Organic &
Biomolecular
Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 5021

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COMMUNICATION

Regioselective dibromination of methyl indole-3-carboxylate and application in the synthesis of 5,6-dibromoindoles†

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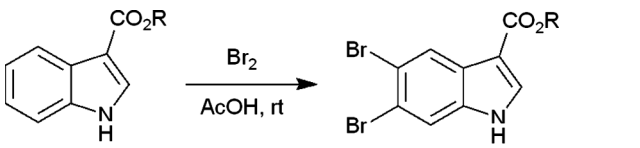
Received 4th April 2011, Accepted 12th May 2011
DOI: 10.1039/c1ob05522d

Treatment of methyl indole-3-carboxylate with bromine in acetic acid gives methyl 5,6-dibromoindole-3-carboxylate regioselectively, from which the parent 5,6-dibromoindole can be accessed *via* a one-pot, microwave-mediated ester hydrolysis and decarboxylation. Application of these building blocks in syntheses of natural and non-natural 5,6-dibromoindole derivatives, including meridianin F and 5,6-dibromo-2′-demethylaplysinopsin, is reported.

Indoles are one of the most important classes of aromatic heterocycle, widespread in nature and in medicinal chemistry, where they are regarded as privileged structures.[1] Brominated indoles have been isolated from a range of marine sources, and have been shown to possess interesting biological activities.[2]

The 5,6-dibromoindole substructure is common to a number of natural products,[3–10] the syntheses of which have barely been addressed.[3b] One possible reason for this is the paucity of effective methods for the concise chemo- and regioselective incorporation of multiple halogen substituents on the indole ring. We were therefore intrigued by a 1930 report on the dibromination of ethyl indole-3-carboxylate to give 5,6-dibromoindole **1** in high yield.[11] The regioselectivity of this reaction was determined by a 3-step degradation of **1** to 3,4-dibromoaniline, and comparison of melting points with an authentic sample (Scheme 1). Analytical data for **1** was unsurprisingly sparse given available techniques of the period, with only microanalysis reported. Surprisingly, given its obvious potential application in organic synthesis, this report has never been followed up.[12] Given the fact that the apparently related bromination of 3-formylindole is reported to be non-regioselective,[13] we decided to reinvestigate this reaction as part of a programme of research directed towards the syntheses of 5,6-dibromoindole-containing natural and non-natural products.

Bromination of commercially available methyl indole-3-carboxylate under the reported conditions did indeed give the 5,6-dibromoindole **2** in a gratifying 70% yield. The indole **2** precipitates from the reaction mixture, requiring minimal purification. The regiochemical outcome of this reaction was initially based on NMR analysis, and further confirmed by X-ray crystallography.‡ Hence the regiochemistry of bromination is consistent with the literature, as originally reported for **1**.



Majima and Kotake 1930: **1** R = Et 84%
structure by 3-step degradation to 3,4-dibromoaniline

This work: **2** R = Me 70%
structure by NMR, X-ray

Scheme 1 Regioselective bromination of indole-3-carboxylates.

With the structure of **2** confirmed, our attention turned to the application of this compound in natural product synthesis. The meridianins are marine natural products that have attracted some interest from the synthetic community due to their promising biological activity, including protein kinase inhibition and antitumour activity.[2a,4] However, a synthesis of meridianin F has not been previously reported, presumably because of the inaccessibility of the 5,6-dibromoindole substitution pattern. A concise, 5-step synthesis of meridianin F (**6**),[4] containing the characteristic 2-aminopyrimidine ring at C-3 common to all the meridianins, is shown in Scheme 2. Protection of **2** as the *N*-Boc carbamate **3**‡ (Boc_2O, 96% yield) was followed by conversion of the ester to the Weinreb amide **4**.[14] Treatment of **4** with lithium(trimethylsilyl)acetylide gave the terminal alkyne **5** directly. Direct conversion of the alkynyl ketone **5** to meridianin F (**6**) was achieved using the conditions of Müller, developed for the synthesis of related meridianins and analogues.[15] This methodology, which occurs with concomitant Boc deprotection, was previously reported on TMS-protected acetylenes and extended to alkyl and aryl substituted alkynes, with reaction times of 38 h at 80 °C, or more generally 120 °C overnight. The shorter reaction time in the case of **5** (2 h, 80 °C) is presumably due to the use of the non-TMS protected compound. Analytical data for **6** were in agreement with those previously reported, and the route shown in Scheme 2 therefore represents the first synthesis of meridianin F (**6**).

