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Organic Chemistry

Arkivoc **2020**, part viii, 0-0

The extended Vilsmeier reaction of dimethoxy-activated indoles

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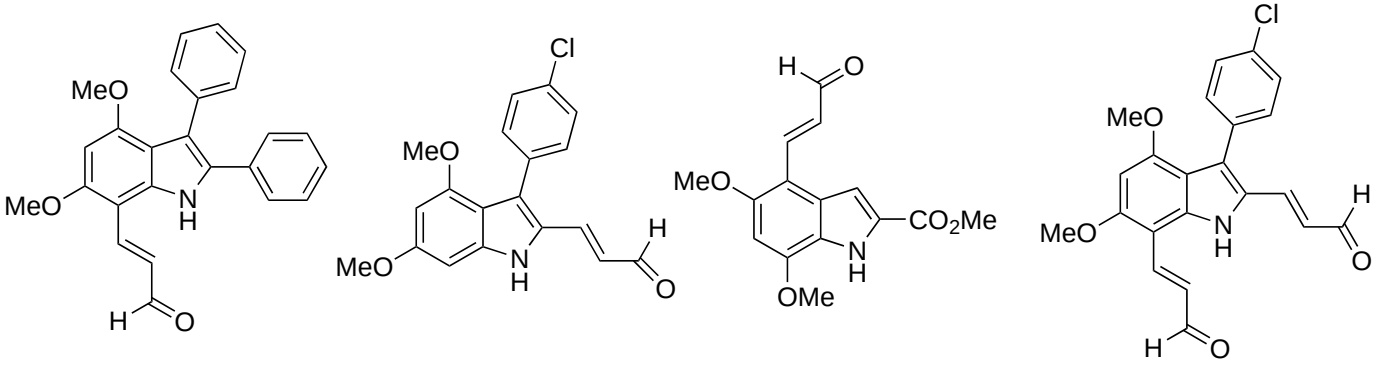
Received 10-16-2020 **Accepted** 12-15-2020 **Published on line** 12-28-2020

Abstract

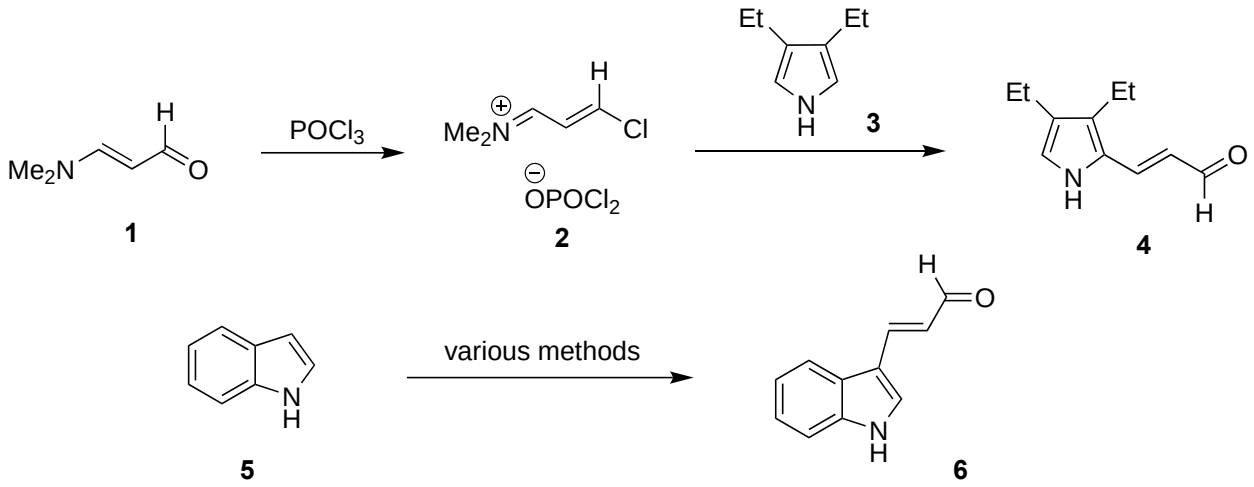
The activated dimethoxyindoles **7**, **9**, **14** and **17** undergo reaction with 3-dimethylaminopropenal **1** and phosphoryl chloride to give high yields of the indolyl-propenals **8**, **10**-**13**, **15**-**16**, and **18**-**19**, with electrophilic substitution taking place at C2, C4 and C7. This extended Vilsmeier methodology provides effective functionalisation of indoles with a propenyl substituent in a single step.



