Synthesis of 2-(Pyrimidin-4-yl)indoles[1)]

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The synthesis of 2-substituted isomers of the meridianins, a familiy of bioactive indole alkaloids isolated from the tunicate *Aplidium meridianum*, was undertaken. The synthetic route comprises six steps, with a microwave promoted Fischer cyclization as the key reaction.

Key words meridianin; Fischer indole synthesis; microwave

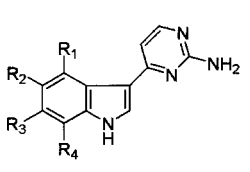
The meridianins (**1**—**6**) are a family of indole alkaloids which were isolated by our group from the subantarctic tunicate *Aplidium meridianum* collected near the South Georgia islands.[2)] The basic structure of these compounds consists of an indole nucleus substituted at C-3 by a 2-aminopyrimidine ring. Other examples of heterocycles substituted by an aminopyrimidine ring have been reported among marine natural products, such as the psammopemmins (**7**—**9**), isolated from the sponge *Psammopemma* sp.,[3)] and variolin B (**10**), from the sponge *Kirkpatrickia varialosa*,[4)] all of which show promising antitumor activity. Prompted by this, we decided to synthesize analogs of the natural meridianins in order to study the structure–activity relationship of this type of compounds. In this paper, we report the synthesis of two analogs of meridianins which we designated iso-meridianins, that bear the pyrimidine ring at C-2 instead of C-3, starting from isocytosine, and using a microwave-assisted Fischer indole cyclization as the key step.

The natural meridianins have previously been synthesized by two different strategies: either the construction of the 2-aminopyrimidine ring from a β-dicarbonylic substituted indole precursor,[5)] or by a cross-coupling reaction between the indole and pyrimidine moieties.[6)] Both strategies have in common the use of a conveniently substituted indole precursor. Since we wanted to study, among other aspects, the influence of diverse substituents on the indole ring, we decided to take a different approach, building the indole ring by a Fischer indole synthesis. This route would give us greater flexibility in the preparation of a wide variety of analogs with different substituents on the indole ring, since available substituted phenylhydrazines or anilines are much more numerous than substituted indoles.

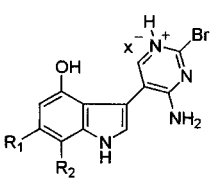
We chose isocytosine as an adequate starting material, since the hydroxyl group at position 4 allows a convenient functionalization and introduction of the required C-2 carbonyl group. As a first step, the amino group of isocytosine (**11**) was protected with a Boc group (**12**) under standard conditions,[7)] and then the hydroxyl group was substituted by chlorine ($POCl_3$) to yield the 4-chloro derivative **13**.[8)] Introduction of a methyl ketone at position 4 was achieved by a cross-coupling reaction of compound **13** with tri-*n*-butyl(1-ethoxyvinyl)tin to yield the vinyl ether **14**, which by acid hydrolysis gave the desired methyl ketone **15**.[9—11)] The latter afforded the corresponding phenylhydrazones **16** and **17** under standard conditions.

The Fischer indole synthesis was the key step of this work. Numerous attempts using a variety of catalysts, solvents and heating conditions are listed in Table 1. The use of $ZnCl_2$ at reflux in a variety of solvents of increasing boiling point gave either no reaction or decomposition of the starting material. Heating the sample in an oven with $ZnCl_2$ at high temperature (180 °C) without solvent for short times gave a low yield of the desired indole, with extense decomposition. Prompted by this we tried heating **16** with $ZnCl_2$ in a domestic microwave oven, which resulted in a low yield of **18**. Use of montmorillonite K-10 and $ZnCl_2$ under microwave conditions gave yields lower than 20%. However, addition of a small volume of DMF prior to microwave heating with $ZnCl_2$ afforded the corresponding indoles **18** and **19** in good yield. In all cases, the use of $ZnCl_2$ and microwave heating produced a fast, clean and quantitative removal of the Boc group. There have been some previous reports on microwave assisted Fischer indole syntheses, either using dry $ZnCl_2$,[12)] dry montmorillonite K-10,[13)] or formic acid.[14)] All these procedures were used for the preparation of indoles bearing simpler and more stable substituents than the 2-aminopyrimidine group. Under all these conditions our compounds mostly failed to give the desired products; for this reason our procedure represents the first successful preparation of an aminopyrimidine substituted indole by a Fischer indole cyclization.

