Three-component synthesis of (*E*)-α,β-unsaturated amides of the piperine family

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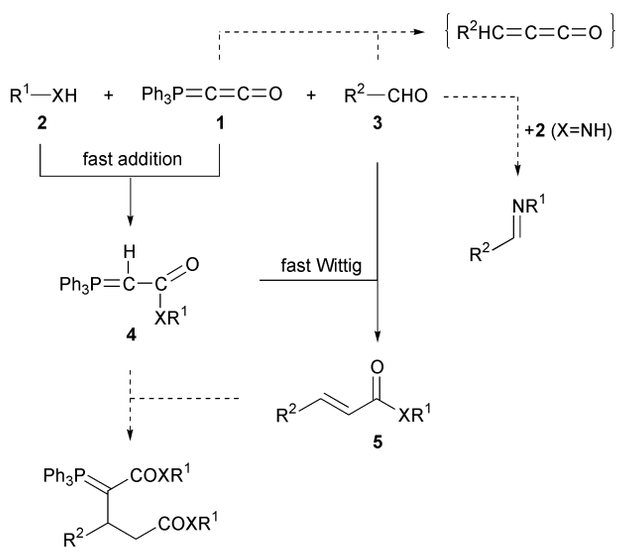
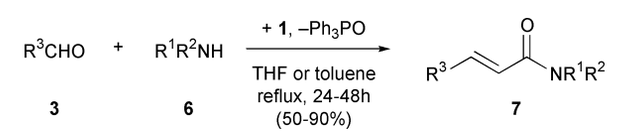
Selective formation of (*E*)-α,β-unsaturated amides by intermolecular three-component reaction between aldehydes, amines (1° or 2°) and ketenylidenetriphenylphosphorane ($Ph_3P{=}C{=}C{=}O$) is described. Natural amides such as *fagaramide* and *piperines* could be prepared from immediately available educts. The method is shown to be extendable to the preparation of thioesters from thiols and aldehydes.

Introduction

Efforts towards an extension and refinement of the Wittig olefination reaction have never abated since the very early days and less common variants such as the 'non-classical' reactions between stabilized phosphorus ylides and less reactive carbonyl compounds are currently experiencing a renaissance.[1] We have frequently used the cumulated ylide ketenylidenetriphenylphosphorane **1** as a 1,2-dipolar C_2-building block for the synthesis of various O-, N- and S-heterocycles from carboxylic esters bearing OH, NHR or SH groups by an addition–intramolecular Wittig olefination sequence.[2] These XH-acidic groups add readily across the C=C bond of **1** leading to X-acylated phosphorus ylides. These can then undergo a non-classical Wittig olefination between the stabilized ylide and the ester terminus. Analogous *inter*molecular three-component reactions between **1**, an XH-acidic and a carbonyl compound are more problematic. In the case of aldehydes and ketones, a direct olefination reaction with the ylide **1** might compete with the addition of R^1XH, especially for the less acidic thiols and amines.[3] For the latter, an unwanted formation of imines or enamines by reaction with the carbonyl component is a further conceivable complication. Finally, Michael addition reactions between stabilized ylides and unsaturated carbonyl compounds are also well-known processes which might interfere with the orderly progress of this 'one-pot' domino procedure (Scheme 1).[4] So far, only three-component reactions of mixtures of alcohols **2** (X = O), ylide **1** and aldehydes **3** to give (*E*)-α,β-unsaturated esters **5** (X = O) have been reported.[5]



Scheme 1



Scheme 2

Results and discussion

We have now found that (*E*)-α,β-unsaturated amides **7** are accessible likewise by three-component reaction between ylide **1**, (alkyl, aryl or vinyl) aldehydes **3**, and (1° or 2°) amines **6**. Yields and conditions are similar to those of the preparation of esters **5** (X = O) from alcohols. None of the above mentioned side and follow-up reactions were observed. Table 1 lists some typical examples. *Fagaramide* **7a**, a natural product occurring in the root cortex of *fagara zanthoxylum lamaire*[6a] and *fagara zanthoxylum rigidifolium*,[6b] was prepared from piperonal **3a**,† isobutylamine **6a** and **1**. A congener of **7c** lacking acetalisation of the diol moiety was isolated from *annona cherimola Mill*[7a] and found to inhibit arachidonate 5-lipoxygenase and PG synthetase.[7b]

The same synthetic concept was then applied to the preparation of the pepper substances *piperine* ‡**7g**[8,9] and $\Delta^{\alpha,\beta}$-*dihydropiperine* **7h**[8,10] from piperonal **3a** and piperidine **6d**. *Piperine* is the principal alkaloid of black pepper (*piper nigrum, piperaceae*) and the substance that gives black pepper its hot taste. It has been used extensively because of its anti-inflammatory, sedative and insecticidal properties.[11] The dihydro derivative **7h** was isolated from *piper guineense*. Chain lengthening of **3a** by a C_2-unit to give the required precursor aldehydes **3d** and **3e** was achieved following a Wittig olefination–redox sequence (Scheme 3). Olefination of **3a** with formylide ($PH_3P{=}CHCHO$), which should have provided the shortest possible synthetic pathway to **3d**, gave a mixture

† The IUPAC name for fagaramide is *N*-isobutyl-3,4-(methylenedioxy)-cinnamamide and the IUPAC name for piperonal is 3,4-(methylenedioxy)benzaldehyde.

