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Synthesis of 3-Acyl- and 3-Carbamoylflavones

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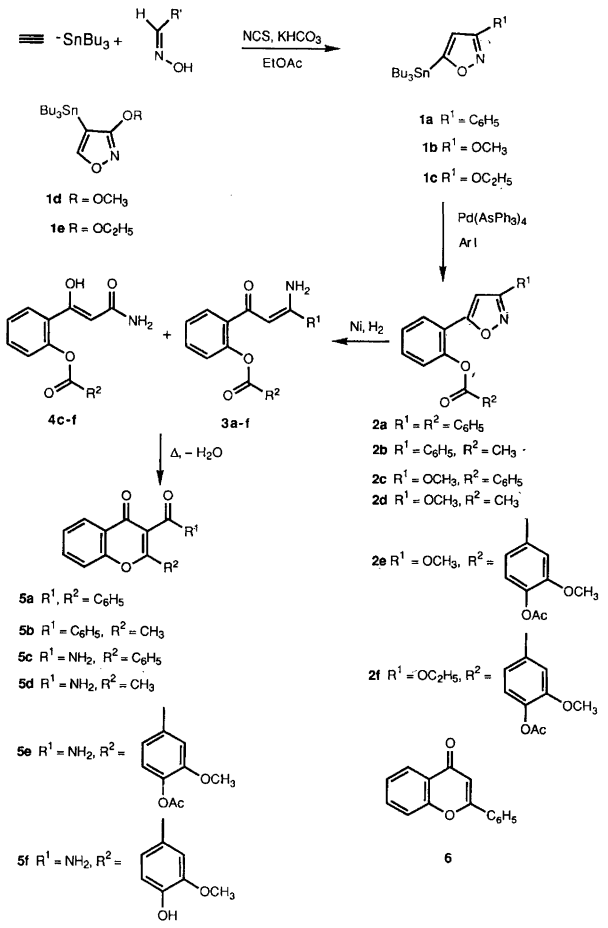
Routes to 3-acyl-, 3-carboxamido- and polyhydroxylated flavones have been devised by application of isoxazole methodology and Heck–Stille couplings. Reductive ring opening of 3-alkoxyisoxazoles gives β-keto carboxamides in contrast with 3-alkoxy-2-isoxazolines, which give β-hydroxy esters.

In previous articles novel synthesis of flavones based on the isoxazole protocol and Heck–Stille couplings have been described.[1,2] In the present work we had two objectives, (a) to investigate the behaviour of *O*-silylated phenolics as reaction partners in these reactions and (b) to devise routes to 3-acyl- and 3-carboxamido-flavones, which are pharmacologically active compounds.

Results and discussion

3-Acyl- and 3-carbamoyl-flavones. Scheme 1 shows the routes to 3-acyl- and 3-carbamoyl-flavones. By acylation of the *ortho*-hydroxy group of the iodophenols an alternative mode of cyclisation of compounds **3** and **4**, derived from Stille coupling and subsequent reductive cleavage of the isoxazole ring, is made possible via condensation of the aryl ester carbonyl with the active methylene group. This reaction was recently tested in our analogous synthesis of 3-acylated 4-quinolones.[3] Functionality in the B-ring of flavones can now be introduced by using substituted 2-iodophenyl esters as demonstrated by the use of 4-acetoxy-3-methoxybenzoyl chloride, compounds **2e,f**. The benzoyl chloride was prepared from vanillic acid. The hydroxy group was first protected by acetylation. Silylation by *tert*-butyldimethylchlorosilane was less suitable because of low yielding steps and the instability of the silyl ether.

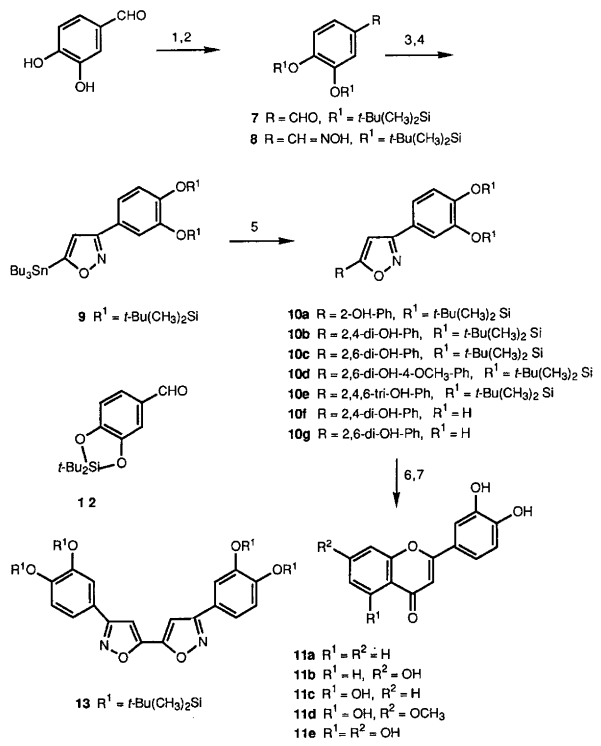
The 3-alkoxy-5-tributylstannylisoxazoles **1b,c** were obtained in good yields by cycloaddition of alkoxynitrile oxides to tributylstannylacetylene.[4] Minor amounts of the 4-isomers **1d,e** were observed in the product by ^{1}H NMR spectroscopy, ca. 15%. We were not able to separate the isomers by chromatography. Use of the mixture did not affect the $Pd(AsPh_3)_4$ catalyzed coupling[1d] to give **2c–f**. It was not possible to prepare the 3-alkoxy-5-tributylstannylisoxazoles from the corresponding 3-chloro derivatives by a chloro–alkoxy exchange under basic conditions. This reaction required drastic conditions, which eliminated the stannyl group. The hydrogenation of **2a,b** gave, according to the ^{1}H,^{13}C NMR spectra, the keto-enamines **3a,b**, which were thermolyzed to give **5a,b** in 77% and 40% yields, respectively. Compound **5b** con-