The activity results of these meridianin analogs were poor and will be included in a more comprehensive structure–activity study. For this reason the preparation of further deriva-



1-6: R_1 - R_4 : H, OH or Br



7-9: R: H or Br

10

Chart 1

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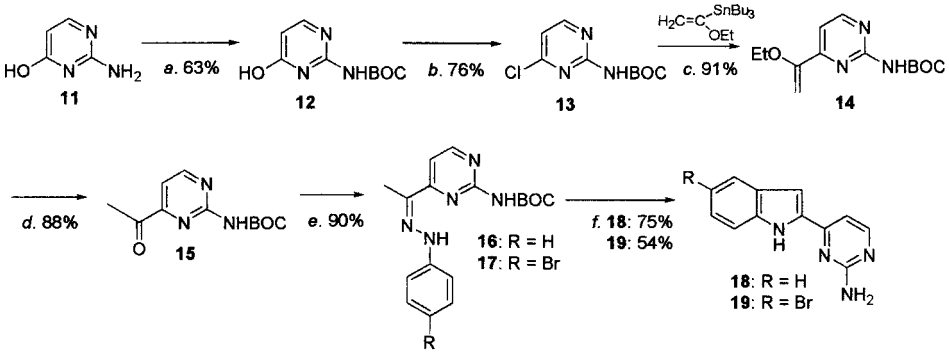

a. (t-BuCO$_2$)$_2$O, py, 85 °C *b*. $POCl_3$, N,N-dimethylaniline, CH_2Cl_2, r.t. *c*. $(Ph_3P)_4Pd$, LiCl, THF, reflux
d. *p*-TSA, acetone, reflux *e*. Phenylhydrazine hydrochloride, NaAcO, MeOH f. $ZnCl_2$, DMF, microwave

Fig. 1

Table 1. Conditions for Fischer Indole Synthesis of Iso-Meridianin G

Catalysis	Solvent or additive	Heating	Time (min)	Yield (%)
$ZnCl_2$ (74% w/w)	Montmorillonite K-10	Microwave irradiation using alumina bath	18	17
$ZnCl_2$ (74% w/w)	Montmorillonite K-10	Oven (180 °C)	120	18
$ZnCl_2$	Solvent free	Microwave irradiation	9	<5
$ZnCl_2$	Solvent free	Oven (180 °C)	50	<5
$ZnCl_2$	MeOH	Reflux	60	NR
$ZnCl_2$	DMF	Reflux under inert atmosphere	1140	9
$ZnCl_2$	Toluene	Reflux under inert atmosphere	360	NR
p-Toluenesulfonic acid	MeOH	Reflux	120	NR
$ZnCl_2$	DMF	Microwave irradiation	9	75
Formic acid 98%		Microwave irradiation	9	NR

All experiments using microwave irradiation were performed on an Amana domestic microwave oven and heated at full power (aproximately 1500 W).

tives with 2-substitution was not pursued. However, this synthetic route remains a viable scheme for the preparation of meridianins and analogs.

Experimental

General Anhydrous $ZnCl_2$ was used in all cases. $ZnCl_2$ was melted in a porcelain crucible, then ground in a mortar and kept in a dissicator till used. Melting points were determined with a Thomas Hoover melting point apparatus and are uncorrected. UV and IR spectra were recorded on a Hewlett Packard Model 8451 A diode array spectrophotometer and a Nicolet Magna-IR^{tm} Model 550 spectrometer, respectively. NMR spectra (δ ppm, J in Hz) were obtained on a Bruker AM-500 Spectrometer at 500.13 MHz (^{1}H) and 125.77 MHz (^{13}C). HR-EI-MS were performed with a VG-ZAB-SEQ4F instrument at 70 eV.