‡ The IUPAC name for piperine is 5-[3,4-(methylenedioxy)phenyl]-penta-2,4-dienylpiperidine.

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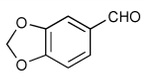
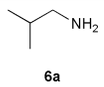
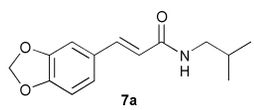
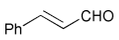
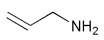
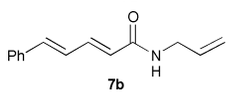
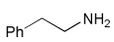
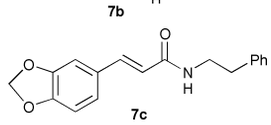
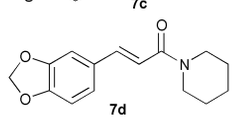
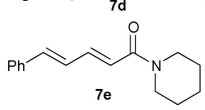
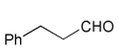
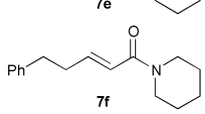
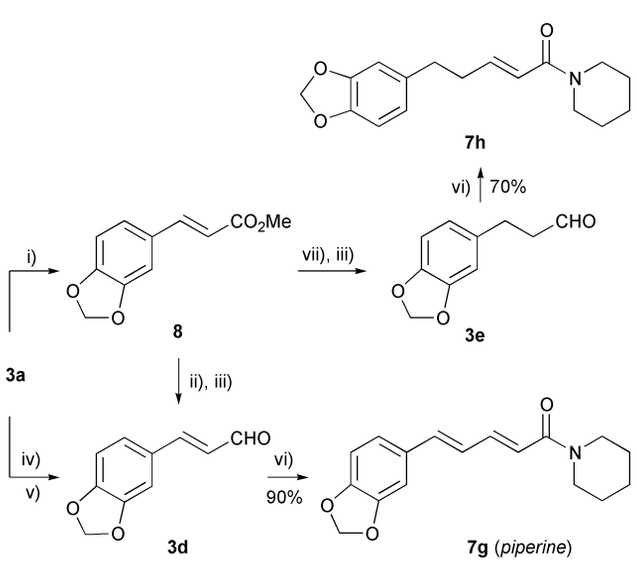
Table 1 (*E*)-α,β-Unsaturated amides **7** from **1**, aldehydes **3** and amines **6**

Educt **3**	Educt **6**	Product **7**	Yield (%)
 **3a**	 **6a**	 **7a**	50 [a]
 **3b**	 **6b**	 **7b**	63 [b]
3a	 **6c**	 **7c**	45 [b]
3a	 **6d**	 **7d**	94 [c]
3b	**6d**	 **7e**	70 [d]
 **3c**	**6d**	 **7f**	51 [d]

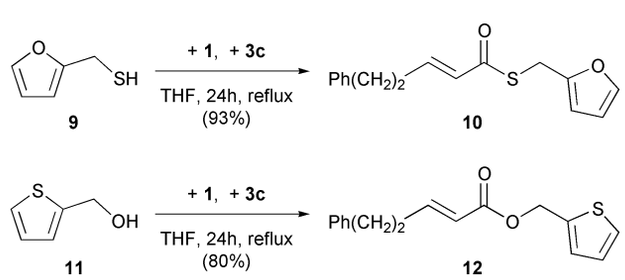
[a] THF, 48 h. [b] Toluene, 24 h. [c] THF, 36 h. [d] THF, 24 h.



Scheme 3 *Reagents and conditions*: i) $Ph_3P{=}CHCO_2Me$, PhH, 24 h, reflux, 94%; ii) DIBAL-H, THF, −10 °C ⟶ rt, 87%; iii) PDC, CH_2Cl_2, rt, 55%; iv) $[Ph_3PCH_2CH_3]^+Br$, *n*-BuLi, 0 °C ⟶ rt, 92% (mixture of *Z*–*E*-isomers); v) SeO_2, 1,4-dioxane, 24 h, reflux, 65%; vi) **1**, **6d**, THF, 24 h, reflux; vii) LAH (2.2 equiv.), THF, rt ⟶ reflux, then H_2O, 73%.

of *cis*- and *trans*-isomers and thus was of no benefit. An alternative route went through the methyl (*E*)-3,4-(methylenedioxy)cinnamoate **8** as obtained by olefination of **3a** with methoxycarbonylmethylenetriphenylphosphorane. The subsequent reduction of **8** with DIBAL-H firstly gave the corresponding alcohol, which was then oxidized with PDC to the aldehyde **3d**. No selective direct reduction of **8** to produce **3d** could be achieved using DIBAL-H at −78 °C. Conversion of **3a** into **3d** was also possible in only two steps. Olefination with ethylidenetriphenylphosphorane produced *cis*–*trans*-isomeric mixtures of 3,4-(methylenedioxy)-β-methylstyrene which were then subjected to a *trans*-selective allylic oxidation with selenium dioxide [12] to furnish the *E*-aldehyde **3d**. The final three-component domino reaction of the latter with **1** and piperidine **6d** yielded *piperine* **7g** in 90%. The preparation of $\Delta^{\alpha,\beta}$-*dihydropiperine* **7h** was analogous. The aldehyde **3e** was obtained by reducing the ester **8** with lithium aluminium hydride with concomitant hydrogenation of the C=C bond, and subsequent oxidation of the intermediate alcohol with PDC. A mixture of **1**, **3e** and **6d** finally produced **7h** upon heating in THF.