Scheme 1.

tained ca. 20% of flavone **6**, which was formed by initial hydrolysis of the acetate and subsequent cyclization. Hydrogenation of **2c–f** gave mixtures of the imidates **3c–f**, the amides **4c–f** and the cyclized products **5c–f** on work-up. The mixture was cyclized to give nearly pure **5c–f** by heating in HOAc, saturated with NaOAc at 110°C for ca. 3 h. The reduction product from **2f** required a prolonged cyclization time, 8–10 h, which gave predominantly the deacetylated flavone **5f**. It is of interest to note that reductive ring opening of 3-alkoxyisoxazoles gave carboxamides whereas 3-alkoxy-2-isoxazolines[4] gave esters as reduction products.

Reactions of O-*silylated derivatives.* Nuclear chlorination of hydroxylated benzaldehyde oximes competes with oxime chlorination to hydroxamic acid chlorides. Thus, NCS (*N*-chlorosuccinimide) chlorination of 2,4-dihydroxybenzaldehyde oxime gave primarily nuclear chlorination. This course of the reaction was efficiently prevented by silylation of the hydroxy groups.[1b] Since most naturally occurring flavones contain hydroxy groups in both the A and B rings we investigated the stability of silyl ethers in the nitrile oxide and the Heck–Stille reactions. 3,4-Dihydroxybenzaldehyde oxime was chosen for the purpose. As expected it was predominantly chlorinated in the nucleus by NCS. Di-*tert*-butylsilyl bis(trifluoromethane sulfonate) was first tested as a protecting reagent on a 0.1 mmol scale, giving the desired cyclic derivative **12** in 62% yield. The yield was difficult to reproduce in larger scale runs and the product was also susceptible to hydrolysis. It was therefore decided to use *tert*-butyldimethylchlorosilane, which gave compound **7**. It had the drawback of being very lipophilic and required large amounts of solvents in the following reactions. It was oximated, chlorinated and finally cycloadded to tributylstannylacetylene to give **9**, Scheme 2. The isomeric 3-[2,4-bis(*tert*-butyldimethylsilyloxy)phenyl]-5-tributylstannylisoxazole was prepared in 57% yield according to the same procedure. Compound **9** gave 3,5-diarylisoxazoles **10** with iodophenols and $Pd(AsPh_3)_4$ as catalyst. The sterically hindered 2,6-dihydroxyiodobenzenes gave poor yields in this reaction. $PdCl_2$ was the best catalyst in this case but favoured also the formation of the dimer **13** in a side reaction. Reductive cleavage and acid-catalyzed desilylation and cyclization gave the polyhydroxylated flavones **11**. The two-step reaction involving separate desilylation by fluoride ions as described for **11b,c** gave better yields than the somewhat simpler procedure described for **11a,d,e**. In this procedure the desilylation and cyclization were carried out in one step after the reductive cleavage of the isoxazole ring.



Scheme 2. 1, t-Bu$(CH_3)_2$SiCl–Et_3N; 2, NH_2OH; 3, NCS; 4, ≡–$SnBu_3$–$KHCO_3$; 5, RI–$Pd(AsPh_3)_4$; 6, H_2–Ni; 7, H^+.

Experimental

The ^1H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 spectrometer and the mass spectra with a V. G. Micromass 7070 F. IR spectra were recorded with a Nicolet MX-S. Melting points were determined with an Electrothermal melting point apparatus and are uncorrected. Preparative TLC were performed on Silica gel 60, $PF_{254+360}$, layers on glass plates (0.2 × 20 × 20 cm). Column chromatography on Silica gel 60 (70–230 mesh) Merck, Alumina 60 (70–230 mesh) Merck or Silica 60 (230–400 mesh, flash chromatography) Merck.