Keywords: Vilsmeier reaction, 3-dimethylaminopropenal, phosphoryl chloride, indoles, electrophilic substitution, iminium cations

Introduction

The extended Vilsmeier reaction refers to the use of the vinylogous tertiary amide 3-dimethylaminopropenal **1** in combination with phosphoryl chloride, to generate a reactive intermediate, believed to be the 3-chloro-2-propeniminium salt **2**, which undergoes attack by soft nucleophiles at C3 leading to α, β-unsaturated aldehyde products.[1] The detailed mechanism is consequently the vinylogous equivalent of that relating to the fundamental Vilsmeier reaction. Gossman and Franck performed the extended Vilsmeier reaction on 3,4-diethylpyrrole **3** to obtain the vinyl aldehyde **4** (Scheme 1).[2] The conversion of indole **5** into the 3-(indol-3-yl)propenal **6** was carried out in a related version of the extended Vilsmeier reaction, using 3-methyl-3-phenylaminopropenal and hexachlorocyclophosphazatriene,[3] but this and related compounds have also been prepared using a variety of other reactions (Scheme 1).[4-13]

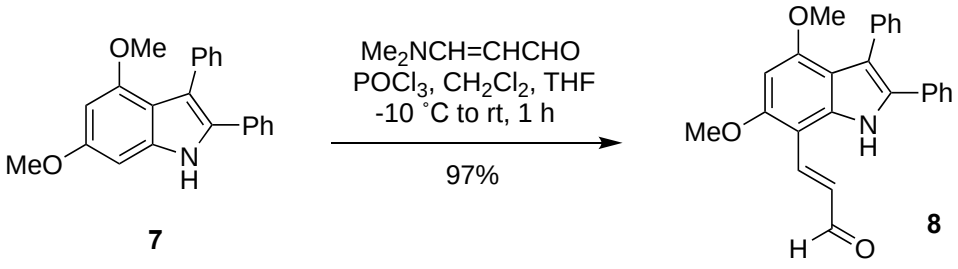


Scheme 1. Formation of 2-pyrrolyl- and 3-indolyl-propenals **4** and **6**.

It is an advantage of the extended Vilsmeier reaction that the complete side chain can be attached to the heterocycle in a single step. The normal Vilsmeier reaction has been very successfully applied to the activated 4,6-dimethoxyindoles[14,15] and 5,7-dimethoxyindoles[16] to give the related 7- and 4-carbaldehydes respectively. It was therefore of interest to investigate the extended version of this reaction for these activated indoles.

