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Stereoselective Synthesis of Isoflavonoids. (*R*)- and (*S*)-Isoflavans

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Abstract: α-Benzylation of (+)- and (-)-N-phenylacetyl imidazolidinones with 2-*O*-methoxymethylbenzyl bromides, followed by reductive removal of the chiral auxiliary and cyclization, afforded oxygenated isoflavans in excellent enantiomeric excess and yield.

The isoflavanoids represents a relatively large group of naturally occurring C_6•C_3•C_6-type secondary metabolites displaying a distinct range of physiological activity[1] and structural diversity.[2] In the non-planar analogues, *viz.* isoflavanones, isoflavan-4-ols, pterocarpans and rotenoids, chirality is confined to two of the carbon atoms of the chroman heterocycle. Among the various synthetic routes to these compounds only one has truly addressed the issue of stereoselection at any of the stereocentres. This method involved the synthesis of pterocarpans *via* asymmetric induction in reactions of 2*H*-chromenes with 1,4-benzoquinones using chiral Ti(IV) complexes.[3] The second attempt at selectivity was based on the resolution of isoflavan-4-ols during the preparation of pterocarpans.[4] Since the configuration at C-3 of the 3-phenylchroman framework would dictate the stereochemistry at C-2 or C-4, a protocol of controlling the former stereocentre would facilitate the stereoselective synthesis of the full range of chiral isoflavonoids. We thus selected isoflavans as targets[5] and opted for a protocol of stereoselective[6] α-benzylation of phenylacetic acid derivatives, subsequent reductive removal of the chiral auxiliary and cyclization, for construction of the isoflavan backbone. Results relevant to the enantioselective synthesis of isoflavans displaying the typical aromatic oxygenation patterns of naturally occurring analogues are discussed here.

Owing to the efficiency of the asymmetric alkylation reactions of chiral imide enolates,[7] the commercially available *R*-(+)- and *S*-(-)-4-benzyl-2-oxazolidinones **1** and **2** were initially considered as chiral auxiliaries in the benzylation reactions. Thus, treatment of the lithio derivative of the *R*-(+)-4-benzyl-2-oxazolidinone **1** with phenylacetyl chloride[8] afforded the 3-phenylacetyl-2-oxazolidinone **3** in 74% yield (Scheme 1). Imide **3** was reacted with lithium isopropylcyclohexylamide (LICA) and the resultant enolate trapped with benzyl bromide in the presence of hexamethylphosphoric triamide (HMPA) to give the 3-(2′,3′-diphenyl)propionyl-2-oxazolidinone **4** in low yield (20%) and diastereoselectivity (20%). Such poor selec-

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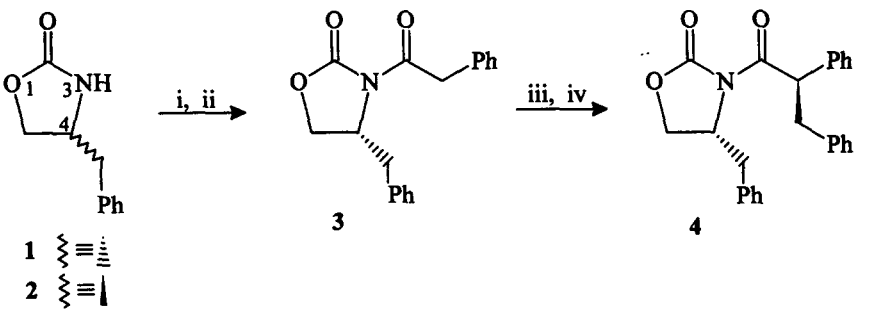
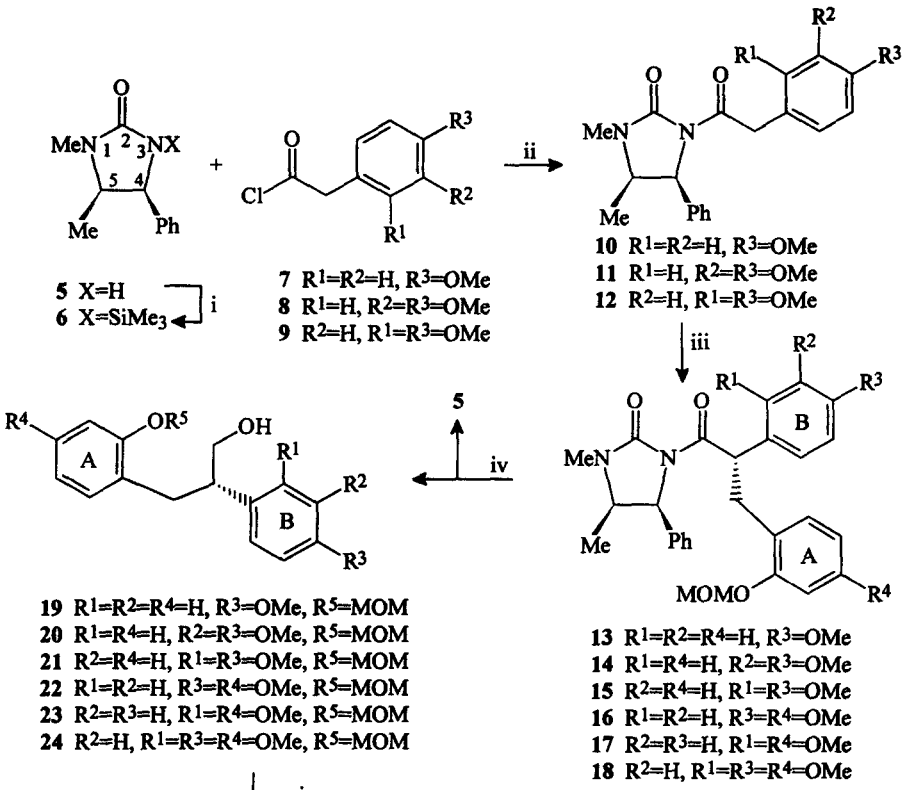