Materials. **1a**,[1d,5] methyl and ethyl formhydroximate,[4] $Pd(AsPh_3)_4$,[6] tributylstannylacetylene,[7] tris(dibenzylideneacetone)dipalladium, $Pd_2(dba)_3$,[8] iodophenols.[9]

3-Methoxy-5-tributylstannylisoxazole **1b** *and the 4-isomer* **1d**. Methyl formhydroximate (20 mmol, 1.5 g), $KHCO_3$ (10 g), tributylstannylacetylene (12 mmol, 3.8 g) were stirred in ethyl acetate (50 ml), and water (0.3 ml) and *N*-chlorosuccinimide (NCS, 22 mmol, 2.9 g) were added. The solution turned blue and CO_2 was liberated. The mixture was kept at 45°C with stirring for two days, filtered, evaporated *in vacuo* and CCl_4 (10 ml) was added. The suspension was dried over $MgSO_4$, filtered and evaporated *in vacuo*. The residue was chromatographed on basic alumina with petroleum containing increasing amounts of diethyl ether as the eluent to give **1b** and the 4-isomer **1d** in a ratio of 6:1, colorless oils, 3.9 g, total yield 84%. ^1H NMR ($CDCl_3$) **1b**: δ 0.8–1.7 (27 H, m), 3.95 (3 H, s), 5.93 (1 H, s). **1d**: δ 7.78 (5-H). ^{13}C NMR ($CDCl_3$) **1b**: δ 10.8, 14.1, 27.6, 29.2, 57.8, 105.8, 163.9, 173.0.

3-Ethoxy-5-tributylstannylisoxazole **1c** *and the 4-isomer* **1e** *(oils)* were prepared as described for **1b,d** from ethyl formhydroximate in a ratio of 5:1. The total yield was 87%. ^{1}H NMR ($CDCl_3$) **1c**: δ 0.8–1.7 (30 H, m), 4.27 (2 H, q), 5.94 (1 H, s). **1e**: δ 7.78 (5-H). ^{13}C NMR ($CDCl_3$) **1c**: δ 10.8, 14.1, 15.2, 27.6, 29.3, 66.5, 106.0, 163.7, 172.3.

4-Acetoxy-3-methoxybenzoyl chloride. 4-Acetylvanillic acid (5.2 mmol, 1.08 g) was heated with thionyl chloride (16 mmol, 1.9 g) at 100°C for 40 min. The excess of thionyl chloride was evaporated off *in vacuo* to give the acid chloride in practically quantitative yield as a brown-reddish oil, which was used directly in subsequent reactions. ^{1}H NMR ($CDCl_3$): δ 2.35 (3 H, s), 3.91 (3 H, s), 7.19 (1 H, d, J = 8.3 Hz), 7.66 (1 H, d, J = 2.0 Hz), 7.81 (1 H, dd, J = 8.3 and 2.0 Hz).

Preparation of the 2-iodophenyl esters.[10] To 2-iodophenol (10 mmol), pulverized NaOH (1.0 g) and TBAH (12 mg) in CH_2Cl_2 (20 ml) was added the acid chloride (12 mmol) in CH_2Cl_2 (10 ml) over ca. 30 min with stirring. After 15 min the suspension was filtered and the filtrate was dried over $MgSO_4$, filtered and evaporated. The crude ester formed was sufficiently pure to be used directly for the Stille coupling. *2-Iodophenyl benzoate*, m.p. 33°C; *2-iodophenyl acetate*, oil; *2-iodophenyl 4-acetoxy-3-methoxybenzoate*, light yellow-brown crystals, m.p. 114°C, ^{1}H NMR ($CHCl_3$): δ 2.37 (3 H, s), 3.94 (3 H, s), 7.03 (1 H, ddd, J = 8.0, 7.6, 1.7 Hz), 7.18–7.28 (2 H, m), 7.43 (1 H, ddd, J = 8.3, 7.6, 1.6 Hz), 7.84–7.95 (3 H, m). The yields were ca. 80%.

General procedure for the Stille coupling of the iodo compounds with 5-tributylstannylisoxazoles. 2-Iodophenyl ester (1 mmol), $Pd_2(dba)_3$ (0.05 mmol, 22 mg) and $AsPh_3$ (0.2 mmol, 61 mg) were stirred for 0.5 h in dry dioxane (5 ml). The stannyl compound (1.3 mmol) in dioxane (2 ml) was added and the temperature was raised to 50°C. The reaction was followed by analytical TLC. The reaction time for the 3-alkoxy derivatives was ca. 24 h. The 3-phenylisoxazole derivatives required longer reaction time, ca. 48 h. The solution was filtered through a thin layer of silica gel, evaporated *in vacuo* and the residue was washed with petroleum to remove stannyl compounds. The isoxazole was filtered off and recrystallized from methanol or ethanol.

3-Phenyl-5-(2-benzoyloxyphenyl)isoxazole **2a**, m.p. 122–124°C from methanol, yield 71%. ^{1}H NMR ($CDCl_3$): δ 6.81 (1 H, s), 7.3–7.8 (11 H, m), 8.06 (1 H, dd, J = 7.7 and 1.8 Hz), 8.30 (2 H, dt, J = 7.0 and 1.6 Hz). MS: *m/z* 341 (M^+), 221, 149, 105 (100%), 77.

3-Phenyl-5-(2-acetoxyphenyl)isoxazole **2b**, m.p. 88–89°C from methanol, yield 89%. ^{1}H NMR ($CDCl_3$): δ 2.43 (3 H, s), 6.85 (1 H, s), 7.24 (1 H, d, J = 6.5 Hz), 7.3–7.6 (5 H, m), 7.85 (2 H, m), 7.94 (1 H, dd, J = 7.6 and 1.9 Hz). MS: *m/z* 279 (M^+, weak), 237 (100%), 117, 69.