Thiols such as **9** are also sufficiently acidic to add to the central C=C bond of **1** in preference of reacting with aldehyde functions. Mixtures of **1**, an aldehyde and a thiol thus undergo a domino reaction upon heating to form (*E*)-α,β-unsaturated thioesters such as **10**. Sulfides and thiophenes do not react under these conditions, which is demonstrated in Scheme 4 by



Scheme 4

the selective conversion of compound **11** into the corresponding ester **12**.

Experimental

Melting points were recorded using a Gallenkamp apparatus and are uncorrected. IR spectra were recorded on a Bruker FT-IR Vektor 22 as potassium bromide (KBr) disks, or films (film). Nuclear magnetic resonance (NMR) spectra were recorded under conditions as indicated using Bruker DPX 300 and DRX 500 spectrometers. Chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as internal standard, and coupling constants (J) are given in Hz. Mass spectra were recorded using a Varian MAT 311A (EI). Microanalyses were obtained using a Perkin–Elmer 2400 CHN elemental analyser. Flash chromatography was effected using Merck Kieselgel 60 (230–400 mesh). Ylide **1** [3a] was prepared by the literature method, all other starting compounds were purchased from ALDRICH and used as such without further purification.

1 General experimental procedure for the three-component synthesis of amides 7 from ylide 1, aldehydes 3 and amines 6

A solution of **1** (2.30 g, 7.50 mmol, 1.5 equiv.), the amine **6** (5.00 mmol) and the aldehyde **3** (5.00 mmol) in THF or toluene (50 mL) was heated under reflux for 12–48 h with exclusion of air and moisture. After cooling to room temperature the solvent was removed under reduced pressure and the residue obtained was purified by column chromatography (silica gel; solvent as indicated).

Fagaramide 7a. White solid (0.63 g, 2.51 mmol, 50%) from isobutylamine **6a** (0.36 g) and piperonal **3a** (0.75 g), reflux in THF for 48 h, R_f 0.48 (ethyl acetate–hexane, 1 : 1, v/v), mp 115 °C (lit.[6b] mp 116 °C); ν_{max}(KBr)/cm^{-1} 3296, 1650, 1614, 1544, 1492, 1447, 1253, 1038; δ_H (500 MHz; $CDCl_3$) 0.94 (6 H, d, *J* 8.93, CH*Me*$_2$), 1.79–1.88 (1 H, m, C*H*Me$_2$), 3.20 (2 H, d, *J* 6.33, NCH$_2$), 5.59 (2 H, s, OCH$_2$O), 6.05 (1 H, s, NH), 6.28 (1 H, d, *J* 15.49, 2-H), 6.75–6.99 (3 H, m, 2′-H, 5′-H, 6′-H), 7.55 (1 H, d, *J* 15.49, 3-H); δ_C (125.7 MHz; $CDCl_3$) 20.2 (Me), 28.7 (*C*Me$_2$), 47.1 (NCH$_2$), 101.4 (OCH$_2$O), 106.3, 108.5, 119.0, 123.7 (C-2, C-2′, C-5′, C-6′), 129.3 (C-1′), 140.5 (C-3), 148.2, 148.9 (C-4′, C-3′), 166.2 (C-1); *m*/*z* (EI) 247 (M$^+$, 37%), 190 (M$^+$ − C$_4$H$_9$, 56%), 175 (M$^+$ − C$_4$H$_{10}$N, 100%).

(*E*,*E*)-*N*-Allyl-5-phenylpenta-2,4-dienamide 7b. White needles (0.79 g, 3.16 mmol, 63%) from allylamine **6b** (0.28 g) and cinnamaldehyde **3b** (0.66 g), reflux in toluene for 24 h, R_f 0.56 (diethyl ether–*n*-pentane, 4 : 1, v/v), mp 131 °C (from diethyl ether) (Found: C, 78.88; H, 6.98; N, 6.51. $C_{14}H_{15}NO$ requires C, 78.84; H, 7.09; N, 6.57%); ν_{max}(film)/cm^{-1} 3249, 1658, 1641, 1604, 1551, 1258, 1006; δ_H (500 MHz; $CDCl_3$) 3.99 (2 H, dt, ^3J 5.69, ^4J 1.42, NCH$_2$), 5.15 (1 H, dd, *J* 10.20, 1.42, =CH*H*^{cis}), 5.22 (1 H, dd, *J* 17.24, 1.42, =CH*H*^{trans}), 5.58–5.91 (1 H, m, H$_2$CC*H*), 6.05 (1 H, d, *J* 14.90, 2-H), 6.12 (1 H, s, NH), 6.84–6.86 (2 H, m, 4-H, 5-H), 7.27–7.43 (6 H, m, 3-H, Ph–H); δ_C (125.7 MHz; $CDCl_3$) 42.1 (NCH$_2$), 116.4 (H$_2$C=), 123.9 (C-2), 126.3 (C-4), 127.0, 128.7, 128.8 (arom. CH), 134.2 (H$_2$C=*C*), 133.2 (C-3), 136.2 (*ipso*–C), 141.2 (C-5), 166.0 (C-1); *m*/*z* (EI) 213 (M$^+$, 87%), 172 (M$^+$ − C$_3$H$_5$, 34%), 157 (M$^+$ − C$_3$H$_6$N, 100%).