Scheme 1. *Reagents and conditions*: i, oxazolidinone **1**, *n*-BuLi, Ph_3CH in THF, -78°C; ii, $PhCH_2COCl$, -78°C; iii, LICA, THF, -78°C; iv, BnBr, HMPA, -78°C to -50°C

tivity presumably results from the presence of HMPA which effects dissociation of metal chelates and hence equilibration of the *E*- and *Z*-enolates of imide **3**.[9] In the absence of HMPA a diastereoselectivity of 99% was observed but the chemical yield could not be improved beyond 30%. Since trapping of the enolate of **3** with methyl iodide afforded the α-methyl analogue of **4** in less than 50% yield, and quenching of the same enolate with D_2O after 30 min. indicated an imide **3**/oxazolidinone **1** ratio of 2:1, the poor yield could not be attributed to steric reasons or to incomplete enolization but rather to decomposition of the enolate of **3** *via* phenylketene formation.

The intrinsic leaving group aptitude of the 2-oxazolidinone moiety prompted a switch of chiral auxiliaries to the (4*S*,5*R*)-(+)- and (4*R*,5*S*)-(-)-1,5-dimethyl-4-phenyl-2-imidazolidinones **5a** and **5b**[10-13] with poorer nucleofugal properties relative to **1** and **2**. The basicity of the imidazolidinones was decreased by utilizing them as trimethylsilyl ethers **6a** and **6b** in the acylation step using the phenylacetyl chlorides **7**, **8** and **9**. The ensuing N-acyl imidazolidinones **10-12** were then alkylated with the appropriate 2-*O*-methoxymethylbenzyl bromides[5] (Scheme 2) in good to excellent yields with only one diastereomer detectable by ^1H NMR (de, >99%). Optimum reproducibility and yields for this step were obtained in a dichloromethane (DCM)-THF (2:3) solvent system. The lower yields observed for compounds **16-18** (60-70% compared to 84-96% for **13-15**) are attributable to the decreased stability of the 2,4-dioxybenzyl bromides compared to the *o*-mono-oxy analogues. Removal of the chiral auxiliary was effected by reductive deamination using $LiAlH_4$[14] in THF for imides **13-15** and a saturated solution of $LiBH_4$[15] in ether for analogues **16-18** to give the 2,3- diarylpropan-1-ols **19-24**. Deprotection with 3M HCl in methanol gave the phenolic propan-1-ols **19-24** (R^5=H) in quantitative yields. Cyclization under Mitsunobu conditions,[16] *i.e.* triphenyl phosphine - diethyl azodicarboxylate (DEAD) in THF, finally afforded the target isoflavans **25-30** in excellent yields and in nearly enantiopure form (ee >96 — >99%). E.e. values for the isoflavans **29** and



Scheme 2. *Reagents and conditions*: i, BuLi, Ph_3CH, THF, 0°C; then Me_3SiCl, -78°C → rt; ii, TBAF, MeCN, rt; iii, LICA (1.4 eq.), 2-*O*-methoxymethylbenzyl bromides (1.5. eq.), DCM-THF, -40°C; iv, $LiAlH_4$/THF for **13**, $LiBH_4/Et_2O$ for **14-18**; v, 3M HCl in MeOH, reflux; vi, Ph_3P (9 eq.), DEAD (4.5 eq.), THF, rt

5, 6, 10-30a = configuration shown
b = enantiomer

30 were determined by ^1H NMR using $Eu(hfc)_3$ and $Pr(hfc)_3$, respectively, as chiral shift reagents.Those for the remaining analogues **25-28** were assessed by HPLC using a chiral adenine glycoprotein column with 9-22% isopropanol in a pH 7 phosphate buffer as eluent.

The stereochemistry of the alkylation step of the acylimides **10-12** is explicable in terms of the preferential formation of a *Z*-enolate.[17] Approach of the electrophile is then directed to the face of the enolate opposite the 4-phenyl substituent of the imidazolidinone moiety. The observed stereoselection is in

accord with that reported by Evans *et al.*,[17] *i.e.* 4*S*- and 4*R*-*N*-acyloxazolidinones led to propanols exhibiting positive and negative $[\alpha]_D$ values, respectively. Thus, benzylation of the (4*S*,5*R*)-(+)-*N*-phenylacetylimidazolidinones **10a-12a** and the subsequent conversions afforded (+)-propanols **19a-24a** and the 3*S*-isoflavans **25a-30a**, and the (4*R*,5*S*)-(-)-*N*-phenyl-acetylimidazolidinones **10b-12b** the (-)-propanols **19b-24b** and the 3*R* series of isoflavans **25b-30b**. The signs of rotation of 7,4′-dimethoxy- and 7,2′,4′-trimethoxy-isoflavan **28a** (-12^0) and **30a** ($+9^0$), respectively, are in agreement with those of 3*S*-7,4′-dihydroxyisoflavan [(-)-equol (-12^0)][18] and 3*S*-(+)-7,2′-di-*O*-methylvestitol ($+9^0$).[19] Similar deductions were possible by comparison of the $[\alpha]_D$ values of 3*R*- and 3*S*-7,2′-di-*O*-methylvestitol, obtained *via* hydrogenolysis of (6a*R*,11a*R*)-(-)-homopterocarpin and (6a*S*,11a*S*)-(+)-medicarpin, respectively,[20] with those of synthetic analogues **30a** and **30b**.

Owing to the unpredictable effect of substitution pattern on the sign of the optical rotation of isoflavans, we used the chiroptical data of the authentic 3*R*- and 3*S*-vestitol derivatives (*vide supra*) to establish the absolute configuration at C-3 of the synthetic isoflavans **25-30**.[21,22] Thus, the CD spectra (Figure 1) of the 3*S*-isoflavans with oxygenation at both the A- and B-rings, *e.g.* **30a**, exhibit positive and negative Cotton effects (CE's) in the 240 and 270-280 nm regions, respectively, and conversely for the 3*R*-analogues, *e.g.* **30b**. The spectra (Figure 2) of the 7-deoxy 3*S*-isoflavans with mono-oxygenation at the B-ring, *e.g.* **25a**, exhibit negative CE's in both the 230-240 and 270-290 nm regions while those with disubstituted B-rings, *e.g.* **27a**, show an additional positive CE near 270 nm. CE's with opposite signs were observed for the 3*R*-series of compounds, *e.g.* **25b** and **27b**.