***tert*-Butyl (4-Hydroxypyrimidin-2-yl)carbamate (12)** 4-Hydroxypyrimidin-2-amine (**11**) (1 g, 9 mmol) was dissolved in pyridine (42 ml) and heated at 65 °C on a water bath with magnetic stirring. After adding di-*tert*-butyl dicabonate (2.94 g, 13.5 mmol) the solution was heated at 85 °C for 4 h. The solution was cooled on an ice bath and concentrated hydrochloric acid (20 ml) was added; finally the reaction mixture was extracted with ethyl acetate. The organic layer was washed with sodium bicarbonate and water. Evaporation under reduce pressure gave 1.21 g (5.7 mmol) (63%) of a white solid (**12**). Compound **12**: mp: 139—142 °C (H_2O–MeOH); IR (film) cm^{-1}: 3428, 3251, 1701, 1281, 796; UV λ_{max} (methanol) nm (ε): 212 (15760), 285 (5550); ^{1}H-NMR ($CDCl_3$) δ: 11.76 (2H, br s, interchangeable), 7.74 (1H, d, J=6.9 Hz), 6.06 (1H, d, J=6.9 Hz), 1.57 (9H, s); ^{13}C-NMR ($CDCl_3$) δ: 160.5 (s), 153.1 (s), 153 (d), 152.2 (s), 109.1 (d), 84.1 (s), 27.9 (q); MS *m*/*z*: 211 (M$^+$), 169, 155, 138, 111.

***tert*-Butyl (4-Chloropyrimidin-2-yl)carbamate (13)** Compound **12** (1.2 g, 5.7 mmol) was suspended in a mixture of 42 ml of dichloromethane and 3.3 ml of *N*,*N*-dimethylaniline. $POCl_3$ (1.58 ml, 17.1 mmol) was then slowly added while cooling on an ice bath with stirring. After the addition was completed, the solution was further stirred at room temperature for 2 h. The solution was washed with aqueous 2 M hydrochloric acid, sodium bicarbonate and water. Evaporation of the dichloromethane layer *in vacuo* gave 0.98 g (4.3 mmol) (75%) of a white residue (**13**). Compound **13**: mp: 134—137 °C (MeOH–H_2O); IR (film) cm^{-1}: 3213, 3049, 1767, 1568, 1512, 1237, 765; UV λ_{max} (methanol) nm (ε): 232 (23310), 275 (4380); ^{1}H-NMR ($CDCl_3$) δ: 8.46 (d, 1H, J=5.2 Hz), 7.85 (br s, 1H), 6.98 (d, 1H, J=5.2 Hz), 1.53 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ: 162.0 (s), 159.5 (d), 157.9 (s), 129.7 (s), 116.0 (d), 82.3 (s), 28.3 (q); MS *m*/*z*: 229 (M$^+$), 227, 174, 158, 156, 131, 129.

