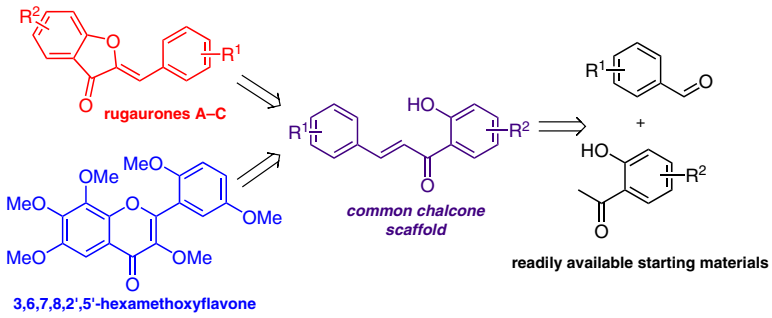
Synlett T. J. Sum et al. Letter

Divergent Total Syntheses of Flavonoid Natural Products Isolated from *Rosa rugosa* and *Citrus unshiu*

Tze Jing Sum
Tze Han Sum
Warren R. J. D. Galloway
David R. Spring*

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK
spring@ch.cam.ac.uk



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Abstract The concise and step-economical total syntheses of three hydroxyaurones and one polymethoxyflavone from readily available starting materials is described. A divergent synthetic strategy is employed, which centres on a common chalcone scaffold from which both the aurone and flavone frameworks can be accessed through the use of different oxidative cyclisation methods. These are the first reported total syntheses of these biologically interesting compounds.

Key words flavonoids, hydroxyaurones, chalcones, divergent, total synthesis, natural products

Aurones[1] and flavones[2] are two subclasses of the flavonoid family of natural products.[3] Flavonoids have been found to exhibit a diverse array of interesting biological properties such as anticancer,[4] antimalarial,[5] anti-inflammatory,[6] antioxidant,[7] antibacterial[8] and antifungal[9] activities. Unsurprisingly therefore, natural flavonoids have attracted considerable interest from both the synthetic and medicinal chemistry communities.[10]

In 2012, Gao et al. reported the isolation and characterisation of three new aurones, named rugaurones A–C (**1**–**3**) from the flowers of *Rosa rugosa* (Figure 1).[11] These compounds were found to have promising cytotoxic and anti-HIV properties. In the same year, Shin et al. reported the isolation of three previously unreported flavonoids from the peels of mature fruits of *Citrus unshiu* Marcow (Rutaceae), one of which was named 3,6,7,8,2′,5′-hexamethoxyflavone (**4**).[12] These peels have been used in traditional Chinese medicine and some isolates from *C. unshiu* have been reported to exhibit antiproliferative effects. Given the interesting biological profiles of compounds **1**–**4** (and the diverse array of properties typically associated with flavonoids in general), we were interested in a more extensive assessment of their biological activities. In view of the very low isolation yields of **1**–**4** from natural sources, it was

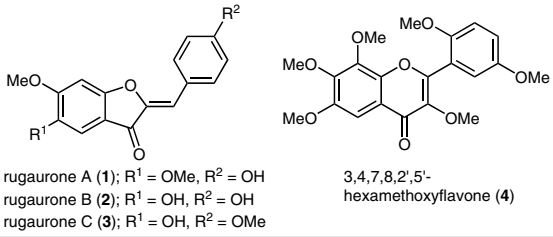
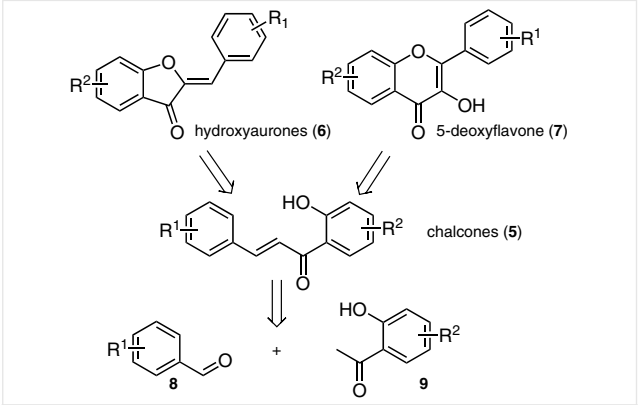


Figure 1 Naturally occurring hydroxyaurones **1**–**3** isolated from *Rosa rugosa* and a 5-deoxyflavone (**4**) isolated from *Citrus unshiu*

thought that sufficient amounts of materials for biological screening studies could only be secured by total synthesis. Herein, we report the first total syntheses of compounds **1**–**4**, which were achieved in a step-efficient fashion by the application of a divergent and concise synthetic strategy.