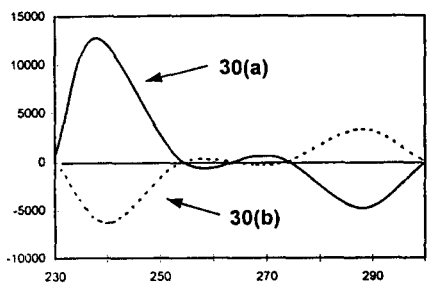


Fig 1: CD curves of the (*S*)-(**30a**) and (*R*)-vestitol derivatives (**30b**)

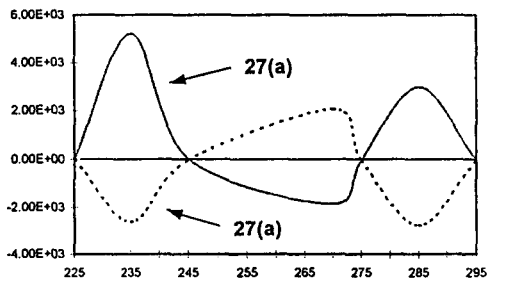


Fig 2: CD curves of the (*S*)-(**27a**) and (*R*)-(**27b**) A-ring deoxyisoflavans

We have thus developed the first direct and highly efficient enantioselective route towards isoflavans. The potential of this protocol in the chemistry of the isoflavonoids is evident and it should contribute in establishing chirality also at C-2 and C-4 of the 3-phenylchroman system in the full range of isoflavonoids. The CD data additionally provide a powerful probe to unequivocally establish the absolute configuration of the naturally occurring isoflavans.

EXPERIMENTAL

^{1}H NMR spectra were recorded at ambient temperature on a Bruker AM-300 spectrometer for solutions in $CDCl_3$ with solvent as internal standard. High and low resolution EI-mass spectra were obtained on a VG70-70E mass spectrometer. M.p.s. were measured on a Reichert hot-stage apparatus and are uncorrected. CD measurements were obtained for solutions in MeOH on a Jasco J-710 spectropolarimeter and optical rotations measured with a Bendix-NPL automatic polarimeter for solutions in $CHCl_3$. Thin layer chromatography (TLC) was performed on DC-Alufolien Kieselgel 60 F_{254} (0.25 mm) plates with visualisation by UV light and/or HCHO-H_2SO_4 spray. Preparative plates (PLC) [Kieselgel PF_{254} (1.0 mm) were air-dried and used without prior activation. Flash column chromatography (FCC) was on Merck Kieselgel 60 (230-400 mesh) under a positive pressure by means of compressed N_2. Mps refer to crystals obtained from Me_2CO.

The imidazolidinones **5a** and **5b**[10-13] and their *N*-trimethylsilylderivatives, **6a** and **6b**,[23] phenylacetyl chlorides 7-9[8] and the 2-*O*-methoxymethyl- and 2′-*O*-methoxymethyl-4-methoxy-benzyl bromides[5] were prepared according to standard literature procedures.

(*R*)-(+)-4-Benzyl-3-phenylacetyl-2-oxazolidinone 3

A soln. of (*R*)-4-benzyl-2-oxazolidinone **1** (450 mg, 2.54 mmol) and Ph_3CH (2 mg) in dry THF (4.8 ml) was stirred under N_2 at -78^{0}C. *n*-BuLi (1.0 eq., 1.59 ml) was added slowly until an orange-red colour persisted after which phenylacetyl chloride (2.69 mmol, 0.36 ml) was added dropwise and the temperature was left to rise to rt. A satd. soln. of $NaHCO_3$ (5.0 ml) was added, the mixture was stirred at rt for 30 min., extracted with DCM (3x15 ml), the combined organic phases dried (Na_2SO_4), evaporated to dryness and separated by PLC in hexane-EtOAc (65:35) to give the title compound **3** as white needles (450 mg, R_F 0.60), mp 76^{0}C (lit.[24] mp 73^{0}C).

(*R*)-(+)-4-Benzyl-3-(2′,3′-diphenyl)propionyl-2-oxazolidinone 4.

LICA (1.05 eq.) was prepared at -78^{0}C under N_2 by treatment of isopropyl-cyclohexylamine (1.75 mmol) with *n*-BuLi (1.75 mmol) in THF (2.0 ml). A soln. of **3** (50 mg) in dry THF (2.0 ml) was cooled to -78^{0}C and added to the LICA. After stirring for 30 min. at -78^{0}C, HMPA (3 eq.) and benzyl bromide (3 eq.) were added and the temperature was allowed to rise to -50^{0}C over 3 h. A satd. NH_4Cl soln. (5 ml) was added and the mixture was extracted with EtOAc (3x10 ml), the combined EtOAc layer was washed with satd. $NaHCO_3$ (5 ml), dried (Na_2SO_4), evaporated to dryness and separated by PLC in hexane-EtOAc (9:1) to give **4** as white needles (12 mg, R_F 0.30), mp 199^{0}C; $[\alpha]_D$ +190^0 (*c* 1.0); δ_H 7.46-7.41 (2xAr-H, m), 7.35-7.19 (11xAr-H, m), 6.95-6.89 (2xAr-H, m), 5.48 (2′-H, dd, J=6.0, 10.0 Hz), 4.60-4.51 (4-H, m), 4.01-3.98 (4-

CH$_2$Ph, m), 3.52 (3'-H, dd, J=10.0, 13.5 Hz), 3.06 (3'-H, dd, J=6.0, 13.5 Hz), 2.96 (5-H, dd, J=13.5, 3.5 Hz), 2.54 (5-H, dd, J=9.0, 13.5 Hz); m/z 385 (M^+, 39%) (Found: M^+, 385.1671. $C_{25}H_{23}O_3N$ requires M, 385.1678).

