%). An analytically pure sample was obtained after recrystallization from methanol. M.p. 276–278°C. MS: $m/z = 328$ (M^+). ^{1}H NMR (CD_3OD–$CDCl_3$ 1:3): δ 3.88 (3 H, s), 3.93 (6 H, s), 6.66 (1 H, s), 6.91 (1 H, dd, *J* 9.2 and 2 Hz), 6.93 (1 H, d, *J* 2 Hz), 7.11 (2 H, s), 7.37 (1 H, s), 7.98 (1 H, d, *J* 9.2).

5,7-Dihydroxy-3',4',5'-trimethoxyflavone **3h**. Yield = 47 mg (27%). An analytically pure sample was obtained after recrystallization from methanol. M.p. 271–272°C. MS: $m/z = 344$ (M^+). ^{1}H NMR (CD_3OD): δ 3.84 (3 H, s), 3.93 (6 H, s), 6.21 (1 H, d, *J* 2.1 Hz), 6.48 (1 H, d, *J* 2.1 Hz), 6.71 (1 H, s), 7.24 (2 H, s).

6-Hydroxy-3',4',5',5,7-pentamethoxyflavone **3i**. Isoxazole **2i** (70 mg, 0.174 mmol) was reduced and cyclodehydrated as described in the general procedure. The reaction mixture was heated with acetic acid and HCl after which the solvent was evaporated off *in vacuo*. The residue was purified by preparative silica gel TLC (EtOAc) to give **3i** (27 mg, 0.07 mmol 40%). The flavone was recrystallized from tetrahydrofuran–petroleum ether. M.p. 191–192°C. MS: $m/z = 388$ (M^+). ^{1}H NMR ($CDCl_3$): δ 3.93 (3 H, s), 3.96 (6 H, s), 4.03 (3 H, s), 4.04 (3 H, s), 6.74 (1 H, s), 6.85 (1 H, s), 7.10 (2 H, s).

2-Iodo-3,5-dimethoxy-1,4-benzoquinone **4**. A mixture of 2,6-dimethoxy-1,4-benzoquinone (615 mg, 3.66 mmol) and iodine monochloride (1039 mg, 6.4 mmol) in dry dichloromethane (15 ml) was stirred at room temperature for 2 days. After being washed with 10% aqueous sodium hydrogen carbonate and dried over magnesium sulfate, the dark organic phase was stirred with cyclohexene until the solution turned yellow. The solvent was evaporated off *in vacuo* and the residue was purified by flash chromatography on silica gel (CH_2Cl_2) to give the

monoiodinated quinone **4** (463 mg, 43%). The product was recrystallized from methanol to give bright orange crystals. M.p. 146–148 °C. MS: $m/z = 294$ (M^+). ^{1}H NMR ($CDCl_3$): δ 3.82 (3 H, s), 4.14 (3 H, s), 5.97 (1 H, s).

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