3-Methoxy-5-(2-benzoyloxyphenyl)isoxazole **2c**, m.p. 73–75°C from methanol–water, yield 53%. ^{1}H NMR ($CDCl_3$): δ 3.95 (3 H, s), 6.11 (1 H, s), 7.1–7.8 (6 H, m), 7.98 (1 H, dd, J = 7.8 and 2.0 Hz), 8.24 (2 H, ddd, J = 7.2, 2.0 and 1.9 Hz). MS: *m/z* 297 (M^+, weak), 105 (100%), 77.

3-Methoxy-5-(2-acetoxyphenyl)isoxazole **2d**, white crystals, m.p. 51°C from methanol–water, yield 73%. ^{1}H NMR ($CDCl_3$): δ 2.36 (3 H, s), 4.01 (3 H, s), 6.15 (1 H, s), 7.19 (1 H, dd, J = 8.1 and 1.3 Hz), 7.33 (1 H, td, J = 7.7 and 1.3 Hz), 7.45 (1 H, ddd, J = 8.1, 7.7 and 1.9 Hz), 7.85 (1 H, dd, J = 7.7 and 1.9 Hz). MS: *m/z* 233 (M^+), 199 (100%), 162, 148, 133, 121, 104.

3-Methoxy-5-[2-(4-acetoxy-3-methoxybenzoyloxy)phenyl]-isoxazole **2e**, greyish crystals, m.p. 134–136°C from methanol–water, yield 86%. ^{1}H NMR ($CDCl_3$): δ 2.37 (3 H, s), 3.93 (3 H, s), 3.95 (3 H, s), 6.10 (1 H, s), 7.22 (1 H, d, J = 8.2 Hz), 7.28 (1 H, dd, J = 8.0 and 1.3 Hz), 7.39 (1 H, ddd, J = 7.9, 7.8 and 1.3 Hz), 7.52 (1 H, ddd, J = 8.0, 7.8 and 1.6 Hz), 7.80 (1 H, d, J = 1.6 Hz), 7.88 (1 H, dd, J = 8.2 and 1.6 Hz), 7.95 (1 H, dd, J = 7.9 and 1.6 Hz). MS: *m/z* 383 (M^+, weak), 341, 293, 227, 193, 151 (100%), 123.

3-Ethoxy-5-[2-(4-acetoxy-3-methoxybenzoyloxy)phenyl]-isoxazole **2f**, white crystals, m.p. 164–166°C from ethanol, yield 84%. ^{1}H NMR ($CDCl_3$): δ 1.38 (3 H, t, J = 7.1 Hz), 2.36 (3 H, s), 3.92 (3 H, s), 4.29 (2 H, q, J = 7.1 Hz), 6.10 (1 H, s), 7.22 (1 H, d, J = 8.2 Hz), 7.28 (1 H, dd, J = 7.9 and 1.3 Hz), 7.39 (1 H, ddd, J = 7.7, 7.6 and 1.3 Hz), 7.51 (1 H, ddd, J = 7.9, 7.6 and 1.8 Hz), 7.80 (1 H, d, J = 1.9 Hz), 7.89 (1 H, dd, J = 8.2 and 1.9 Hz), 7.95 (1 H, dd, J = 7.7 and 1.8 Hz). MS: *m/z* 397 (M^+), 355, 193, 151.

Hydrogenations of **2a–f** were carried out over Raney-Ni in mixtures of ethanol, dioxane and/or water. The reduction was stopped when one equivalent of hydrogen had been absorbed. The solution was filtered through a thin layer of Celite to remove the catalyst and was evaporated. The crude products, **3–5**, were submitted directly to cyclisation. The reduction products from **2a,b** consisted principally of the enamines **3a,b**. ^{1}H NMR ($CDCl_3$), **3a**: δ 5.89 (1 H, s), 7.19–7.68 (11 H, m), 7.81 (1 H, dd, J = 7.4 and 2.0 Hz), 8.22 (2 H, ddd, J = 7.2, 2.0 and 1.3 Hz). **3b**: δ 2.29 (3 H, s), 5.89 (1 H, s), 7.09 (1 H, dd, J = 8.0 and 1.3 Hz), 7.29 (1 H, ddd, J = 7.6, 7.4 and 1.3 Hz), 7.38–7.63 (6 H, m), 7.71 (1 H, dd, J = 7.6 and 1.8 Hz).

3-Benzoyl-2-phenylchromone **5a**. The crude reduction product from **2a** (1 mmol) was heated in DMSO (5 ml) at 150°C for 3 h. Ether (50 ml) was added and the solution was washed twice with water (5 ml). The organic phase was dried over $MgSO_4$ and evaporated *in vacuo* to give **5a**, crude yield, 251 mg, 77%, contaminated by small amounts of **6**. ^{1}H NMR ($CDCl_3$): δ 7.3–7.6 (10 H, m), 7.72–7.82 (1 H, m), 7.93 (2 H, m), 8.27 (1 H, dd, J = 8.1 and 1.8 Hz). MS: *m/z* 326 (M^+), 325, 324, 298, 297 (100%), 249, 129, 105, 77.