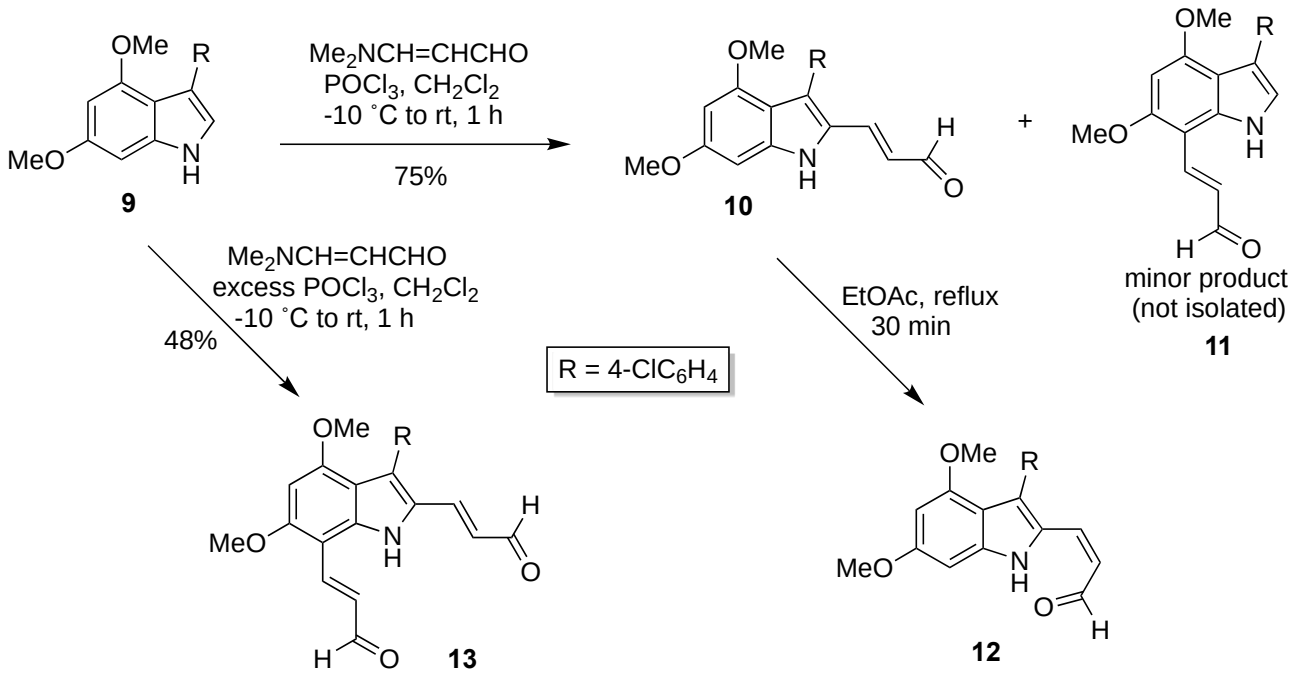
Results and Discussion

The 4,6-dimethoxy-2,3-diphenylindole **7** was reacted with 3-dimethylaminopropenal **1** and phosphoryl chloride and following work-up with aqueous sodium hydroxide afforded the orange-red 7-substituted indole **8** in 97% yield (Scheme 2).



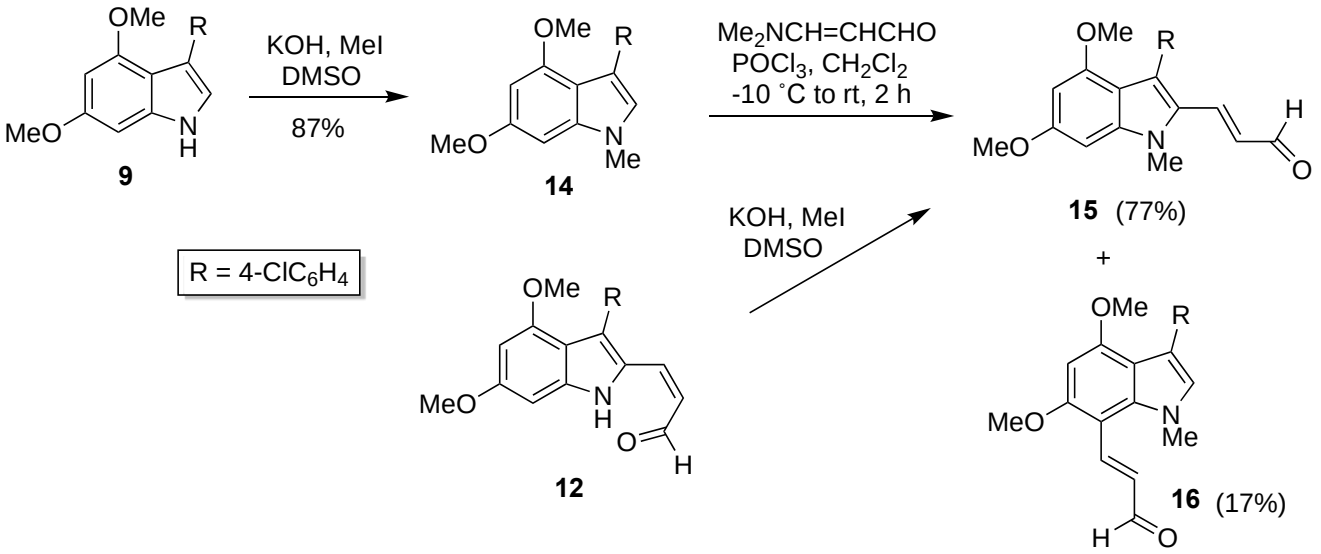
Scheme 2. Formation of 7-indolylpropenal **8**.

However, a similar reaction of the 3-aryl indole **9** gave the yellow 2-substituted indole **10** as the major product in 75% yield: it was accompanied by a small amount of the isomeric 7-substituted indole **11**, which could not be isolated (Scheme 3). The ratio of 2:7 isomers was identified by ^{1}H NMR spectroscopy to be 90:10. Compound **10** was assigned the *trans* configuration on the basis of the alkenyl proton coupling constant of 15.9 Hz. The result of this reaction is in stark contrast to the outcome of Vilsmeier formylation of compound **9** (and many similar indoles) where the overwhelmingly major product is the 7-isomer.[17] In this situation, the indole-7-carbaldehyde oxygen atom is able to form a strong hydrogen bond to the indole NH proton forming a 6-membered ring, but this is not available for the vinylogous example. The *trans*-propenal **10** was observed to undergo isomerization to the dark red *cis*-propenal **12** at room temperature in a variety of non-hydrogen bonding solvents and this process was accelerated at higher temperatures. The *cis*-isomer **12** displayed an alkenyl proton coupling constant of 12.2 Hz in its ^{1}H NMR spectrum. The *cis*-structure is presumably stabilized to some extent by formation of a hydrogen bond between the aldehyde oxygen atom and the indole NH proton to form a 7-membered ring. Treatment of the 3-aryl indole **9** with an excess of 3-dimethylaminopropenal **1** and phosphoryl chloride gave the rather insoluble orange 2,7-disubstituted indole **13** in 48% yield (Scheme 3).