(*E*)-*N*-Phenethyl-3′,4′-(methylenedioxy)cinnamamide 7c. White solid (0.63 g, 2.29 mmol, 45%) from 2-phenylethylamine **6c** (0.61 g) and piperonal **3a** (0.75 g), reflux in toluene for 24 h, R_f 0.83 (ethyl acetate), mp 117 °C (Found: C, 73.34; H, 5.84; N, 4.71. $C_{18}H_{17}NO_3$ requires C, 73.20; H, 5.80; N, 4.74%); ν_{max}(KBr)/cm^{-1} 3291, 1650, 1617, 1544, 1249; δ_H (300 MHz; $CDCl_3$) 2.79 (2 H, t, *J* 6.62, NCCH$_2$), 3.64 (2 H, m, NCH$_2$), 5.86 (2 H, s, OCH$_2$O), 5.94 (1 H, s, NH), 6.17 (1 H, d, *J* 15.49, 2-H), 6.66 (1 H, d, *J* 8.46, 5′-H), 6.85 (1 H, d, *J* 8.46, 6′-H), 7.10–7.25 (6 H, m, Ph–H, 2′-H), 7.44 (1 H, d, *J* 15.49, 3-H); δ_C (75.6 MHz; $CDCl_3$) 34.7 (NC*C*H$_2$), 39.8 (NCH$_2$), 100.4 (OCO), 105.3, 107.1 (C-2′, C-5′), 117.8 (C-2), 122.8 (C-6′), 125.8 (C-1′), 127.3, 127.6, 129.0 (Ph–CH), 137.9 (*ipso*–C), 139.6 (C-3), 147.0 (C-3′), 148.0 (C-4′), 165.2 (C-1); *m*/*z* (EI) 296 (MH$^+$, 9%), 295 (M$^+$, 38%), 190 (M$^+$ − C$_8$H$_9$, 42%), 175 (M$^+$ − C$_8$H$_{10}$N, 100%).

(*E*)-1-[3′,4′-(Methylenedioxy)cinnamoyl]piperidine 7d. White solid (1.22 g, 4.71 mmol, 94%) from piperidine **6d** (0.42 g) and piperonal **3a** (0.75 g), reflux in THF for 36 h, R_f 0.53 (ethyl acetate–*n*-hexane, 2 : 1, v/v), mp 83 °C (lit.[13] mp 85–87 °C); ν_{max}(KBr)/cm^{-1} 3067, 2939, 1645, 1590, 1492, 1443, 1250; δ_H (300 MHz; $CDCl_3$) 1.59–1.72 (6 H, m, NCCH$_2$, NCCCH$_2$), 3.74 (4 H, m, NCH$_2$), 5.98 (2 H, s, OCH$_2$O), 6.74 (1 H, d, *J* 15.49, 2-H), 6.77–7.03 (3 H, m, 2′-H, 5′-H, 6′-H), 7.56 (1 H, d, *J* 15.49, 3-H); δ_C (75.6 MHz; $CDCl_3$) 25.0, 26.1, 27.1 (NC*C*H$_2$, NCC*C*H$_2$), 43.7, 47.3 (NCH$_2$), 101.8 (OCO), 106.7, 108.8, 116.0, 123.9 (C-2′, C-5′, C-6′, C-2), 130.3 (C-1′), 142.3 (C-3), 148.5, 149.2 (C-3′, C-4′), 165.0 (C-1); *m*/*z* (EI) 259 (M$^+$, 27%), 206 (27%), 175 (M$^+$ − C$_5$H$_{10}$N, 73%), 89 (100%).

(*E*,*E*)-1-(5′-Phenylpenta-2′,4′-dienoyl)piperidine 7e. Pale yellow lamellas (0.84 g, 3.48 mmol, 70%) from piperidine **6d** (0.42 g) and cinnamaldehyde **3b** (0.66 g), reflux in THF for 24 h, R_f 0.30 (diethyl ether–*n*-hexane, 4 : 1, v/v), mp 91 °C (from diethyl ether) (lit.[14] mp 91–92 °C); ν_{max}(KBr)/cm^{-1} 3026, 2934, 1636, 1613, 1597, 1588, 1432, 1002; δ_H (300 MHz; $CDCl_3$) 1.54–1.70 (6 H, m, NCCH$_2$, NCCCH$_2$), 3.43–3.48 and 3.52–3.62 (each 2 H, each m, NCH$_2$), 6.48 (1 H, d, *J* 14.67, 2-H), 6.85–6.89 (2 H, m, 4-H, 5-H), 7.26–7.46 (6 H, m, 3-H, Ph-H); δ_C (75.6 MHz; $CDCl_3$) 25.6 (NCC*C*H$_2$), 26.6, 27.7 (NC*C*H$_2$), 44.2, 47.9 (NCH$_2$), 121.9 (C-2), 127.9, 128.0 (Ph–C), 128.7 (C-4), 129.5 (Ph–C), 137.5 (*ipso*-C), 139.4, 143.3 (C-3, C-5), 166.3 (C-1); *m*/*z* (EI) 241 (M$^+$, 76%), 164 (M$^+$ − C$_6$H$_5$, 6%), 157 (M$^+$ − C$_5$H$_{10}$N, 100%), 128 (C$_{10}$H$_8^+$, 63%).