Although the ester at C-3 of **2** represents a useful functional group for further transformations, we recognized that

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† Electronic supplementary information (ESI) available: Experimental procedures and analytical data for all compounds; determination of double bond geometry for **19** and **21**; X-ray crystal structures of **2**, **3**, **7**, **10** and **11**, CCDC reference numbers 818707–818711; copies of ^{1}H and ^{13}C NMR spectra. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05522d

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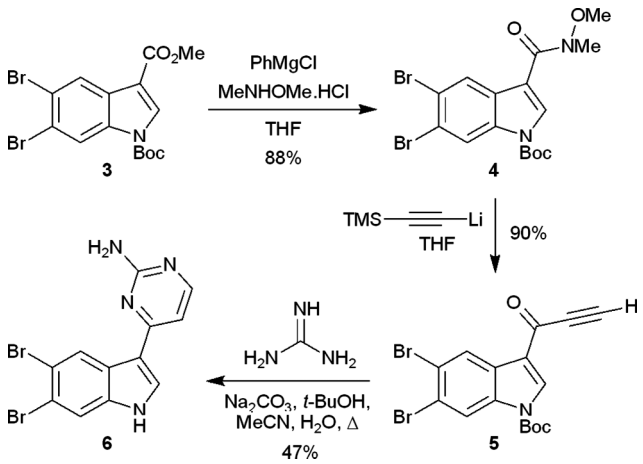
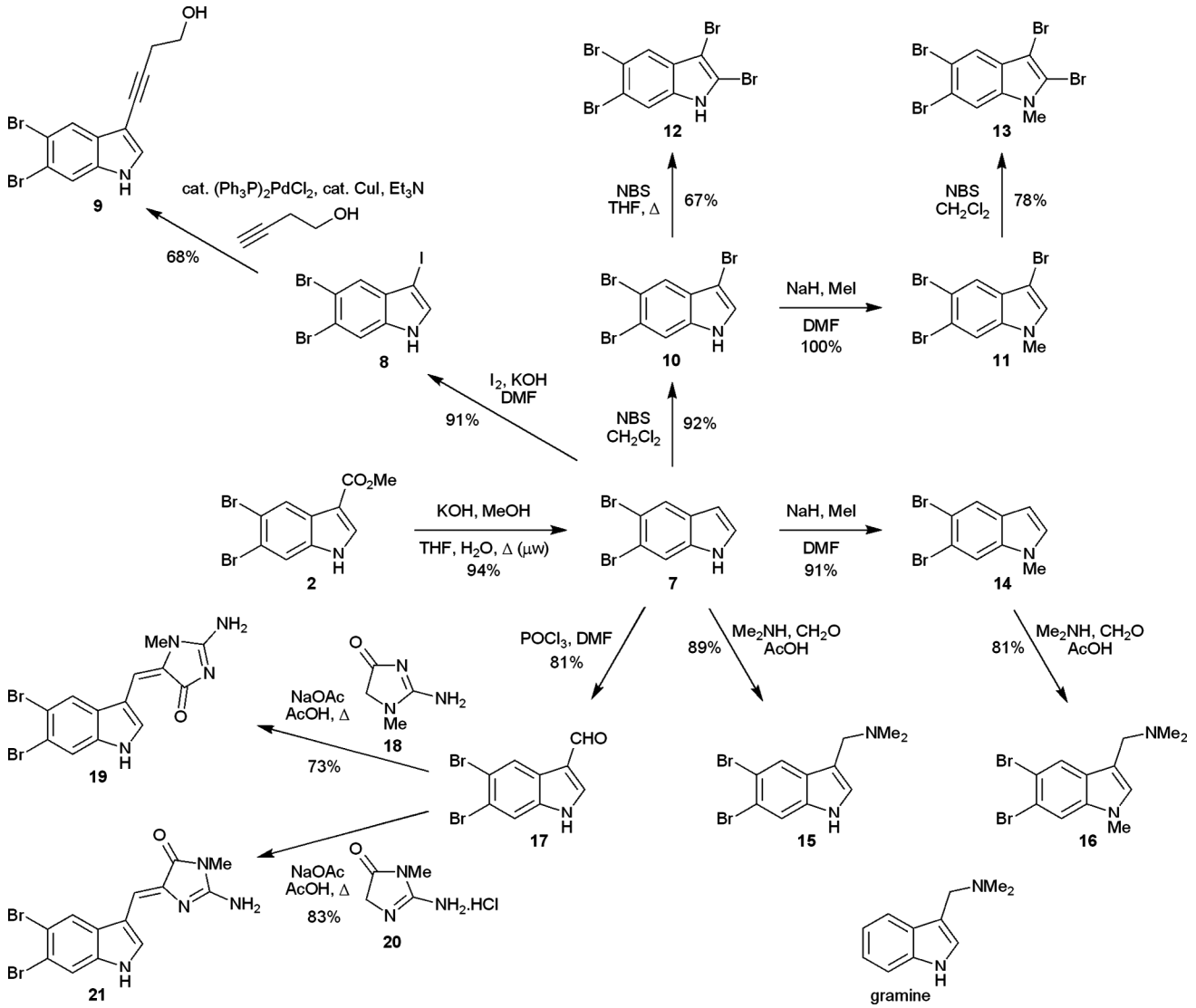