General procedure for preparation of *N*-arylacetyl-2-imidazolidinones 10-12

To a suspension of TBAF (30-85 mg) and 1,5-dimethyl-4-phenyl-3-trimethylsilyl-2-imidazolidinones **6a/b** (0.00967-0.015 ml) in CH_3CN (20-40 ml) was added the arylacetyl chlorides **7-9** (1.0 eq. rel. to **6a/b**) and the mixture was stirred at rt for 6-24 h, the solvent evaporated and the residue dissolved in DCM. The solution was washed with a satd. $NaHCO_3$ soln. (5.0 ml) and water (5.0 ml), dried (Na_2SO_4), the solvent evaporated and the mixture separated by FCC.

(+)-(4*S*,5*R*)- and (-)-(4*R*,5*S*)-1,5-*dimethyl*-4-*phenyl*-3-(4-*methoxyphenyl-acetyl*)-2-*imidazolidinone* **10a/b**, resp.: time 24, 6 h; yield, 75, 80%; R_F 0.24 [hexane-Me_2CO (8:2)]; $[\alpha]_D$ +57.8^0, -55.8^0 (*c* 1.0, 1.03); both white needles, mp 129^{0}C; δ_H 7.29-7.25 (3xAr-H, m), 7.18 [2,6-H(B), d, J=8.5 Hz], 7.07-7.04 (2xAr-H, m), 6.80 [3,5-H(B), d, J=8.5 Hz], 5.29 (4-H, d, J=8.5 Hz), 4.27 (s, *CH*$_2$Ar),

(+)-(4*S*,5*R*)- and (-)-(4*R*,5*S*)-1,5-*dimethyl*-4-*phenyl*-3-(3,4-*dimethoxyphenylacetyl*)-2-*imidazolidinone* **11a/b**, resp.: time, both 24 h; yield, 70, 75%; R_F 0.31 [hexane-Me_2CO (7:3)]; $[\alpha]_D$ +56.7^0, -56.2^0 (*c* 1.0, 1.0), both white needles, mp 117^{0}C; δ_H 7.27-7.25 (3xAr-H, m), 7.06-7.02 (2xAr-H, m), 6.85 [6-H(B), dd, J=2.5, 8.0 Hz], 6.80-6.75 [2-/5-H(B), 2nd order], 5.30 (4-H, d, J=8.5 Hz), 4.32, 4.23 (-*CH*$_2$Ar, both d, both J=15.0 Hz), 3.94-3.85 (5-H, m), 3.85, 3.77 (2xOMe, both s), 2.84 (N*Me*, s), 0.78 (5-CH_3, d, J=6.5 Hz); m/z 368 (M^+, 31%) (Found: M^+ 368.1731. $C_{21}H_{24}O_4N_2$ requires M 368.1736).

(+)-(4*S*,5*R*)- and (-)-(4*R*,5*S*)-1,5-*dimethyl*-4-*phenyl*-3-(2,4-*dimethoxyphenylacetyl*)-2-*imidazolidinone* **12a/b**, resp.: time, both 24 h; yield, 60, 63%; R_F 0.33 [hexane-Me_2CO (8:2)]; $[\alpha]_D$ +97.8^0, -91.2^0 (*c* 1.0, 1.06); both white needles, mp 120^{0}C; δ_H 7.33-7.22 (3xAr-H, m), 7.17-7.13 (2xAr-H, m), 6.97 [6-H(B), d, J=8.5 Hz], 6.39-6.35 [3,5-H(B), 2nd order], 5.31 (4-H, d, J=8.5 Hz), 4.31, 4.15 (-*CH*$_2$Ar, both d, both J=17.5 Hz), 3.99-3.87 (5-H, m), 3.75, 3.66 (2xOMe, both s), 2.85 (N*Me*, s), 0.81 (5-CH_3, d, J=6.5 Hz); m/z 368 (M^+, 24%) (Found: M^+ 368.1734. $C_{21}H_{24}O_4N_2$ requires M 368.1736).

General procedure for preparation of the *N*-(2',3'-biphenyl)propionyl-2-imidazolidinones 13-18

A soln. of the *N*-arylacetyl-2-imidazolidinone **10-12** (1.62 mmol) in dry THF (5.0 ml) was added at -78^{0}C to a THF soln. of LICA (2.3 mmol) (*vide supra*), the temp. was allowed to rise to -50^{0}C after which a soln. of the oxygenated benzylbromides[5] in DCM (2.5 mmol) was added and the mixture stirred for 30-90 min. at -40^{0}C. A satd. NH_4Cl soln. (3.0 ml) was added and the mixture was extracted with EtOAc (3x10 ml), the combined layers were washed with satd. $NaHCO_3$ (10 ml), water (10 ml), dried (Na_2SO_4), the solvent was evaporated and the mixture separated by PLC or FCC.

(+)-(4*S*,5*R*)- and (-)-(4*R*,5*S*)-1,5-*dimethyl*-4-*phenyl*-3-[2′-(4-*methoxyphenyl*)-3′-(2-*O*-*methoxymethyl*-*phenyl*)]*propionyl*-2-*imidazolidinones* **13a/b**, resp.: time, both 1 h; yield, 84, 96%; R_F 0.46 [hexane-EtOAc-Me_2CO (7:1.5:1.5)]; $[\alpha]_D$ +119°, -116° (*c* 1.19, 1.08); both yellow oils; δ_H 7.39 [2,6-H(B), d, J=8.5 Hz], 7.22-7.14 (3xAr-H, m), 7.11-7.04 (1xAr-H, m), 6.99 (1xAr-H, dd, J=1.5, 8.0 Hz), 6.89-6.79 (3xAr-H, m), 6.81 [3,5-H(B), d, J=8.5 Hz], 6.68 (1xAr-H, ddd, J=1.5, 7.0, 7.0 Hz), 5.74 [-C*H*(Bn)Ar, dd, J=5.5, 9.5 Hz], 5.15 (4-H, d, J=9.0 Hz), 5.13, 5.06 (-OCH_2OMe, both d, both J=7.0 Hz), 3.76 (OMe, s), 3.74-3.64 (5-H, m), 3.45 (-OCH_2O*Me*, s), 3.31, 2.94 (-CH_2Ar, both dd, J=9.5, 13.5 and 5.5, 13.5 Hz), 2.69 (N*Me*, s), 0.66 (5-CH_3, d, J=6.0 Hz); m/z 488 (M^+, 8%) (Found: M^+ 488.2303. $C_{29}H_{32}O_5N_2$ requires M 488.2311).