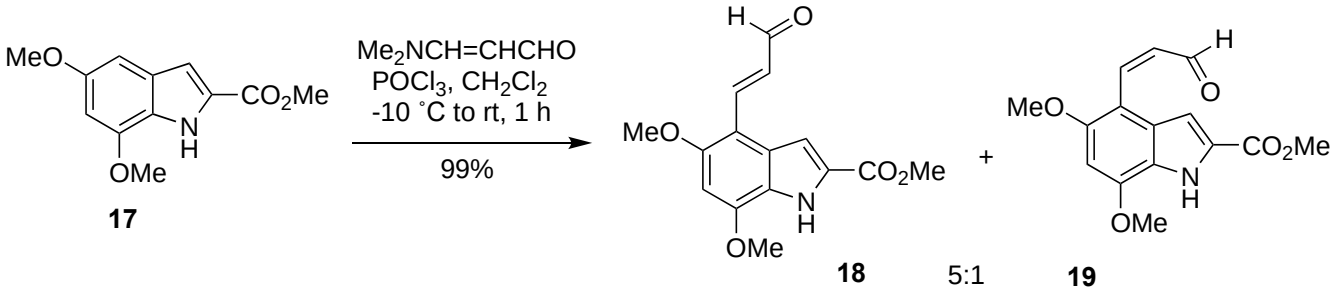
Scheme 3. Formation of 2-indolyl-, 7-indolyl- and 2,7-diindolylpropenals **10**-**13**.

The *N*-methyl indole **14** was prepared by methylation of indole **9**, and when treated with 3-dimethyl-aminopropenal **1** and phosphoryl chloride gave a mixture of the 2- and 7- isomeric propenals **15** and **16** in yields of 77% and 17% respectively (Scheme 4). In both cases the alkenyl systems were *trans*, as identified by ^{1}H NMR proton coupling constants of 16.4 and 15.5 Hz respectively. No isomerization of the *trans*-configuration of compound **15** was observed. Furthermore, methylation of the cis-propenal **12** generated compound **15** as a result of *cis*-*trans* isomerization.



Scheme 4. Formation of 2-indolyl- and 7-indolyl-*N*-methyl-propenals **15** and **16**.

The extended Vilsmeier methodology was also applied to methyl 5,7-dimethoxyindole-2-carboxylate **17**. Thus, reaction with 3-dimethylaminopropenal **1** and phosphoryl chloride under the same conditions as used in the case of indole **9** gave the 4-indolylpropenal in a 99% yield, as a 5:1 mixture of the *trans*-propenal **18** and the *cis*-propenal **19** respectively (Scheme 5). The respective structures showed ^{1}H NMR proton coupling constants of 16.2 and 11.3 Hz for the alkenyl protons. Substitution occurred exclusively at C4 and not at all at C3: this is consistent with similar reported Vilsmeier formylation behaviour.[16] The *trans*-isomer **18** was isolated as crimson rhombs by recrystallization from dichloromethane/light petroleum. Furthermore, no isomerization to the *cis*-isomer **19** was observed on heating.



Scheme 5. Formation of 4-indolylpropenals **18** and **19**.

The various propenylated indoles offer a wide range of further functionalization developments. The early work of Gosmann and Franck was directed to the synthesis of a macrocyclic tetrapyrrole, via acid-catalysed tetramerisation of the allylic alcohol obtained by reduction of their pyrrolylpropenal.[2] Given our previous conversion of activated indolylmethanols into calix[3]- and calix[4]-arenes,[17] we carried out preliminary investigations in a search for expanded calixindoles. The various indolylpropenals were reduced with sodium borohydride in a mixture of methanol and tetrahydrofuran, and the crude indolylmethanol products were treated with *p*-toluenesulfonic acid in dichloromethane. No discrete macrocyclic or oligomeric products could be isolated from the resulting polymeric mixtures. A more prolonged investigation of different reaction conditions is needed to try to achieve the formation of expanded calixindoles from the indolylpropenal structures.