Scheme 2 Synthesis of meridianin F.

its removal would permit access to the wealth of aromatic substitution chemistry known for the 3-position of indole. We have found that ester hydrolysis and decarboxylation can be achieved in a single step through treatment of **2** with 3 equivalents of KOH in THF/MeOH/H_2O under microwave heating, providing 5,6-dibromoindole (**7**)‡ in 94% isolated yield (Scheme 3).

We have used **7** in the synthesis of both natural and non-naturally occuring 5,6-dibromoindole derivatives (Scheme 3).[16] Iodination at the 3-position of **7** occurs readily using iodine and KOH in DMF. The resulting iodide **8** can be used in a palladium-catalyzed Sonogashira cross-coupling reaction with but-4-yn-1-ol to give **9** in 68% yield (unoptimized). Bromination of **7** using NBS gave 3,5,6-tribromoindole (**10**),‡ which upon *N*-methylation gave **11**.‡ Further bromination of **10** and **11** using NBS occurs regioselectively at C-2 to give the tetrabromides **12** and **13**, respectively. Bromoindoles **10–13** are all natural products,[17–19] with only the preparation of **12** and **13** having been previously reported.[13,20–22]

Mannich reaction of **7** and the corresponding *N*-methylated indole **14** gave dimethylaminomethyl indoles **15** and **16** respectively, both brominated analogues of gramine. Brominated



Scheme 3 Synthesis and reactions of 5,6-dibromoindole.

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gramine derivatives have previously been investigated for anti-inflammatory and analgesic activity.[23]

Vilsmeier–Haack formylation of **7** gave the C-3 aldehyde **17** in high yield. Condensation of **17** with creatinine (**18**) gave the non-natural 5,6-dibromo-4′-demethylaplysinopsin **19**, isolated as a single double bond isomer. The (*E*)-double bond geometry in **19** was elucidated by NMR analysis (see ESI for details†). The 5 days reaction time can be reduced to 1 h through heating a solution of **17** and **18** in piperidine in a microwave reactor (200 W, 150 °C), with a slight erosion in selectivity (61% yield, 22 : 1 *E* : *Z*).