(*E*)-1-(5′-Phenylpent-2′-enoyl)piperidine 7f. Colourless viscous oil (0.62 g, 2.56 mmol, 51%) from piperidine **6d** (0.42 g) and 3-phenylpropanal **3c** (0.67 g), reflux in THF for 24 h, R_f 0.79 (ethyl acetate–*n*-hexane, 10 : 1, v/v), bp 128 °C/0.1 mmHg (lit.[14] bp 164–169 °C/0.2 mmHg); ν_{max}(film)/cm^{-1} 3025, 2935, 1656, 1616, 1440; δ_H (300 MHz; $CDCl_3$) 1.45–1.65 (6 H, m, NCCH$_2$, NCCCH$_2$), 2.51 (2 H, m, 4-H), 2.77 (2 H, t, *J* 7.16, 5-H), 3.31–3.37 and 3.55–3.57 (each 2 H, each m, NCH$_2$), 6.20 (1 H, dt, *J* 15.14, 1.45, 2-H), 6.81 (1 H, dt, *J* 15.14, 6.90, 3-H), 7.15–7.27 (5 H, m, Ph–H); δ_C (75.6 MHz; $CDCl_3$) 24.5 (NCC*C*H$_2$), 25.5, 26.5 (NC*C*H$_2$), 34.2, 35.1 (C-4, C-5), 43.0, 46.8 (NCH$_2$), 121.4 (C-2), 126.0, 128.3, 128.4 (Ph-C), 141.1 (*ipso*-C), 144.0 (C-3), 165.5 (C-1); *m*/*z* (EI) 243 (M$^+$, 83%), 217 (58%), 159 (M$^+$ − C$_5$H$_{10}$N, 39%), 126 (M$^+$ − C$_9$H$_9^+$, 72%), 91 (100%).

2 Synthesis of piperine 7g

Methyl (*E*)-3′,4′-(methylenedioxy)cinnamoate 8. A solution of methoxycarbonylmethylenetriphenylphosphorane (16.70 g, 50 mmol) and piperonal **3a** (7.50 g, 50 mmol) in dry benzene (100 mL) was heated under exclusion of air and moisture for 24 h. After cooling to room temperature the solvent was evaporated on a rotary evaporator and the crude product thus obtained was recrystallized from ethanol to yield **8** (9.77 g, 47.30 mmol, 94%) as white needles, mp 69 °C (lit.[15] mp 68 °C); ν_{max}(KBr)/cm^{-1} 2996, 1702, 1625, 1599, 1254; δ_H (300 MHz; $CDCl_3$) 3.79 (3 H, s, Me), 6.00 (2 H, s, OCH$_2$), 6.23 (1 H, d, *J* 19.86, 2-H), 6.75–7.02 (3 H, m, arom. H), 7.53 (1 H, d, *J* 19.86, 3-H); δ_C (75.6 MHz; $CDCl_3$) 52.0 (CH$_3$), 101.9 (OCH$_2$), 106.8, 108.9, 116.1, 124.8 (arom. CH), 129.2 (C-1′), 144.9 (C-3), 148.7, 150.0 (C-3′, C-4′), 168.0 (C-1); *m*/*z* (EI) 206 (M$^+$, 100%), 175 (M$^+$ − CH$_3$O, 92%), 145 (70%), 117 (44%), 89 (83%).

(*E*)-3,4-(Methylenedioxy)cinnamyl alcohol. To a stirred solution of **8** (1.0 g, 5.0 mmol) in dry THF (75 mL), a solution of diisobutylaluminium hydride (DIBAL-H; 15.0 mL of a 1.0 M solution in hexane, 15 mmol) was added dropwise over a period of 30 min at −10 °C. The mixture was stirred at this temperature for 2 h and then at room temperature for a further 4 h. It was then quenched by slowly adding water (20 mL). The precipitate of aluminium salts was treated with 1 M aqueous HCl solution, the organic layer was separated, the aqueous phase extracted four times with diethyl ether and the combined organic extracts were finally dried over $MgSO_4$. After filtration and evaporation of the solvent the residue was purified by column chromatography, R_f 0.42 (diethyl ether–*n*-hexane, 2 : 1, v/v) yielding (*E*)-3′,4′-(methylenedioxy)cinnamyl alcohol (0.78 g, 4.35 mmol, 87%) as a white solid, mp 71 °C (lit.[16] mp 72–73 °C); ν_{max}(KBr)/cm^{-1} 3398, 2894, 1651, 1503, 1445, 1036; δ_H (300 MHz; $CDCl_3$) 1.70 (1 H, s, OH), 4.27 (2 H, dd, *J* 5.85, 1.30, 1-H), 5.94 (2 H, s, OCH$_2$O), 6.18 (1 H, dt, *J* 15.80, 5.85, 2-H),

6.51 (1 H, dd, *J* 15.80, 1.30, 3-H), 6.37–6.91 (3 H, m, arom. H); δ_C (75.6 MHz; $CDCl_3$) 64.1 (C-1), 101.5 (OCO), 106.2, 108.7, 121.6, 127.1, 131.4 (C-2, C-3, arom. CH), 131.5 (*ipso*-C), 147.7, 148.4 (arom. C^{qu}); *m*/*z* (EI) 178 (M^+, 100%), 147 ($M^+ - CH_3O$, 11%), 135 (93%), 122 (42%), 103 (18%).