Conclusions

A variety of indoles, activated by methoxy groups placed at C4 and C6, or C5 and C7, undergo reaction with 3-dimethylaminopropenal **1** and phosphoryl chloride to give high yields of the indolyl-propenals resulting from electrophilic substitution taking place at C2, C4 and C7. This extended Vilsmeier methodology provides effective functionalisation of indoles with a propenyl substituent in a single step. These products provide a range of opportunities for further structural variation and development.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC300F (^{1}H: 300MHz, ^{13}C: 75.5 MHz) or a Bruker AM500 spectrometer. The chemical shifts (δ) and coupling constants (J) are expressed in ppm and hertz respectively. Carbon attributions C, CH, CH_2 and CH_3 were determined by ^{13}C, DEPT and HMQC experiments. Infrared (IR) spectra were recorded on a Mattson Genesis Series FTIR spectrometer using potassium bromide disks, except where specified. Ultraviolet and visible (UV/Vis) spectra were recorded in tetrahydrofuran or methanol using a Carey 100 spectrometer. Mass spectra were recorded on a VG Quattro MS (EI) or a Finnigan MAT (MALDI). High resolution mass spectrometry (HRMS) was carried out at the Research School of Chemistry, Australian National University. Melting points were measured using a Mel-Temp melting point apparatus and are uncorrected. Microanalyses were performed at the UNSW Microanalytical Unit and at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. Column chromatography was carried out using Merck 230-400 mesh silica gel or Merck 70-230 mesh silica gel, whilst preparative TLC was performed using Merck 60GF_{254} silica gel.

***trans*-3-(4,6-Dimethoxy-2,3-diphenylindol-7-yl)propen-1-al (8)**. The diphenylindole **7** (2.05g, 6.22 mmol) and 3-dimethylaminopropenal **1** (1.2 mL, 11.98 mmol) were dissolved together in a mixture of anhydrous dichloromethane (50 mL) and anhydrous tetrahydrofuran (1 mL). The resulting solution was stirred at -10 ˚C in an ice-salt bath and phosphoryl chloride (1.2 ml, 12.87 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for a further 1 h. Sodium hydroxide (10% aqueous solution) was added and the reaction mixture was stirred vigorously for 1.5 h. The mixture was then extracted with ethyl acetate and the organic phase was washed with water, brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the *trans*-propenal **8** (2.31 g, 97%) as orange-red rhombs, mp 246-247 ˚C (from ethanol). IR (ν_{max} cm^{-1}): 3378, 1646, 1566, 1170, 977, 760, 696. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 262 (28,800), 337 (15,600), 400 (14,500). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.81, 4.02 (6H, 2s, OMe), 6.29 (1H, s, indole H5), 6.78 (1H, dd, *J* 16.3 Hz, 7.7 Hz, H2), 7.26-7.40 (10H, m, aryl), 8.12 (1H, d, *J* 16.3 Hz, H3), 8.59 (1H, br, NH), 9.71 (1H, d, *J* 7.7 Hz, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 56.0, 57.3 (OMe), 89.0 (indole C5), 126.2, 127.0, 128.1, 128.2, 128.7, 129.3, 132.0 (aryl CH, C2), 146.4 (C3), 101.5, 114.3, 116.2, 132.8, 134.0, 135.9, 136.8, 159.1, 159.6 (aryl C), 195.5 (CHO). MS (+EI, *m/z*, %): 383 (M, 45), 366 (100). Anal. calcd for $C_{25}H_{21}NO_3$: C, 78.3; H, 5.5; N, 3.7. Found: C, 78.5; H, 5.8; N, 3.5%.

***trans*-3-(3-(4'-Chlorophenyl)-4,6-dimethoxyindol-2-yl)propen-1-al (10)**. The indole **9** (0.14 g, 0.49 mmol) and 3-dimethylaminopropenal **1** (94 µL, 0.94 mmol) were dissolved together in anhydrous dichloromethane (20 mL) and the resulting solution was cooled to -10 ˚C in an ice-salt bath and phosphoryl chloride (94 µL, 1.01 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for 1 h. Sodium hydroxide (10% aqueous solution) was added and the reaction mixture was stirred vigorously for 1.5