(+)-(4*S*,5*R*)- and (-)-(4*R*,5*S*)-1,5-*dimethyl*-4-*phenyl*-3-[2′-(3,4-*dimethoxyphenyl*)-3′-(2-*O*-*methoxymethylphenyl*)]*propionyl*-2-*imidazolidinones* **14a/b**, resp.: time, both 2 h; yield, 95, 87%, R_F 0.33 [hexane-EtOAc-Me_2CO (8:1:1)]; $[\alpha]_D$ +112°, -105° (*c* 0.95, 0.99); both yellow oils; δ_H 7.23-7.15 (3xAr-H, m), 7.12-6.80 (7xAr-H, m), 6.76 [5-H(B), d, J=8.0 Hz], 6.68 [4-H(A) or 5-H(A), ddd, J=1.5, 7.5, 7.5 Hz], 5.73 [-C*H*(Bn)Ar, dd, J=5.5, 9.5 Hz), 5.17 (4-H, d, J=8.5 Hz), 5.14, 5.07 (-OCH_2OMe, both d, both J=6.5 Hz), 3.85, 3.83 (2xOMe, both s), 3.76-3.65 (5-H, m), 3.45 (-OCH_2O*Me*, s), 3.31, 2.95 (-CH_2Ar, both dd, J=9.0, 13.0 and 5.5, 13.0 Hz), 2.70 (N*Me*, s), 0.67 (5-CH_3, d, J=6.5 Hz); m/z 518 (M^+, 27%) (Found: M^+ 518.2422. $C_{30}H_{34}O_6N_2$ requires M 518.2417).

(+)-(4*S*,5*R*)- and (-)-(4*R*,5*S*)-1,5-*dimethyl*-4-*phenyl*-3-[2′-(2,4-*dimethoxyphenyl*)-3′-(2-*O*-*methoxy*-*methylphenyl*)]*propionyl*-2-*imidazolidinones* **15a/b**, resp.: time, 1.5, 2.0 h; yield, both 92%; R_F 0.40 [hexane-Me_2CO (7:3)]; $[\alpha]_D$ +108°, -131° (*c* 1.0, 1.01); both white needles, mp 95°C; δ_H 7.30-7.16 (6xAr-H, m), 7.09-6.87 (4xAr-H, m), 6.73 [4- or 5-H(A), ddd, J=1.5, 7.5, 7.5 Hz], 6.41-6.37 (2xAr-H, m), 6.00 [-C*H*(Bn)Ar, dd, J=6.5, 8.5 Hz], 5.21 (4-H, d, J=9.0 Hz), 5.08, 5.00 (-OCH_2OMe, both d, both J=7.0 Hz), 3.75, 3.70 (2xOMe, both s), 3.41 (-OCH_2O*Me*, s), 3.21, 2.86 (-CH_2Ar, both dd, J=8.5, 13.5 and 6.5, 13.5 Hz), 2.70 (N*Me*, s), 0.69 (5-CH_3, d, J=7.0 Hz); m/z 518 (M^+, 3%) (Found: M^+ 518.2421. $C_{30}H_{34}O_6N_2$ requires M 518.2417).

(+)-(4*S*,5*R*)- and (-)-(4*R*,5*S*)-1,5-*dimethyl*-4-*phenyl*-3-[2′-(4-*methoxyphenyl*)-3′-(4-*methoxy*-2-*O*-*methoxymethylphenyl*)]*propionyl*-2-*imidazolidinones* **16a/b**, resp.: time, 16, 18 h (both at -30°C); yield, both 65%; R_F 0.53 [hexane-EtOAc-Me_2CO (7:2.5:0.5, x3)]; $[\alpha]_D$ +183°, -110° (*c* 1.0, 1.0); both white needles, mp 100°C; δ_H 7.42 [2,6-H(B), d, J=9.0 Hz], 7.26-7.15 (3xAr-H, m), 6.86-6.80 (4xAr-H, m), 6.78 [6-H(A), d, J=8.5 Hz], 6.63 [3-H(A), d, J=2.6 Hz], 6.23 [5-H(A), dd, J=2.5, 8.5 Hz], 5.73 [C*H*(Bn)Ar, dd, J=5.5, 10.0 Hz], 5.17 (4-H, d, J=8.5 Hz), 5.13, 5.05 (-OCH_2OMe, both d, both J=6.5 Hz), 3.77 (2xOMe, s), 3.71-3.65 (5-H, m), 3.46 (-OCH_2O*Me*, s), 3.25, 2.88 (-CH_2Ar, both dd, J=10.0, 13.5 and 5.0, 13.5 Hz), 2.71 (N*Me*, s), 0.67 (5-CH_3, d, J=7.0 Hz); m/z 519 (M^+, 19%) (Found: M^+ 519.2481. $C_{30}H_{34}O_6N_2$ requires M 519.2495).