3-Benzoyl-2-methylchromone **5b** *and flavone* **6**. The crude reduction product from **2b**, (0.2 mmol) was heated in acetic acid (2 ml) saturated with NaOAc at 110°C for 3 h. Water (2 ml) was added and the solution extracted three times with diethyl ether (10 ml). The organic phase was dried over $MgSO_4$, filtered and evaporated. The residue was purified by preparative TLC to give a fraction (27 mg) consisting of **5b** and **6** in a ratio of 4:1. We did not succeed in separating the two compounds. ^1H NMR ($CDCl_3$), **5b**: δ 2.46 (3 H, s), 7.4–7.8 (6 H, m), 7.92 (2 H, d, $J = 7.0$ Hz), 8.26 (1 H, dd, $J = 8.1$ and 1.8 Hz).

3-Carbamoyl-2-phenylchromone **5c**. The crude reduction product **3,4,5c** from **2c** (1 mmol) was heated to ca. 100°C for 1 h and chloroform was added to precipitate the amide **5c** as white crystals, m.p. 251–254°C. The filtrate, which contained some uncyclized product, was evaporated and the residue cyclized as described for **2b** to give an additional amount of **5c**, total yield 212 mg, 83%. ^1H NMR (DMSO), **5c**: δ 3.85 (NH_2, br s), 7.14 (H-8, d, $J = 7.1$ Hz), 7.24 (H-6, t, $J = 7.6$ Hz), 7.48 (H-7, dd, $J = 7.6$ and 7.1 Hz), 8.02 (H-5, d, $J = 7.6$ Hz). ^{13}C NMR (DMSO): δ 98.1, 116.7, 122.9, 125.3, 125.7, 127.8, 128.0, 130.0, 133.8, 141.8, 152.5, 166.5, 173.8, 195.4. MS: *m/z* 265 (M^+), 264, 236, 188, 121.

2-Methyl-3-carbamoylchromone **5d**, was prepared from the crude reduction product **3,4,5d** (1 mmol) as described for **5c**, yield 181 mg, 89%, m.p. 233°C. ^{13}C NMR ($CDCl_3$), **5d**: δ 33.1, 100.0, 116.5, 123.2, 125.6, 126.7, 133.8, 152.4, 167.8, 176.6, 200.4. MS: 203 (M^+), 188, 160, 132, 121, 104, 92, 77. IR (KBr): 3200, 3075, 1635, 1590, 1560 cm^{-1}.

2-(4-Acetoxy-3-methoxyphenyl)-3-carbamoylchromone **5e**, was obtained according to the procedure described for **5c**. The yield was 329 mg, 93%, m.p. 201–205°C. ^1H NMR (DMSO): δ 2.28 (3 H, s), 3.77 (3 H, s), 7.0–7.2 (2 H, m), 7.25 (1 H, s), 7.3–7.5 (2 H, m), 7.71 (1 H, dd, $J = 8.2$ and 7.9 Hz), 7.91 (1 H, d, $J = 7.7$ Hz). ^{13}C NMR (DMSO): δ 20.7, 56.1, 98.2, 112.2, 116.7, 121.1, 122.3, 123.0, 125.3, 125.8, 133.8, 140.5, 141.4, 150.4, 152.6, 166.5, 168.7, 173.9, 194.3. MS: *m/z* 353 (M^+), 312, 311 (100%), 294, 188, 151, 121.

2-(4-Hydroxy-3-methoxyphenyl)-3-carbamoylchromone **5f**, was obtained by heating the crude product **3,4,5f**, obtained by catalytic reduction of **2f** (1 mmol), in acetic acid (7 ml) saturated with NaOAc at 110°C for 9 h. Water (10 ml) was added and the mixture was extracted three times with diethyl ether (25 ml). The organic phase was dried over $MgSO_4$ to give **5f**, 42%, m.p. 215–216°C. ^1H NMR ($CDCl_3$): δ 3.77 (3 H, s), 6.76 (1 H, d, $J = 8.3$ Hz), 7.15 (1 H, dd, $J = 8.2$ and 1.8 Hz), 7.25 (1 H, s), 7.35–7.49 (2 H, m), 7.70 (1 H, ddd, $J = 8.3$, 7.0 and 1.3 Hz), 7.93 (1 H, d, $J = 8.0$ Hz), 8.62 (NH_2, br s), 9.73 (OH, br s). MS: *m/z* 311 (M^+, 100%).