***tert*-Butyl [4-(1-Ethoxyvinyl)pyrimidin-2-yl]carbamate (14)** Tri-*n*-butyl(1-ethoxyvinyl)tin (387 μl, 1.15 mmol) was added to a suspension of compound **13** (0.263 g, 1.15 mmol) and LiCl (0.146 g, 3.44 mmol) in dry THF (2.6 ml) under nitrogen at room temperature. After adding tetrakis(triphenylphosphine)palladium (0.039 g, 0.034 mmol) the solution was heated under reflux for 3.5 h. The cold reaction mixture was diluted with THF, treated with an aqueous 0.16 M potassium fluoride solution (10 ml) and stirred at ambient temperature for 1 h. The precipitated tri-*n*-butylstannyl fluoride was removed by filtration. The filtrate was evaporated under reduced pressure to give an aqueous suspension which was extracted with ethyl acetate. The organic layer was washed with water, evaporated *in vacuo* and the residual material was flash chromatographed on reversed phase silica using a H_2O–MeOH (100 : 0—30 : 70) gradient to yield 0.274 g of **14** (1.03 mmol) (91%). Compound **14** had mp: 133—137 °C (MeOH–H_2O); IR (film) cm^{-1}: 3186.4, 2977.7, 1752.3, 1600, 1556.3, 1366.8, 1243.1, 768.7; UV λ_{max} (methanol) nm (ε): 202 (10430), 228 (15940), 294 (5590); ^{1}H-NMR ($CDCl_3$) δ: 8.61 (d, 1H, J=5.1 Hz), 7.38 (br s, 1H), 7.27 (d, 1H, J=5.1 Hz), 5.58 (d, 1H, J=2.2 Hz), 4.46 (d, 1H, J=2.2 Hz), 3.94 (q, 2H, J=6.8 Hz), 1.54 (s, 9H), 1.42 (t, 3H, J=6.8 Hz); ^{13}C-NMR ($CDCl_3$) δ: 161.7 (s), 159.3 (d), 157.1 (s), 156.5 (s), 150.5 (s), 110.5 (d), 88.1 (t), 81.3 (s), 63.7 (t), 28.2 (q), 14.3 (q); MS *m*/*z*: 250 (M$^+$−15), 221, 194, 192, 165, 150, 121. HR-MS (EI): Found: 250.1185 (M$^+$−15). Calcd for $C_{12}H_{16}N_3O_3$: 250.1192.

***tert*-Butyl (4-Acetylpyrimidin-2-yl)carbamate (15)** A mixture of compound **14** (6 mg, 0.022 mmol) and *p*-toluenesulfonic acid (0.5 mg, 2.9×10^{-3} mmol) in acetone (0.5 ml) was heated under reflux for 75 min. Evaporation under reduced pressure gave a white solid which was purified using flash chromatography on silica gel (dichloromethane/acetone= 100 : 0—95 : 5), to yield 4.7 mg (88%) of **15**. Compound **15** had mp 136—137 °C (MeOH–H_2O); IR (film) cm^{-1}: 3218.9, 2985.7, 1753, 1713, 1573.1, 1426.5, 1236.5, 769.4; UV λ_{max} (methanol) nm (ε): 204 (18420), 233 (16330), 300 (2600); ^{1}H-NMR ($CDCl_3$) δ: 8.81 (d, 1H, J=5 Hz), 7.58 (br s, 1H), 7.50 (d, 1H, J=5 Hz), 2.66 (s, 3H), 1.56 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ: 198.9 (s), 160.4 (d), 159.9 (s), 157.8 (s), 150.1 (s), 111.4 (d), 81.8 (s), 28.1 (q), 25.3 (q); MS *m*/*z*: 237 (M$^+$), 193, 181, 164, 137, 121.

General Procedure for the Preparation of Phenylhydrazones 16 and 17 To a mixture of compound **15** (0.28 g, 1.029 mmol) and sodium acetate

(0.218 g, 2.67 mmol), was added 1.029 mmol of the appropriate phenylhydrazine hydrochloride in methanol (19.5 ml) and the reaction mixture was stirred at room temperature for 1 h. Evaporation *in vacuo* gave a yellow solid which was suspended in dichloromethane and the inorganic salts were removed by filtration. The filtrate was evaporated to dryness to give **16** and **17** in 90% yield. These products were used without further purification.