The naturally occurring 5,6-dibromo-2′-demethylaplysinopsin **21** has been shown to selectively inhibit the neoronal isozyme of nitric oxide synthase (nNOS).[8] 3-Formylindole **17** was readily converted into **21** through condensation with the known 2-aminoimidazolone hydrochloride salt **20**.[24] The (*Z*)-double bond geometry was obtained exclusively, and confirmed through NMR analysis (see ESI for details†). The 5 day reaction time could again be reduced to 1 h using microwave irradiation (200 W, 150 °C), with **21** isolated in 68% yield as a 21 : 1 *Z* : *E* mixture of double bond isomers.

In conclusion, the use of a reaction first reported in 1930, but which has since lain dormant in the literature, has allowed ready access to a range of both natural and non-natural 5,6-dibrominated indoles. This work should pave the way for future synthetic applications and biological studies.

Acknowledgements

We thank the EPSRC for funding, and acknowledge the UK National Crystallography Service for X-ray crystallographic data collection on compounds **2** and **3**. The NMR spectrometers used in this research were obtained through Birmingham Science City: Innovative Uses for Advanced Materials in the Modern World (West Midlands Centre for Advanced Materials Project 2), with support from Advantage West Midlands (AWM) and part funded by the European Regional Development Fund (ERDF).

Notes and references

‡ Crystallographic data: **2**: $C_{10}H_7Br_2NO_2$, M = 332.99, Triclinic, a = 7.1280(4), b = 7.3609(4), c = 10.9238(6) Å, α = 90.492(3), β = 98.609(3), γ = 112.463(3)°, U = 522.34(5) Å^3, T = 120(2) K, space group $P\bar{1}$, Z = 2, 9706 reflections measured, 2390 unique (R_{int} = 0.0302) which were used in all calculations. The final $R1$ was 0.0276 ($I > 2\sigma(I)$) and $wR(F_2)$ was 0.0598 (all data); CCDC 818707. **3**: $C_{15}H_{15}Br_2NO_4$, M = 433.10, Triclinic, a = 7.0596(3), b = 10.6930(4), c = 11.4729(4) Å, α = 96.062(2), β = 94.194(2), γ = 106.037(2)°, U = 822.95(5) Å^3, T = 120(2) K, space group $P\bar{1}$, Z = 2, 17723 reflections measured, 3762 unique (R_{int} = 0.0561) which were used in all calculations. The final $R1$ was 0.0387 ($I > 2\sigma(I)$) and $wR(F_2)$ was 0.0763 (all data); CCDC 818708. **7**: $C_8H_5Br_2N$, M = 274.95, Orthorhombic, a = 11.0874(6), b = 7.5403(4), c = 18.872(1) Å, U = 1577.7(2) Å^3, T = 150(2) K, space group *Pbca*, Z = 8, 14874 reflections measured, 1491 unique (R_{int} = 0.0310) which were used in all calculations. The final $R1$ was 0.0279 ($I > 2\sigma(I)$) and $wR(F_2)$ was 0.0778 (all data); CCDC 818709. **10**: $C_8H_4Br_3N$, M = 353.85, Monoclinic, a = 8.8688(4), b = 6.0886(3), c = 16.8852(8) Å, β = 91.443(3)°, U = 911.49(7) Å^3, T = 150(2) K, space group $P2_1/c$, Z = 4, 8715 reflections measured, 1603 unique (R_{int} = 0.0396) which were used in all calculations. The final $R1$ was 0.0251 ($I > 2\sigma(I)$) and $wR(F_2)$ was 0.0666 (all data); CCDC 818710. **11**: $C_9H_6Br_3N$, M = 367.88, Triclinic, a = 7.6033(4), b = 8.0327(4), c = 9.6610(5) Å, α = 68.061(3), β = 66.835(3), γ = 73.873(3)°, U = 497.24(4) Å^3, T = 120(2)K, space group $P\bar{1}$, Z = 2, 4842 reflections measured, 1695 unique (R_{int} = 0.0172) which were used in all calculations. The final $R1$ was 0.0234 ($I > 2\sigma(I)$) and $wR(F_2)$ was 0.0621 (all data); CCDC 818711.†

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