3,4-Di(tert-*butyldimethylsilyloxy)benzaldehyde* **7** *and the oxime* **8**. To 3,4-dihydroxybenzaldehyde (5.0 g, 36.5 mmol) and *tert*-butyldimethylchlorosilane (13.0 g, 87 mmol) in dry acetonitrile (20 ml) was slowly added triethylamine (9.0 g, 90 mmol) dissolved in acetonitrile (10 ml) with stirring. The mixture was heated under reflux for 6.5 h. Most of the solvent was evaporated off *in vacuo*, chloroform (100 ml) was added and the mixture was washed with water (2 × 25 ml). The organic phase was dried over $MgSO_4$, filtered and evaporated to give crude **7** as a brown oil, 13.7 g, which was sufficiently pure for the oximation. ^1H NMR ($CDCl_3$) **7**: δ 0.20 (6 H, s), 0.24 (6 H, s), 0.97 (18 H, s), 6.92 (1 H, d, $J = 9$ Hz), 7.30 (1 H, s), 7.35 (1 H, d, $J = 9$ Hz), 9.79 (1 H, s). Crude **7** was suspended in CH_3OH–H_2O (9:1, 50 ml) and triethylamine (6.5 g, 65 mmol) and hydroxylamine hydrochloride (2.9 g, 41 mmol) dissolved in CH_3OH–H_2O (9:1, 45 ml) were added and the mixture was stirred for 25 h. Most of the CH_3OH was evaporated off *in vacuo*, water (100 ml) was added and the oily oxime extracted with chloroform. The organic phase was dried over $MgSO_4$ and evaporated *in vacuo* to give a crystalline mass, which was recrystallized from hexane, **8**, m.p. 103–104°C, 8.6 g, 62%. ^1H NMR ($CDCl_3$): δ 0.19 (12 H, s), 0.97 (18 H, s), 6.81 (1 H, d, $J = 8$ Hz), 6.92 (1 H, dd, $J = 8$ and 2 Hz), 7.09 (1 H, d, $J = 2$ Hz), 8.01 (1 H, s), 8.44 (1 H, br s).

3-[3,4-Di(tert-*butyldimethylsilyloxy)phenyl]-5-tributylstannylisoxazole* **9**. To the oxime **8** (2.0 g, 5.3 mmol) in ethyl acetate (5 ml) were added potassium hydrogencarbonate (1.0 g), one drop of water, tributylstannylacetylene (1.1 g, 3.6 mmol) and NCS (0.71 g, 5.3 mmol) and the mixture was stirred for 24 h at 25°C then washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was chromatographed on silica (petroleum–EtOAc, 2.5%) to give **9** as an oil, 1.7 g, 48%. A second fraction of slightly impure **9**, 0.55 g (15%) was also obtained. ^1H NMR ($CDCl_3$): δ 0.20 (6 H, s), 0.22 (6 H, s), 0.90 (9 H, t, $J = 7.5$ Hz), 0.98 (9 H, s), 0.99 (9 H, s), 1.18 (6 H, t, $J = 9$ Hz), 1.25–1.70 (12 H, m), 6.51 (1 H, s), 6.83 (1 H, d, $J = 8.5$ Hz), 7.20 (1 H, dd, $J = 8.5$ and 1 Hz), 7.33 (1 H, d, $J = 1$ Hz).

3-[2,4-Di(tert-*butyldimethylsilyloxy)phenyl]-5-tributylstannylisoxazole* was obtained as an oil in a yield of 57% from 2,4-di(*tert*-butyldimethylsilyloxy)benzaldehyde oxime[1b] according to the procedure described for **9**. ^1H NMR ($CDCl_3$): δ 0.13 (6 H, s), 0.19 (6 H, s), 0.90 (9 H, s), 0.97 (9 H, s), 0.75–1.6 (27 H, m), 6.39 (1 H, d, $J = 2.3$ Hz), 6.56 (1 H, dd, $J = 2.3$ and 8.5 Hz), 6.71 (1 H, s), 7.59 (1 H, d, $J = 8.5$ Hz).

3-[3,4-Di(tert-*butyldimethylsilyloxy)phenyl]-5-(2-hydroxyphenyl)isoxazole* **10a**. 2-Iodophenol (58 mg, 0.26 mmol), $Pd_2(dba)_3$ (12 mg, 0.013 mmol) and triphenylarsine (16 mg, 0.052 mmol) was stirred for ca. 10 min in dry dioxane (2 ml) under N_2. Compound **9** (217 mg,

0.31 mmol in dioxane, 1 ml) was injected and the mixture was stirred under N_2 for 24 h at 50°C. The suspension was filtered through Celite, washed with hot acetonitrile and evaporated *in vacuo*. The residue was recrystallized from acetonitrile to give **10a**, 97 mg, 63%, m.p. 216–217°C. Chromatographic purification of the mother liquor by TLC (SiO_2, CH_2Cl_2) gave a second crop of impure **10a**, ca. 40 mg. ^{1}H NMR ($CDCl_3$): δ 0.24 (12 H, s), 1.00 (18 H, s), 6.72 (1 H, s, OH), 6.83 (1 H, s), 6.90 (1 H, d, J = 8.5 Hz), 7.00 (1 H, d, J = 7.5 Hz), 7.01 (1 H, t, J = 7.5 Hz), 7.28 (1 H, dd, J = 8.5 and 2 Hz), 7.29 (1 H, td, J = 7.7 and 2 Hz), 7.38 (1 H, d, J = 2 Hz), 7.77 (1 H, dd, J = 7.7 and 2 Hz). MS: m/z 497.8 (M^+), 440.7 ($M^+ - t$-Bu), 235.6.