(+)-(4*S*,5*R*)- and (-)-(4*R*,5*S*)-1,5-*dimethyl*-4-*phenyl*-3-[2'-(2-*methoxyphenyl*)-3'-(4-*methoxy*-2-*O*-*methoxymethylphenyl*)]*propionyl*-2-*imidazolidinone* **17a/b**, resp.: time, both 18 h at -30^{0}C; yield, 65, 70%; R_F 0.60 [$PhCH_3$-EtOAc-Me_2CO (72:18:10)]; $[\alpha]_D$ +740^0, -765^0 (*c* 1.17, 0.10); both yellow oils; δ_H 7.37 (1xAr-H, dd, J=2.0, 8.0 Hz), 7.20-7.10 (4xAr-H, m), 6.91 [6-H(A), d, J=8.5 Hz], 6.88-6.77 (4xAr-H, m), 6.57 [3-H(A), d, J=2.5 Hz], 6.26 [5-H(A), dd, J=2.5, 8.5 Hz], 6.06 [-C*H*(Bn)Ar, dd, J=6.5, 9.0 Hz], 5.20 (4-H, d, J=8.5 Hz), 5.04, 4.94 (-OCH_2OMe, both d, J=6.5 Hz), 3.74, 3.72 (2xOMe, both s), 3.71-3.63 (5-H, m), 3.40 (-OCH_2O*Me*, s), 3.13, 2.93 (-CH_2Ar, dd, J=9.0, 13.5 and 6.5, 13.5 Hz), 2.67 (N*Me*, s), 0.66 (5-CH_3, d, J=6.5 Hz); m/z 519 (M^+, 78%) (Found: M^+ 519.2488. $C_{30}H_{34}O_6N_2$ requires 519.2495).

(+)-(4*S*,5*R*)- and (-)-(4*R*,5*S*)-1,5-*dimethyl*-4-*phenyl*-3-[2'-(2,4-*dimethoxyphenyl*)-3'-(4-*methoxy*-2-*O*-*methoxymethylphenyl*)]*propionyl*-2-*imidazolidinone* **18a/b**, resp.: time, 8, 18 h at -30^{0}C; yield, both 60%; R_F 0.48 [$PhCH_3$-Me_2CO-MeOH (90:7:3)]; $[\alpha]_D$ +212^0, -200^0 (*c* 0.10, 1.177); both white needles, mp 92^{0}C; δ_H 7.31 [6-H(B), d, J=9.0 Hz], 7.25-7.17 (3xAr-H, m), 6.94 [6-H(A), d, J=9.0 Hz], 6.92-6.88 (2xAr-H, m), 6.60 [3-H(A) or 3-H(B), d, J=2.5 Hz], 6.43-6.38 (2xAr-H, m), 6.29 [5-H(A) or 5-H(B), dd, J=3.0, 9.0 Hz], 6.00 [-C*H*(Bn)Ar, dd, J=6.5, 9.0 Hz], 5.23 (4-H, d, J=9.0 Hz), 5.08, 4.98 (-OCH_2OMe, both d, J=7.0 Hz), 3.75 (3xOMe, s), 3.76-3.70 (5-H, m), 3.42 (-OCH_2O*Me*, s), 3.15, 2.92 (-CH_2Ar, both dd, J=9.0, 14.0 and 6.5, 14.0 Hz), 2.71 (N*Me*, s), 0.70 (5-CH_3, d, J=6.5 Hz); m/z 539 (M^+, 1%) (Found: M^+ 539.1742. $C_{31}H_{26}O_7N_2$ requires M 538.1740).

General procedure for preparation of the 2,3-diarylpropan-1-ols 19-24.

The *N*-acyl-2-imidazolidinones **13a/b** were reduced in dry THF using a suspension of $LiAlH_4$ (2.0 eq.) in dry THF at -10^{0}C under N_2. The mixture was stirred at this temp. for 1 h and for a further 1 h at rt, MeOH and a satd. NH_4Cl soln. were slowly added and the mixture was extracted with EtOAc (3x10 ml). The extract was washed with satd. $NaHCO_3$ soln. (10 ml), H_2O (10 ml), dried (Na_2SO_4), the solvent evaporated and the mixture separated by PLC or FCC.

The *N*-acylimidazolidinones **14-18** were reduced in dry Et_2O/THF (4:1) using a satd. soln. of $LiBH_4$ in Et_2O under N_2 at rt. The mixture was stirred at rt for 18 h, diluted with EtOAc and quenched with 3M HCl, washed with satd. $NaHCO_3$ soln., dried (Na_2SO_4) and the solvent evaporated. Sepn. by PLC or FCC afforded the 2,3-diarylpropan-1-ols.

(*S*)- and (*R*)-2-(4-*methoxyphenyl*)-3-(2-*O*-*methoxymethylphenyl*)-1-*propanols* **19a/b**, resp.: yield, 89, 85%; R_F 0.15 [hexane-C_6H_6-Me_2CO (7:2:1)]; $[\alpha]_D$ +73^0, -85^0 (*c* 0.98, 0.97); both clear oils; δ_H, ref. 5; m/z 302 (M^+, 3%) (Found: M^+ 302.1520. $C_{18}H_{22}O_4$ requires M 302.1517).

(*S*)- and (*R*)-2-(3,4-*dimethoxyphenyl*)-3-(2-*O*-*methoxymethylphenyl*)-1-*propanols* **20a/b**, resp.: yield, 86, 84%; R_F 0.16 [hexane-C_6H_6-Me_2CO (6:3:1)]; $[\alpha]_D$ +50^0, -50^0 (*c* 1.04, 1.04); both clear oils; δ_H, ref. 5; m/z 332 (M^+, 33%) (Found: M^+ 332.1628. $C_{19}H_{24}O_5$ requires M 332.1622).

(*S*)- and (*R*)-2-(2,4-*dimethoxyphenyl*)-3-(2-*O*-*methoxymethylphenyl*)-1-*propanols* **21a/b**, resp.: yield, 88, 86%; R_F 0.24 [hexane-C_6H_6-Me_2CO (8:1:1)]; $[\alpha]_D$ $+30^0$, -40^0 (*c* 1.23, 1.07); both light yellow oils; δ_H, ref. 5; m/z 332 (M^+, 7%) (Found: M^+ 332.1621. $C_{19}H_{24}O_5$ requires M 332.1623).