h. The solution was extracted with ethyl acetate and the organic phase was washed with water, saturated brine solution and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the *trans*-propenal **10** (0.13 g, 75%) as a yellow *solid*, mp 212-214 ˚C. IR (ν_{max} cm^{-1}): 3300, 1651, 1605, 1132, 667. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 275 (20,800), 402 (29,300). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.71, 3.88 (6H, 2s, OMe), 6.17 (1H, d, *J* 1.7 Hz, indole H5), 6.42 (1H, dd, *J*, 15.9, 7.4 Hz, H2), 6.48 (1H, d, *J* 1.7 Hz, indole H7) 7.28 (1H, d, *J* 15.9 Hz, H3), 7.37, 7.41 (4H, 2d, *J* 8.6 Hz, aryl), 8.68 (1H, br, NH), 9.52 (1H, d, *J* 7.4 Hz, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 55.8, 56.4 (OMe), 86.7 (indole C5), 93.8 (indole C7), 124.2 (C2), 140.9 (C3), 128.4, 133.2 (aryl CH), 113.8, 128.5, 128.7, 129.1, 132.9, 140.7, 156.5, 161.6 (aryl C), 193.6 (CHO). MS (+EI, *m/z*, %): 343 ($M^{37}Cl$, 35), 341 ($M^{35}Cl$, 100), 326 (17), 312 (14), 300 (14), 287 (14), 277 (33). Anal. calcd for $C_{19}H_{16}ClNO_3$: C, 66.8; H, 4.7; N,4.1. Found: C, 66.7; H, 4.9; N, 4.0%.

***cis*-3-(4-Chlorophenyl-4,6-dimethoxyindol-2-yl)propen-1-al (12)**. *trans*-Propen-3-al **10** was heated under reflux in ethyl acetate for 30 min. The resulting isomeric mixture was fractionally recrystallized from ethyl acetate/light petroleum to yield the *cis*-propen-3-al **12** as a dark red *solid*, mp 187-188 ˚C. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.70, 3.85 (6H, 2s, OMe), 5.98 (1H, dd, *J* 12.3 Hz, 2.3 Hz, H2), 6.13, 6.54 (2H, 2d, *J* 1.8 Hz, indole H5 and H7), 6.69 (1H, dd, *J* 12.3 Hz, 1.9 Hz, H3), 7.35, 7.38 (4H, 2d, *J* 9.2 Hz, aryl), 9.45 (1H, t, *J* 1.9 Hz, CHO), 12.23 (1H, br, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 55.7, 56.3 (OMe), 86.8 (indole C5), 93.8 (indole C7), 116.9 (C2), 134.4 (C3), 128.1, 133.5 (aryl CH), 114.0, 127.4, 128.3, 131.2, 133.8, 139.0, 156.4, 161.8 (aryl C), 190.5 (CHO). MS (+EI, *m/z*, %): 343 ($M^{37}Cl$, 30), 341 ($M^{35}Cl$, 100), 326 (15), 300 (20), 277 (35).

***trans*-3-[3-(4-Chlorophenyl)-4,6-dimethoxy-7-(3-propen-1-al)indol-2-yl]propen-1-al (13)**. The indole **9** (2.02 g, 7.02 mmol) and 3-dimethylaminopropenal **1** (1.50 mL, 15.0 mmol) were dissolved together in anhydrous dichloromethane (100 mL) and the resulting solution was cooled to -10°C in an ice-salt bath. Phosphoryl chloride (1.50 mL, 16.1 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for 5 h. Sodium hydroxide (10% aqueous solution) was added and the reaction mixture was stirred vigorously overnight. The remaining solution was extracted with ethyl acetate/tetrahydrofuran and the organic phase was washed with water, saturated brine solution and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the dipropenal **13** (1.34 g, 48%) as an orange solid. Recrystallization from acetone resulted in orange *needles*, mp 269-270 ˚C. IR (ν_{max} cm^{-1}): 3380, 3360, 1670, 1660, 1585, 1295, 1285, 1140, 1110. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 220 (17,500), 272 (22,100), 298 (11,000), 383 (28,300). ^{1}H NMR (300 MHz, d_6-DMSO): δ_H 3.90, 4.13 (6H, 2s, OMe), 6.60 (1H, s, indole H5), 7.03-7.11 (2H, m, H2), 7.41 (1H, d, *J* 15.9 Hz, H3), 7.50, 7.59 (4H, 2d, *J* 7.7 Hz, aryl), 8.33 (1H, d, *J* 15.4 Hz, H3), 9.65, 9.74 (2H, 2d, *J* 7.7 Hz, CHO), 11.59 (1H, s, NH). ^{13}C NMR (75 MHz, d_6-DMSO): δ_C 59.7, 60.5 (OMe), 93.4 (indole C5), 131.5, 136.8 (aryl CH), 130.2, 131.9, 143.5, 149.1, alkenyl CH), 103.8, 115.8, 127.4, 134.0, 136.0, 136.2, 143.4, 162.2, 164.9 (aryl C), 198.0, 198.6 (CO). MS (+EI, *m/z*, %): 397 ($M^{37}Cl$, 25), 395 ($M^{35}Cl$, 70), 378 (100), 364 (50), 114 (60). Anal. calcd for $C_{22}H_{18}ClNO_4.0.5H_2O$: C, 65.3; H, 4.7; N, 3.5. Found: C, 65.6; H, 4.9; N, 3.2%.