3-[3,4-Di(tert-*butyldimethylsilyloxy)phenyl]-5-(2,4-dihydroxyphenyl)isoxazole* **10b** was prepared from **9** and 4-iodoresorcinol[9] as described for **10a**. The crude residue was chromatographed (SiO_2; $CHCl_3$–MeOH 12:1) to give **10b**, brownish crystals, yield 27%, m.p. 190–193°C. ^{1}H NMR ($CDCl_3$): δ 0.23 (12 H, s), 1.00 (18 H, s), 6.30 (1 H, s), 6.33 (1 H, dd, J = 7.5 and 2 Hz), 6.77 (1 H, d, J = 8.3 Hz), 6.84 (1 H, s), 7.16 (1 H, dd, J = 8.3 and 2 Hz), 7.22 (1 H, d, J = 2 Hz), 7.58 (1 H, dd, J = 7.5 and 2 Hz). MS: m/z 513.4 (M^+, <1%), 456 ($M^+ - t$-Bu), 404, 361, 359, 305, 303, 247, 152.

3-[3,4-Di(tert-*butyldimethylsilyloxy)phenyl]-5-(2,6-dihydroxyphenyl)isoxazole* **10c**. 2-Iodoresorcinol,[9] (123 mg, 0.52 mmol), $PdCl_2$ (3.5 mg, 0.02 mmol) and **9** (278 mg, 0.4 mmol) were heated in dry dioxane (5 ml) at 110°C under N_2 for 2.25 h. The mixture was filtered through Celite, washed with dioxane and the filtrate evaporated *in vacuo*. The residue was chromatographed on a small column (SiO_2; $CHCl_3$, 0–5% CH_3OH) to give **10c**, contaminated by Bu_3SnI, which was removed by washing the product with petroleum. Compound **10c** is a greyish solid, 113 mg, 55%, m.p. 208–212°C (from petroleum). ^{1}H NMR ($CDCl_3$): δ 0.20 (12 H, s), 1.00 (18 H, s), 6.56 (2 H, d, J = 8 Hz), 6.92 (1 H, d, J = 8 Hz), 6.94 (2 H, br s, OH), 7.10 (1 H, s), 7.16 (1 H, t, J = 8 Hz), 7.30 (1 H, dd, J = 8 and 2 Hz), 7.41 (1 H, d, J = 2 Hz). MS: m/z 513.5 (M^+, 4%), 456.4 ($M^+ - t$-Bu), 306.

3-[3,4-Di(tert-*butyldimethylsilyloxy)phenyl]-5-(2,6-dihydroxy-4-methoxyphenyl)isoxazole* **10d** was prepared from **9** and 2-iodo-4-methoxyresorcinol,[9] as described for **10c**. The crude product was chromatographed (SiO_2; CH_2Cl_2–MeOH 30:1) to give **10d**, 33%. ^{1}H NMR ($CDCl_3$): δ 0.23 (12 H, s), 1.00 (18 H, s), 3.76 (3 H, s), 6.14 (2 H, s), 6.91 (1 H, d, J = 8 Hz), 7.29 (1 H, dd, J = 8 and 2 Hz), 7.40 (1 H, d, J = 2 Hz), 7.7 (2 H, br s). MS: m/z 543.3 (M^+), 486.3. It was not possible to crystallize the compound.

3-[3,4-Di(tert-*butyldimethylsilyloxy)phenyl]-5-(2,4,6-trihydroxyphenyl)isoxazole* **10e** was prepared from **9** and iodophloroglucinol,[9] as described for **10c**. The reaction time was 2 h at 110°C. The crude product was chromatographed (SiO_2; $CHCl_3$–MeOH 9:1) to give **10e**, 26% as a brown amorphous solid. ^{1}H NMR ($CDCl_3$–CD_3OD 9:1): δ 0.24 (12 H, s), 1.00 (18 H, s), 5.96 (2 H, s), 6.82 (1 H, s), 6.88 (1 H, d, J = 8 Hz), 7.31 (1 H, dd, J = 8 and 2.3 Hz), 7.38 (1 H, d, J = 2 Hz). MS: m/z 529.7 (M^+), 514.7, 471.8. It was not possible to crystallize the compound.

3',4'-Dihydroxyflavone **11a**. The isoxazole **10a** (136 mg) in dioxane–water was reduced over Raney-Ni in the presence of H_3BO_3. The reaction mixture was filtered through a layer of Celite, and the filtrate evaporated *in vacuo*. The product was heated in refluxing HOAc (5 ml) and conc. HCl (0.3 ml) for 2 h. The solvent was evaporated off *in vacuo* and the residue was purified by TLC (SiO_2; CH_2Cl_2–MeOH 30:1 and Et_2O–MeOH 10:1) to give **11a**, 35 mg, 51%, as a semisolid with UV absorptions identical with lit.[11] data. ^{1}H NMR ($CDCl_3$): δ 6.69 (1 H, s), 6.93 (1 H, d, J = 8 Hz), 7.37 (1 H, d, J = 2 Hz), 7.40 (1 H, dt, J = 1.5 and 8 Hz), 7.44 (1 H, dd, J = 2 and 8 Hz), 7.53 (1 H, dd, J = 1.5 and 8 Hz), 7.68 (1 H, dt, J = 1.75 and 8 Hz), 8.16 (1 H, dd, J = 1.75 and 7 Hz).