Iso-Meridianin G (18) A mixture of *tert*-butyl 4-((1*E* and *Z*)-*N*-phenylethanehidrazonoyl)pyrimidin-2-ylcarbamate (**16**) (0.041 g, 0.125 mmol) and $ZnCl_2$ (0.182 g, 1.325 mmol) was taken in a glass tube and suspended in small amount of DMF (0.6 ml). The test tube was placed inside an Amana domestic microwave oven and heated at full power (approximately 1500 W) for 9 min. Evaporation under reduce pressure gave a black syrup which was purified using flash chromatography on reversed phase silica using a H_2O–MeOH (100 : 0—30 : 70) gradient to yield 0.0195 g (75%) of **18**. Compound **18** had mp 163—164 °C (MeOH–H_2O); IR (film) cm^{-1}: 3463, 2927, 1627, 1592, 813.9, 733.9; UV λ_{max} (methanol) nm (ε): 218 (28330), 342 (26810); ^{1}H-NMR (CD_3OD) δ: 8.17 (d, 1H, J=5.5 Hz), 7.58 (br d, 1H, J=7.9 Hz), 7.44 (dd, 1H, J=8.2, 0.9 Hz), 7.19 (ddd, 1H, J=8.2, 7.0, 0.9 Hz), 7.18 (br s, 1H), 7.12 (d, 1H, J=5.5 Hz), 7.03 (ddd, 1H, J=7.9, 7.0, 0.9 Hz); ^{13}C-NMR (CD_3OD) δ: ppm: 164.6 (s), 160.6 (s), 158.2 (d), 139.0 (s), 136.0 (s), 129.9 (s), 124.9 (d), 122.4 (d), 121.1 (d), 112.8 (d), 107.0 (d), 105.2 (d); MS *m*/*z*: 210 (M^+), 169, 115; HR-MS (EI): Found: 210.0971. Calcd for $C_{12}H_{10}N_4$: 210.0905. *Anal.* Calcd for $C_{12}H_{10}N_4$: C, 68.56; H, 4.79; N, 26.65; Found: C, 68.43; H, 4.80; N, 26.37.

Iso-Meridianin C (19) A mixture of *tert*-butyl 4-((1*E* and *Z*)-*N*-(4 bromophenyl)phenylethanehidrazonoyl)pyrimidin-2-ylcarbamate (**17**) (0.0036 g, 8.8×10^{-3} mmol) and $ZnCl_2$ (0.0118 g, 0.085 mmol) was taken in a glass tube and suspended in small amount of DMF (170 μl). The test tube was placed inside an Amana domestic microwave oven and heated at full power (approximately 1500 W) for 25 min. Evaporation under reduce pressure gave a black syrup which was dissolved in ethyl acetate and extracted with water. The organic layer was evaporated *in vacuo* and was purified using preparative thin layer silica gel chromatography (dichloromethane : acetone 6 : 4) to yield 0.0014 g (55%) of **19**. Compound **19** had mp: 190—192 °C (MeOH–H_2O); IR (film) cm^{-1}: 3408, 3308, 2930.7, 2859.4, 1622.3, 1585.4, 792.1; UV λ_{max} (methanol) nm (ε): 221 (16800), 341 (12640), 354 (11920); ^{1}H-NMR (DMSO-d_6) δ: 11.7 (br s, 1H), 8.30 (d, 1H, J=5.4 Hz), 7.80 (d, 1H, J=1.8 Hz), 7.44 (d, 1H, J=8.8 Hz), 7.27 (dd, 1H, J=8.8, 1.8 Hz), 7.18 (br d, 1H, J=1 Hz), 7.13 (d, 1H, J=5.4 Hz), 6.55 (br s, 2H); ^{13}C-NMR (DMSO-d_6) δ: 163.7 (s), 158.9 (d), 157.2 (s), 137.1 (s), 136.0 (s), 129.8 (s), 125.7 (d), 123.2 (d), 114.3 (d), 112.3 (s), 105.8 (d), 102.6 (d); MS *m*/*z*: 290, 288 (M^+), 249, 247, 208, 168, 140; HR-MS (EI): Found: 288.0002. Calcd for $C_{12}H_{10}N_4$: 288.0011.

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References and Notes

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