3,4-(Methylenedioxy)-β-methylstyrene. To a well stirred suspension of ethyltriphenylphosphonium bromide (7.5 g, 20.2 mmol) in dry THF (100 mL), a solution of *n*-butyllithium (12.6 mL of a 1.6 M solution in hexane, 20.2 mmol) was added dropwise over a period of 30 min at 0 °C. The mixture was warmed to room temperature and stirred for 60 min. A solution of piperonal **3a** (3.0 g, 20.0 mmol) in THF (25 mL) was then slowly added and the resulting mixture left stirring for a further 6 h. Water (100 mL) was added, the organic layer was separated, the aqueous phase extracted twice with diethyl ether and the combined organic phases were finally dried over $MgSO_4$. After filtration and evaporation of the solvents the residue was eluted from silica gel with CH_2Cl_2 to remove phosphine oxide and the residue was purified by distillation, bp 121 °C/15 Torr (lit.[17] bp 123 °C/11.5 Torr), 3.0 g (18.5 mmol, 92%) as a colourless oil, mixture of *Z*- and *E*-isomers (*Z*–*E* = 1 : 10); ν_{max}(film)/cm^{-1} 3022, 2994, 1501, 1490, 1444, 1249, 1040; δ_H (300 MHz; $CDCl_3$) *mixture of Z- and E-isomer:* 1.84 and 1.87 (3 H, each dd, ^3J 6.57/7.20 and ^4J 1.62/1.86, CH_3), 5.64 and 5.70 (2 H, each s, OCH_2), 5.92–6.57 (1 H, m, MeC*H*), 6.26–6.33 (1 H, m, MeCC*H*), 6.72–6.87 (3 H, arom. CH); δ_C (75.6 MHz; $CDCl_3$), *major isomer*: 18.3 (Me), 100.8 (OCO), 105.3, 109.0, 120.0, 123.9, 130.5 (Me*C*, MeC*C*, arom. CH), 132.4 (*ipso*-C), 146.4, 147.8 (arom. C^{qu}); *minor isomer*: 14.7 (Me), 101.0 (OCO), 108.0, 109.0, 122.5, 125.5, 129.4 (Me*C*, MeC*C*, arom. CH), 131.7 (*ipso*-C), 145.4, 146.7 (arom. C^{qu}).

(*E*)-3′,4′-(Methylenedioxy)cinnamaldehyde 3d. *a) Oxidation of 3′,4′-(methylenedioxy)cinnamyl alcohol with pyridinium dichromate (PDC).* To a vigorously stirred suspension of pyridinium dichromate (2.36 g, 7.00 mmol) in CH_2Cl_2 (20 mL) a solution of 3′,4′-(methylenedioxy)cinnamyl alcohol (0.89 g, 5.00 mmol) in CH_2Cl_2 (10 mL) was added dropwise over a period of 20 min. The mixture was then allowed to stir overnight at room temperature. While being stirred, the mixture was finally diluted with diethyl ether (100 mL), the resulting precipitation of chromium oxide was removed by filtration, and the filtrate thus obtained was washed twice with small portions of water and then dried over $MgSO_4$. After evaporation of the solvent the residue was purified by column chromatography, R_f 0.57 (diethyl ether–*n*-hexane, 1 : 1, v/v) to leave pure **3d** (0.49 g, 2.78 mmol, 55%) as a white solid, mp 77 °C (lit.[18a] mp 77–79 °C, lit.[18b]: mp 83–84 °C).

b) Oxidation of 3,4-(methylenedioxy)-β-methylstyrene with selenium dioxide. A suspension of selenium dioxide (0.40 g, 3.00 mmol) in dry 1,4-dioxane (20 mL) was treated with 3,4-(methylenedioxy)-β-methylstyrene (0.53 g, 3.00 mmol) and then heated under reflux with the exclusion of air and moisture for 16 h. After cooling to room temperature the precipitate of selenium was removed by filtration over a pad of Celite and the product was eluted with 1,4-dioxane (50 mL). The solvent was evaporated under reduced pressure and the residue was purified by column chromatography as described above to give pure **3d** (0.36 g, 1.96 mmol, 65%); ν_{max}(KBr)/cm^{-1} 2916, 1655, 1623, 1502, 1449, 1259; δ_H (300 MHz; $CDCl_3$) 6.11 (2 H, s, OCH_2), 6.56 (1 H, dd, *J* 15.81, 7.74, 2-H), 6.51–7.08 (3 H, m, arom. CH), 7.38 (1 H, d, *J* 15.81, 3-H), 9.92 (1 H, d, *J* 7.74, 1-H); δ_C (75.6 MHz; $CDCl_3$) 102.2 (OCO), 107.1, 109.1, 125.6, 127.2 (C-2, arom. CH), 128.9 (*ipso*-C), 149.0, 150.9 (arom. C^{qu}), 152.9 (C-3), 192.9 (C-1); *m*/*z* (EI) 176 (M^+, 100%), 147 (M^+ − CHO, 32%), 135 (6%), 122 (17%), 118 (27%).