3-(3,4-Dihydroxyphenyl)-5-(2,4-dihydroxyphenyl)isoxazole **10f** *and 3',4',7-trihydroxyflavone* **11b**. The silyl groups were removed by heating **10b** (240 mg) in HOAc (6 ml) with KF (270 mg) and NaOAc (170 mg) under N_2 for 2 h at 110°C. The solvent was evaporated off *in vacuo*, water was added and the suspension was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$ and evaporated to give **10f**, which was purified by TLC (SiO_2; $CHCl_3$–MeOH 6:1), 130 mg, brownish crystals, 98%, m.p. 256–260°C. A sample was recrystallized from ethanol–water, 10:1, m.p. 271–275°C. ^{1}H NMR ($CDCl_3$–CD_3OD 3:1): δ 6.39 (1 H, s), 6.42 (1 H, dd, J = 7.5 and 2 Hz), 6.86 (1 H, d, J = 8 Hz), 6.94 (1 H, s), 7.16 (1 H, dd, J = 8 and 2 Hz), 7.28 (1 H, d, J = 2 Hz), 7.66 (1 H, dd, J = 7.2 and 1 Hz). MS: m/z 285 (M^+), 283, 281, 270, 149, 137. The isoxazole **10f** was hydrogenated over Raney-Ni in methanol, and the reaction mixture was filtered through a thin layer of Celite and concentrated *in vacuo*. The residue was cyclized by being heated in glacial acetic acid (4 ml) and a few drops of conc. H_2SO_4 at 120°C for 2.5 h. Half of the solvent was evaporated off and the flavone **11b** was precipitated by adding double the volume of water and the mixture was kept in the refrigerator for 2 days. The precipitate was filtered, washed with water and dissolved in methanol directly from the filter. Evaporation of the methanol gave **11b**, 80%, m.p. 318–322°C (decomp.). A sample was recrystallized for analytical purposes from ethanol–water 10:1, m.p. 325–330°C, (decomp.) lit.[12] 331–332°C, brownish crystals, which decomposed slowly. ^{1}H NMR ($CDCl_3$–CD_3OD 3:1): δ 6.67 (1 H, s), 6.83–6.94 (3 H, m), 7.35 (1 H, dd, J = 8 and 2 Hz), 7.37 (1 H, s), 7.95 (1 H, d, J = 9 Hz).

3-(3,4-Dihydroxyphenyl)-5-(2,6-dihydroxyphenyl)isoxazole **10g** *and 3',4',5-trihydroxyflavone* **11c**. The desilylation of **10c** to give **10g** was carried out as described for **10b**. The crude **10g** was purified by TLC (SiO_2; $CHCl_3$–CH_3OH 6:1), brownish crystals, m.p. 236–238 °C. The chromatographic yield was 90%. ^1H NMR ($CDCl_3$–CD_3OD 3:1): δ 6.47 (2 H, d, J = 8 Hz), 6.87 (1 H, d, J = 8 Hz), 7.02 (1 H, s), 7.08 (1 H, t, J = 8 Hz), 7.19 (1 H, dd, J = 8 and 2 Hz), 7.31 (1 H, d, J = 2 Hz). Isoxazoline **10g** was reduced and cyclized to **11c** according to the procedures described for **10f**. The precipitated flavone **11c** was dissolved in methanol–ethyl acetate and evaporation of the solvent gave 84% of a brownish solid, decomp. ca. 300 °C. ^1H NMR (CD_3OD): δ 6.69 (1 H, s), 6.78 (1 H, dd, J = 8 and 2 Hz), 6.92 (1 H, d, J = 8 Hz), 7.08 (1 H, dd, J = 8 and 2 Hz), 7.43 (1 H, s), 7.45 (1 H, dd, J = 8 and 2 Hz), 7.61 (1 H, t, J = 8 Hz). MS: m/z 270 (M^+), 252, 149, 137, 134. UV (CH_3OH); λ_{max} 252, 351 nm.

3',4',5-Trihydroxy-7-methoxyflavone (luteolin 7-methyl ether) **11d** was obtained in a yield of 22%, slightly impure, from **10d** according to the procedure described for **11a**. Its UV spectrum agreed with published data.[13] ^1H NMR ($CDCl_3$): δ 3.90 (3 H, s), 6.36 (1 H, d, J = 2 Hz), 6.59 (1 H, s), 6.65 (1 H, d, J = 2 Hz), 6.92 (1 H, d, J = 8 Hz), 7.4–7.5 (2 H, m).

3',4',5,7-Tetrahydroxyflavone (luteolin) **11e** was obtained as a brown solid in a yield of 11% from **10e** according to the procedure described for **11a**. The crude product was purified by TLC (SiO_2; Et_2O–MeOH 10:1). The spectral data agreed with the lit.[11] data.

Compound **13** was obtained as a by-product by dimerization of **9** from the Heck–Stille coupling of 2,6-dihydroxy-substituted iodobenzenes with $PdCl_2$ as catalyst. It eluted with the solvent front on the column, m.p. 201–209 °C (from methanol–dichloromethane). ^1H NMR ($CDCl_3$): δ 0.22 (24 H, s), 0.98 (36 H, s), 6.91 (2 H, d, J = 8 Hz), 6.97 (2 H, s), 7.29 (2 H, dd, J = 8 and 2 Hz), 7.36 (2 H, d, J = 2 Hz).

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