(*S*)- and (*R*)-2-(4-*methoxyphenyl*)-3-(4-*methoxy*-2-*O*-*methoxymethylphenyl*)-1-*propanols* **22a/b**, resp.: yield, 81, 80%; R_F 0.4 [hexane-C_6H_6-Me_2CO (6:2:2)]; $[\alpha]_D$ $+10^0$, -8^0 (*c* 1.07, 1.03); both light yellow oils; δ_H, 7.14 [2,6-H(B), d, J=8.5 Hz], 6.88-6.81 (1xAr-H, m), 6.84 [3,5-H(B), d, J=8.5 Hz], 6.67 [3-H(A), d, J=2.5 Hz], 6.41 [5-H(A), dd, J=2.5, 8.5 Hz], 5.17-5.12 (OC*H*$_2$OMe, m), 3.78, 3.75 (2xOMe, each s), 3.77-3.69 (1-CH_2, m), 3.48 (-OCH$_2$O*Me*, s), 3.09-2.96 (2-H, m), 2.96, 2.79 (3-C*H*$_2$, both dd, J=8.0, 13.0 and 6.5, 13.0 Hz), 1.80-1.74 (-OH, br. s); m/z 332 (M^+, 16%) (Found: M^+ 332.1628. $C_{19}H_{24}O_5$ requires M 332.1624).

(*S*)- and (*R*)-2-(2-*methoxyphenyl*)-3-(4-*methoxy*-2-*O*-*methoxymethylphenyl*)-1-*propanols* **23a/b**, resp.: yield, 74, 77%; R_F 0.36 [hexane-C_6H_6-Me_2CO (6:2:2)]; $[\alpha]_D$ $+14^0$, -11^0 (*c* 1.02, 0.96); both light yellow oils; δ_H, 7.24-7.14 (2xAr-H, m), 6.91 [6-H(A), d, J=8.5 Hz], 6.93-6.82 (2xAr-H, m), 6.67 [3-H(A), d, J=2.5 Hz], 6.41 [5-H(A), dd, J=2.5, 8.5 Hz], 5.16, 5.13 (-OC*H*$_2$OMe, both d, J=6.5 Hz), 3.76-3.70 (1-CH_2, m), 3.72, 3.71 (2xOMe, each s), 3.62-3.52 (2-H, m), 3.47 (-OCH$_2$O*Me*, s), 3.04, 2.82 (3-C*H*$_2$, both dd, J=8.0, 13.5 and 6.5, 13.5 Hz), 2.01-1.05 (-OH, br. s); m/z 332 (M^+, 18%) (Found: M^+ 332.1624. $C_{19}H_{24}O_5$ requires M 332.1624).

(*S*)- and (*R*)-2-(2,4-*dimethoxyphenyl*)-3-(4-*methoxy*-2-*O*-*methoxymethylphenyl*)-1-*pro-panols* **24a/b**, resp.: yield, 80, 84%; R_F 0.20 [hexane-C_6H_6-Me_2CO (7:2:1)]; $[\alpha]_D$ $+33^0$, -25^0 (*c* 1.0, 1.02); both light yellow oils; δ_H, 7.12, 6.91 [6-H(A)/6-H(B), d, J=9.0 Hz], 6.67 [3-H(A) or 3-H(B), d, J=2.5 Hz], 6.46-6.39 (4xAr-H, m), 5.16 (-OC*H*$_2$OMe, s), 3.78, 3.75, 3.74 (3xOMe, each s), 3.75-3.70 (1-C*H*$_2$, m), 3.49 (2-H/-OCH$_2$O*Me*, br. s), 3.00, 2.79 (3-C*H*$_2$, both dd, J=8.0, 13.5 and 6.5, 13.5 Hz), 1.92-1.88 (-OH, br. s); m/z 362 (M^+, 9%) (Found: M^+ 362.1711. $C_{20}H_{26}O_6$ requires M 362.1729).

General procedure for preparation of the 3-(2-hydroxyphenyl)-1-propanols 19-24 (R^5=H).

The 2-*O*-methoxymethylphenyl propanols **19-24** (R^5=MOM) (0.3 mmol) were refluxed for 1 h in MeOH (2 ml) containing 3M HCl (5 drops), water (2 ml) was added and the mixture was extracted with Et_2O (3x10 ml). The ethereal layer was washed with satd. $NaHCO_3$ soln. (5 ml) and water (10 ml), was dried (Na_2SO_4) and the solvent evaporated to give the 2-hydroxyphenyl-1-propanols **19-24** (R^5=H) in yields exceeding 95%. The purity and identity of these deprotected phenols were assessed by ^1H NMR and since compounds **19-24** (R^5=MOM) were fully identified, there is no need to do the same for the phenolic analogues.

General procedure for preparation of the isoflavans 25-30.

A soln. of Ph_3P (9.5 eq.) and DEAD (4.0 eq.) in dry THF (2.5 ml) was added to the phenolic propanols, *e.g.* **19a** (R^5=H), in dry THF (3.0 ml) and the mixture was stirred for 1.5 h at rt. The THF was evaporated, the mixture dissolved in DCM and purified by PLC.

(*S*)- and (*R*)-4'-*methoxyisoflavans* **25a/b**, resp.: ee, both >99%; yield, 85, 80%; R_F 0.38 [hexane-Me_2CO (98:2)]; $[\alpha]_D$ -3^0, $+4^0$ (*c* both 1.2); both white needles, mp 80°C; δ_H, ref. 5; CD $[\theta]_{295}$ +10, +2.9, $[\theta]_{283}$ -4010, +4000, $[\theta]_{279}$ -3090, +3200, $[\theta]_{263}$ -170, +139, $[\theta]_{235}$ -1230, +816, $[\theta]_{232}$ -627, +281; m/z 240 (M^+, 34%) (Found: M^+, 240.1151. $C_{16}H_{16}O_2$ requires M 240.1150).