Piperine 7g. Following the general procedure for the preparation of amides **7**, piperine **7g** (1.28 g, 4.48 mmol, 90%) was obtained from piperidine **6d** (0.42 g, 5.00 mmol), (*E*)-3,4-(methylenedioxy)cinnamaldehyde **3d** (0.88 g, 5.00 mmol) and ylide **1** (2.30 g, 7.50 mmol), THF, reflux, 24 h, pale yellow solid, mp 126–127 °C (lit.[9] mp 125–126 °C); ν_{max}(KBr)/cm^{-1} 2938, 1636, 1620, 1598, 1490, 1443, 1244, 1029; δ_H (500 MHz; $CDCl_3$) 1.65–1.69 (6 H, m, $NCCH_2$, $NCCCH_2$), 3.52–3.59 (4 H, m, NCH_2), 5.97 (2 H, s, OCH_2), 6.43 (1 H, d, *J* 14.86, 2-H), 6.72–6.97 (5 H, m, 4-H, 5-H, arom. CH), 7.40 (1 H, ddd, *J* 14.86, 8.79, 1.42, 3-H); δ_C (125.7 MHz; $CDCl_3$) 24.7 ($NCC*C*H_2$), 26.2, 26.5 ($NC*C*H_2$), 43.4, 46.8 (NCH_2), 101.3 (OCO), 105.7, 108.5, 120.1, 122.1, 125.4 (C-2, C-4, arom. CH), 131.2 (*ipso*-C), 138.2, 142.5 (C-3, C-5), 148.1, 148.2 (arom. C^{qu}), 165.4 (C-1); *m*/*z* (EI) 285 (M^+, 86%), 201 ($M^+ - C_5H_{10}N$, 100%), 173 (33%), 115 (74%).

3 Synthesis of $\Delta^{\alpha,\beta}$-dihydropiperine 7h

3′,4′-(Methylenedioxy)dihydrocinnamyl alcohol. To a well stirred slurry of lithium aluminium hydride (1.70 g, 44.80 mmol) in dry THF (150 mL), methyl 3′,4′-(methylenedioxy)-cinnamoate **8** (4.12 g, 20.00 mmol) was added in small portions over a period of 60 min at 0 °C. The reaction mixture was then warmed to room temperature, stirred for another 60 min and finally heated for 2 h. It was then cooled in an ice-bath to 0 °C and quenched by the careful addition of water until no further hydrogen gas evolved. The precipitate of aluminium salts was treated with 1 M aqueous HCl solution and the organic phase was separated. The aqueous layer was extracted four times with diethyl ether (100 mL), the combined organic phases were washed with brine and dried over $MgSO_4$. After filtration, the solvent was removed and the product was purified by column chromatography, R_f 0.46 (diethyl ether–*n*-pentane, 2 : 1, v/v) and distillation, bp 109 °C/0.1 Torr, to yield 3′,4′-(methylenedioxy)dihydrocinnamyl alcohol (2.63 g, 14.63 mmol, 73%) as a colourless oil (Found: C, 66.74; H, 6.74. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.71%); ν_{max}(film)/cm^{-1} 3349, 2939, 1503, 1489, 1441, 1246, 1038; δ_H (300 MHz; $CDCl_3$) 1.67 (1 H, s, OH), 1.83 (2 H, tt, *J* 7.65, 6.40, 2-H), 2.62 (2 H, t, *J* 7.65, 3-H), 3.64 (2 H, t, *J* 6.40, 1-H), 5.94 (2 H, s, OCH_2O), 6.61–6.79 (3 H, arom. H); δ_C (75.6 MHz; $CDCl_3$) 34.4, 37.0 (C-2, C-3), 64.6 (C-1), 103.3 (OCO), 110.7, 111.4, 123.7 (arom. CH), 138.2 (*ipso*-C), 148.2, 150.2 (arom. C^{qu}); *m*/*z* (EI) 180 (M^+, 74%), 162 ($M^+ - H_2O$, 27%), 149 (27%), 135 (100%).

3′,4′-(Methylenedioxy)dihydrocinnamaldehyde 3e. Following the procedure described above for the preparation of **3d**, aldehyde **3e** (0.49 g, 2.76 mmol, 55%) was obtained from PDC (2.63 g, 7.00 mmol) and 3′,4′-(methylenedioxy)dihydrocinnamyl alcohol (0.90 g, 5.00 mmol) as a colourless oil, R_f 0.95 (diethyl ether–*n*-pentane, 2 : 1, v/v) (Found: C, 67.44; H, 5.74. $C_{10}H_{10}O_3$ requires C, 67.41; H, 5.66%); ν_{max}(film)/cm^{-1} 3070, 2895, 1724, 1504, 1489, 1445, 1248, 1036; δ_H (300 MHz; $CDCl_3$) 2.61–2.67 (2 H, m, 2-H), 2.80 (2 H, t, *J* 7.17, 3-H), 5.83 (2 H, s, OCH_2O), 6.49–6.68 (3 H, m, arom. CH), 9.72 (1 H, d, *J* 4.75, 1-H); δ_C (75.4 MHz; $CDCl_3$) 26.0 (C-3), 43.6 (C-2), 99.0 (OCO), 106.4, 106.9, 119.2 (arom. CH), 132.2 (*ipso*-C), 144.1, 145.7 (arom. C^{qu}), 199.5 (C-1); *m*/*z* (EI) 178 (M^+, 83%), 150 (M^+ − CO, 36%), 135 (100%).