3-(4-Chlorophenyl)-4,6-dimethoxy-*N*-methylindole (14). The indole **9** (0.51g, 1.78 mmol) and crushed potassium hydroxide were dissolved together in dimethylsulfoxide (20 mL) and the solution was stirred at room temperature for 10-15 min. Methyl iodide (0.13 mL, 2.1 mmol) was added and the mixture stirred for 1 h. Water was added and the resulting precipitate was collected to yield *N*-methylindole **14** (0.46 g, 87%) as a pale yellow solid. Recrystallization from ethyl acetate/light petroleum resulted in yellow *rhombs*, mp 135-136 ˚C. IR (ν_{max} cm^{-1}): 1582, 1211, 1146, 837, 811. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 226 (ε28,100), 279nm (16,700). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.78, 3.85, 3.94 (9H, OMe, NMe), 6.31, 6.44 (2H, d, *J* 2.0 Hz, H5, H7), 6.92 (1H, s, H2), 7.46 (4H, dd, *J* 2.7 Hz, 8.5 Hz, aryl). ^{13}C NMR (75 MHz, d_6-DMSO): δ_C 32.6 (NMe), 54.9, 55.3 (OMe), 85.9 (C5), 91.9 (C7), 126.2 (C2), 127.4, 130.3 (aryl CH), 109.4, 114.7, 129.6, 134.8, 138.9, 154.0, 156.9 (aryl C). MS

(+EI, *m/z*, %): 303 ($M^{37}Cl$, 30), 301 ($M^{35}Cl$, 100), 286 (25), 258 (16), 251 (85), 236 (16). Anal. calcd for $C_{17}H_{16}ClNO_2$: C, 67.7; H, 5.3; N, 4.6. Found: C, 67.5; H, 5.4; N, 4.5%.

***trans*-3-[3-(4-Chlorophenyl)-4,6-dimethoxy-1-methylindol-2-yl]propen-1-al (15) and *trans*-3-[3-(4-chlorophenyl)-4,6-dimethoxy-1-methylindol-7-yl]propen-1-al (16)**. The *N*-methylindole **14** (200 mg, 0.66 mmol) and 3-dimethylaminopropenal **1** (80 µL, 0.80 mmol) were dissolved together in anhydrous dichloromethane (20 mL) and the soution cooled to -10 ˚C with an ice-salt bath. Phosphoryl chloride (80 µL, 0.85 mmol) was added slowly and the solution warmed to room temperature and stirred for a further 2 h. Sodium hydroxide (10% aqueous solution) was added and the reaction mixture was stirred overnight. The mixture was extracted with dichloromethane, the extract washed with water, saturated brine solution and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography with dichloromethane to dichloromethane/ethyl acetate (80:20) eluant to yield a mixture of the two propenals **15** and **16** in a combined yield of 94%. The indol-2-ylpropenal **15** (0.18 g, 77%) was obtained as a yellow solid. Recrystallization from ethyl acetate/light petroleum resulted in yellow *rhombs*, mp 184-185 ˚C. IR (ν_{max} cm^{-1}): 1667, 1601, 1260, 1117. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 273 (19,700). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.72 (3H, s, NMe), 3.91, 3.95 (6H, 2s, OMe), 6.21, 6.40 (2H, 2d, *J* 1.9 Hz, indole H5, H7), 6.48 (1H, dd, *J* 16.4 Hz, 7.6 Hz, H2), 7.36 (1H, d, *J* 16.4 Hz, H3), 7.36, 7.43 (4H, 2d, *J* 8.7 Hz, aryl), 9.48 (1H, d, *J* 7.6 Hz, CHO). ^{13}C NMR (75 MHz, d_6-DMSO): δ_C 31.8 (NMe), 55.2, 55.6 (OMe), 85.4 (indole C5) 92.9 (indole C7), 125.8 (C2), 140.3 (C3), 127.6, 132.5 (aryl CH), 111.3, 122.3, 128.9, 131.8, 133.6, 141.3, 155.0, 159.6 (aryl C), 193.9 (CO). MS (+EI, *m/z*, %): 357 ($M^{37}Cl$, 35), 355 ($M^{35}Cl$, 100), 326 (25), 314 (25), 291 (50), 146 (40), 139 (60). Anal. calcd for $C_{20}H_{18}ClNO_3$: C, 67.5; H, 5.1; N, 3.9. Found: 67.6; H, 5.3; N, 3.9%.