(*S*)- and (*R*)-3',4'-*dimethoxyisoflavans* **26a/b**, resp.: ee, both >99%; yield, 85, 84%; R_F 0.62 [hexane-C_6H_6-Me_2CO (6:2:2)]; $[\alpha]_D$ $+1^0$, -6^0 (*c* both 1.03); both white needles, mp 69°C; δ_H, ref. 5; CD $[\theta]_{298}$ -86, -2.0, $[\theta]_{284}$ -5110, +4230, $[\theta]_{272}$ +24, 0, $[\theta]_{269}$ +475, -295, $[\theta]_{260}$ -32, -18, $[\theta]_{238}$ +1670, -1290, $[\theta]_{234}$ +348, -832; m/z 270 (M^+ 68%) (Found: M^+, 270.1255. $C_{17}H_{18}O_3$ requires M 270.1255).

(*S*)- and (*R*)-2',4'-*dimethoxyisoflavans* **27a/b**, resp.: ee, both >99%; yield, 70, 75%; R_F 0.75 [hexane-C_6H_6-Me_2CO (6:2:2)]; $[\alpha]_D$ $+14^0$, -17^0 (*c* 1.0, 1.03); both white needles, mp 75°C; δ_H, ref. 5; CD $[\theta]_{295}$ -37, -75, $[\theta]_{285}$ -2770, +2990, $[\theta]_{272}$ +2060, -2230, $[\theta]_{245}$ -94, -39, $[\theta]_{237}$ -2610, +52200, $[\theta]_{228}$ -394, +251; m/z 270 (M^+, 33%) (Found: M^+, 270.1255. $C_{17}H_{18}O_3$ requires M 270.1256).

(*S*)- and (*R*)-7,4'-*dimethoxyisoflavans* **28a/b**, resp.: ee, both >96%; yield, 80, 81%; R_F 0.24 [hexane-Me_2CO (9:1)]; $[\alpha]_D$ -12^0, $+21^0$ (*c* 1.05, 1.0); both white needles, mp 103°C (lit.[25] 105-107°C); δ_H, 7.16 [2,6-H(B), d, J=8.5 Hz], 6.98 [5-H(A), d, J=9.0 Hz], 6.89 [3,5-H(B), d, J=8.5 Hz], 6.47 [6-H(A), dd, J=2.5, 8.0 Hz], 6.42 [8-H(A), d, J=2.5 Hz], 4.30 (2-$H_{eq.}$, ddd, J=2.0, 3.5, 10.0 Hz), 3.96 (2-$H_{ax.}$, dd, J=10.5, 10.5 Hz), 3.80, 3.76 (2xOMe, each s), 3.22-3.11 (3-H, m), 2.95-2.88 (4-CH_2, m); CD $[\theta]_{312}$ -37, 0, $[\theta]_{282}$ -2590, +2660, $[\theta]_{248}$ +9, +10, $[\theta]_{237}$ +2560, -2290, $[\theta]_{232}$ -390, -460; m/z 270 (M^+, 60%) (Found: M^+, 270.1252. Calculated for $C_{17}H_{18}O_3$, M 270.1256).

(*S*)- and (*R*)-7,2'-*dimethoxyisoflavans* **29a/b**, resp.: ee, both >99%; yield, 90, 83%; R_F 0.28 [hexane-Me_2CO (98:2)]; $[\alpha]_D$ $+1^0$, -4^0 (*c* 1.05, 1.0); both white needles, mp 80°C (lit.[26], 81°C); δ_H, 7.27-7.20 (1xAr-H, m), 7.12 [3- or 6-H(B), dd, J=2.0, 8.5 Hz], 6.98 [5-H(A), d, J=8.0 Hz], 6.96-6.87 (2xAr-H, m), 6.47 [6-H(A), dd, J=2.5, 8.0 Hz], 6.42 [8-H(A), d, J=2.5 Hz], 4.34 (2-$H_{eq.}$, ddd, J=2.0, 3.5, 10.5 Hz), 4.04 (2-$H_{ax.}$, dd, J=10.5, 10.5 Hz), 3.83, 3.76 (2xOMe, each s), 3.71-3.59 (3-H, m), 3.00 (4-$H_{ax.}$, ddd, J=1.5, 10.5, 15.5 Hz), 2.89 (4-$H_{eq.}$, ddd, J=2.0, 5.5, 15.5 Hz); CD $[\theta]_{298}$ -77, +50, $[\theta]_{283}$ -4610, +1810, $[\theta]_{261}$ 0, -37, $[\theta]_{237}$ +25000, -8500, $[\theta]_{225}$ +160, -1090; m/z 270 (M^+, 76%) (Found: M^+, 270.1254. Calculated for $C_{17}H_{18}O_3$, M 270.1256).

(*S*)- and (*R*)-7,2',4'-*trimethoxyisoflavans* **30a/b**, resp.: ee, both >99%; yield, 88, 82%; R_F 0.34 [hexane-Me_2CO (9:1)]; $[\alpha]_D$ $+9^0$, -12^0 (*c* 0.98, 1.0); both white needles, mp 63°C (lit.[27], 61°C); δ_H, 7.01, 6.97 [5-H(A)/6-H(B), both d, J=8.5 Hz], 6.49-6.40 (4xAr-H, m), 4.30 (2-$H_{eq.}$, ddd, J=2.0, 3.0, 10.0 Hz), 3.99

(2-$H_{ax.}$, dd, J=10.0, 10.0 Hz), 3.81, 3.79, 3.76 (3xOMe, each s), 3.61-3.51 (3-H, m), 2.97 (4-$H_{ax.}$, ddd, J=1.5, 11.0, 16.0 Hz), 2.86 (4-$H_{eq.}$, ddd, J=2.0, 5.5, 16.0 Hz); CD $[\theta]_{300}$ -78, +21, $[\theta]_{288}$ -4780, +3310, $[\theta]_{274}$ +17, +35, $[\theta]_{268}$ +570, -310, $[\theta]_{254}$ +130, -84, $[\theta]_{237}$ +12800, -6290, $[\theta]_{230}$ +650, +100; m/z 300 (M^+, 34%) (Found: M^+, 300.1361. Calculated for $C_{18}H_{20}O_4$, M 300.1362).

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