$\Delta^{\alpha,\beta}$-Dihydropiperine 7h. Following the general procedure for the preparation of amides **7**, $\Delta^{\alpha,\beta}$-dihydropiperine **7h** (0.41 g, 1.41 mmol, 70%) was obtained from piperidine **6d** (0.17 g, 2.00 mmol), (*E*)-3′,4′-(methylenedioxy)dihydrocinnamaldehyde **3e** (0.36 g, 2.00 mmol) and ylide **1** (0.91 g, 3.00 mmol), THF, reflux, 24 h, as a white solid, mp 78 °C (lit.[10a] mp 74 °C, lit.[10b] mp 79–80 °C); ν_{max}(KBr)/cm^{-1} 3000, 2935, 1657, 1612, 1503, 1489, 1442, 1247, 1038; δ_H (500 MHz; $CDCl_3$) 1.54–1.66 (6 H, m, $NCCH_2$, $NCCCH_2$), 2.46 (2 H, tdd, *J* 7.30, 6.95, 1.52, 4-H), 2.69 (2 H, t, *J* 7.30, 5-H), 3.46–3.57 (4 H, m, NCH_2), 5.90 (2 H, s, OCH_2), 6.21 (1 H, dt, *J* 15.14, 1.52, 2-H), 6.61–6.72 (3 H, m,

arom. CH), 6.79 (1 H, dt, *J* 15.14, 6.95, 3-H); δ_C (125.7 MHz; $CDCl_3$) 24.6, 25.5, 26.6 ($NCCCH_2$, $NCCH_2$), 34.5, 34.6 (C-4, C-5), 43.0, 46.0 (NCH_2), 100.8 (OCO), 108.2, 108.8, 121.2, 122.4 (C-2, arom. CH), 131.2 (*ipso*-C), 144.0 (C-3), 145.7, 147.6 (arom. C^{qu}), 165.5 (C-1); *m*/*z* (EI) 287 (M^+, 58%), 202 ($M^+ - C_5H_{11}N$, 16%), 174 (21%), 135 (100%).

4 Synthesis of thioester 10 and ester 12 (according to the general procedure for the preparation of amides 7)

Furan-2′-ylmethyl (*E*)-5-phenylpent-2-enethioate 10. Colourless oil (1.26 g, 4.63 mmol, 93%) from 2-furylmethanethiol **9** (0.57 g, 5.00 mmol), 3-phenylpropanal **3c** (0.67 g, 5.00 mmol), and ylide **1** (2.30 g, 7.50 mmol), THF, reflux for 24 h, R_f 0.74 (diethyl ether–hexane, 1 : 1, v/v), bp 116 °C/1 Torr (Found: C, 70.65; H, 5.91. $C_{16}H_{16}O_2S$ requires C, 70.56; H, 5.92%); ν_{max}(film)/cm^{-1} 3026, 2927, 1719, 1675, 1497, 1010; δ_H (300 MHz; $CDCl_3$) 2.48–2.55 (2 H, m, 4-H), 2.78 (2 H, t, *J* 7.26, 5-H), 4.20 (2 H, s, SCH_2), 6.12 (1 H, dt, *J* 15.56, 1.40, 2-H), 6.21–6.29 (2 H, m, 3′-H, 4′-H), 6.95 (1 H, dt, *J* 15.56, 6.95, 3-H), 7.18–7.64 (6 H, m, arom CH); δ_C (75.6 MHz; $CDCl_3$) 25.8 (C-4), 34.3, 34.7 (C-5, SCH_2), 108.3, 111.0 (C-3′, C-4′), 126.7, 128.7, 129.0 (arom. CH), 140.9 (*ipso*-C), 142.6, 145.5 (C-2, C-5′), 149.8 (C-2′), 150.9 (C-3), 189.0 (C-1); *m*/*z* (EI) 272 (M^+, 42%), 191 ($M^+ - C_5H_5OS$, 29%), 131 (80%), 91 (100%).

Thiophen-2′-ylmethyl (*E*)-5-phenylpent-2-enoate 12. Colourless oil (1.09 g, 4.03 mmol, 80%) from 2-hydroxymethylthiophene **11** (0.57 g, 5.00 mmol), 3-phenylpropanal **3c** (0.67 g, 5.00 mmol), and ylide **1** (2.30 g, 7.50 mmol), THF, reflux for 24 h, R_f 0.66 (diethyl ether–hexane, 1 : 4, v/v) (Found: C, 70.49; H, 6.01. $C_{16}H_{16}O_2S$ requires C, 70.56; H, 5.92%); ν_{max}(film)/cm^{-1} 3062, 2942, 1720, 1653, 1258, 1188; δ_H (300 MHz; $CDCl_3$) 2.50 (2 H, m, 4-H), 2.75 (2 H, t, *J* 7.24, 5-H), 5.30 (2 H, s, OCH_2), 5.86 (1 H, dt, *J* 15.64, 1.49, 2-H), 6.97–7.31 (9 H, m, 3-H, 3′-H, 4′-H, 5′-H, PhH); δ_C (75.6 MHz; $CDCl_3$) 33.6, 33.9 (C-4, C-5), 60.3 (OCH_2), 121.3 (C-2), 126.2, 126.8, 128.1, 128.3, 128.4, 128.5 (C-3′, C-4′, C-5′, arom. CH), 138.1, 140.7 (C-2′, *ipso*-C), 149.0 (C-3), 166.1 (C-1); *m*/*z* (EI) 272 (M^+, 19%), 175 ($M^+ - C_5H_5S$, 15%), 159 (33%), 97 (100%).

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