The indol-7-ylpropenal **16** (40 mg, 17%) was obtained as a green solid. Recrystallization from ethyl acetate/light petroleum resulted in olive green *needles*, mp 219-220 ˚C. IR (ν_{max} cm^{-1}): 1678, 1574, 1146, 1046, 793. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 232 (29,000), 272 (5,900). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.95 (3H, s, NMe), 4.02, 4.03 (6H, 2s, OMe), 6.35, 6.86 (2H, 2s, indole H5 and H2), 6.99 (1H, dd, *J* 15.5, 7.7 Hz, H2), 7.42 (4H, dd, *J* 8.3, 2.0 Hz, aryl), 8.14 (1H, d, *J* 15.5 Hz, H3), 9.69 (1H, d, *J* 7.7 Hz, CHO). MS (+EI, *m/z*, %): 357 ($M^{37}Cl$, 35) 355 ($M^{35}Cl$, 100), 326 (25), 324 (85), 301 (50), 261 (20), 251 (20), 160 (30). Anal. calcd for $C_{20}H_{18}ClNO_3$: C, 67.5; H, 5.1; N, 3.9. Found: C, 67.3; H, 5.4; N, 3.7%.

Methyl *trans*-3-(5,7-dimethoxyindol-4-yl)propen-1-al-2-carboxylate (18) and methyl *cis*-3-(5,7-dimethoxy-indol-4-yl)propen-1-al-2-carboxylate (19). A mixture of methyl 5,7-dimethoxyindole-2-carboxylate **17** (0.107 g, 0.455 mmol) and 3-dimethylaminopropenal **1** (0.10 mL, 0.91 mmol) in dichloromethane (2.0 mL) was stirred with cooling in a salt-ice slurry. A similarly cooled solution of phosphoryl chloride (0.09 mL, 1 mmol) in dichloromethane (1.0 mL) was added dropwise over 3 min and stirring was continued for 1 h with cooling below 0 ˚C. Stirring was then continued at ambient temperature for 50 min before the solution was re-cooled in a salt-ice slurry and made strongly alkaline with 5M NaOH. After dilution with water and ethyl acetate the mixture was stirred vigorously for 30 min at ambient temperature. The mixture was then extracted with further ethyl acetate and the organic phase was washed with water, then brine, and dried ($MgSO_4$). Evaporation of the solvent *in vacuo* gave an isomeric mixture of the *title compounds* (0.130 g, 99%) as a yellow powder, consisting of a 5:1 ratio of the *trans*/*cis* propen-1-al. Recrystallization from dichloromethane/light petroleum gave methyl *trans*-3-(5,7-dimethoxyindol-4-yl)propen-1-al-2-carboxylate **18** as crimson prisms, mp 200-202 ˚C. Rf (2% MeOH/CH_2Cl_2) 0.25. IR (ν_{max} cm^{-1}): 3314, 1703, 1655, 1578, 1530, 1439, 1342, 1265, 1214, 1167, 1143, 979, 821, 772, 742. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 240 (30,100), 278 (8,900), 307 (11,400), 337 (11,700), 380 (14,700). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.95, 3.97 and 4.04 (9H, s, OMe), 6.50 (1H, s, indole H6), 6.95 (1H, dd, *J* 7.9, 16.2 Hz, H2), 7.41 (1H, d, *J* 1.9 Hz, indole H3), 8.01 (1H, d, *J* 16.2 Hz, H3), 9.13 (1H, bs, NH), 9.68 (1H, d, *J* 7.9 Hz, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 57.1, 55.7, 52.1 (OMe), 92.7 (indole C6), 107.6 (indole

C3), 127.9, 146.7 (C2 and C3), 108.2, 123.6, 127.0, 128.5, 149.8, 156.7 (aryl C), 161.7 ($\underline{C}O_2Me$), 195.1 (CHO). MS (+EI, *m/z*, %): 290 (10), 289 (M, 65), 258 (100), 235 (21), 229 (15), 228 (17), 226 (67), 214 (21), 203 (56), 200 (17), 186 (21). Anal. calcd for $C_{15}H_{15}NO_5$: C, 62.3; H, 5.2; N, 4.8. Found: C, 62.5; H, 5.2; N, 4.7%.

Methyl cis-3-(5,7-dimethoxyindol-4-yl)propen-1-al-2-carboxylate (19). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.88, 3.92, 4.02 (9H, s, OMe), 6.16 (1H, dd, *J* 8.6, 11.3 Hz, H2), 6.54 (1H, s, indole H6), 7.06 (1H, d, *J* 2.3 Hz, indole H3), 7.65 (1H, d, *J* 11.3 Hz, H3), 9.04 (1H, bs, NH), 9.78 (1H, d, *J* 8.3 Hz, CHO).

Acknowledgements

We thank the Australian Research Council for financial support.

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