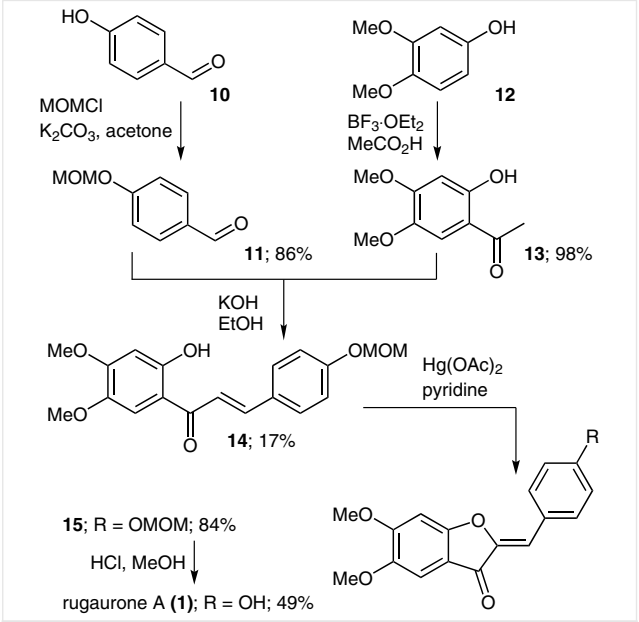
Based on our previous work on flavonoid synthesis,[13] we envisaged a divergent strategy for the construction of natural products **1**–**4** which used a chalcone scaffold (of the general form **5**) as the key branch point (Scheme 1). It was anticipated that both the aurone and flavone frameworks (general structures **6** and **7**, respectively) could be accessed from **5** by the application of different oxidation methods;[4] mercury(II) acetate mediated oxidative cyclisation of chalcones **5** would yield aurones **6**,[1] whereas Algar–Flynn–Oyamada oxidation with H_2O_2 under alkaline conditions would furnish the 5-deoxyflavone framework **7**.[4] Based on our previous study,[13] it was presumed that the chalcone precursors **5** could be easily accessed via a Claisen–Schmidt aldol condensation between benzaldehydes **8** and acetophenones **9**.[4]

The total syntheses of rugaurones A–C (**1**–**3**) was achieved by the application of this divergent synthetic strategy (Schemes 2 and 3). Benzaldehyde precursor **11** was prepared from commercially available 4-hydroxybenzaldehyde (**10**) by MOM protection (Scheme 2). In parallel, the acetophenone building block **13** was accessed from 3,4-dimethoxyphenol (**12**). Claisen–Schmidt aldol condensation



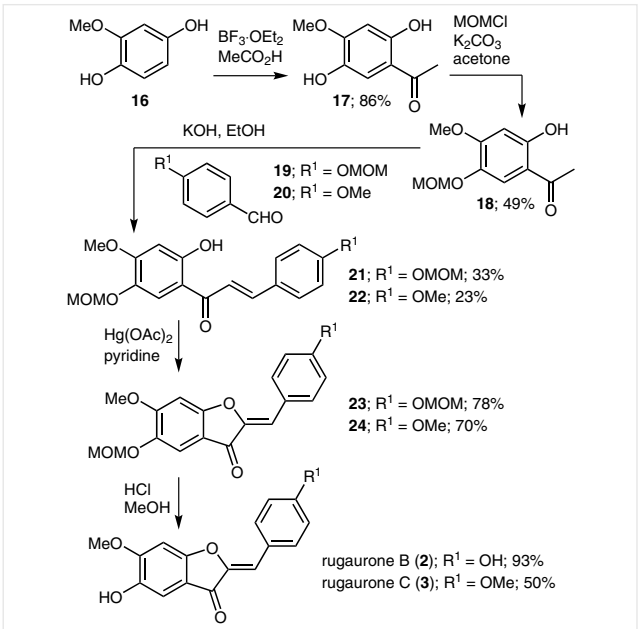
Scheme 1 Retrosynthetic analysis of the hydroxyaurones **6** and 5-deoxyflavone **7**

of **11** and **13** proceeded smoothly to afford the key chalcone intermediate **14**.[4,14] Intramolecular mercury(II) acetate mediated oxidative cyclisation[1] produced the intermediate aurone **15** in high yield and subsequent acid-mediated MOM deprotection afforded the desired natural product, rugaurone A (**1**).



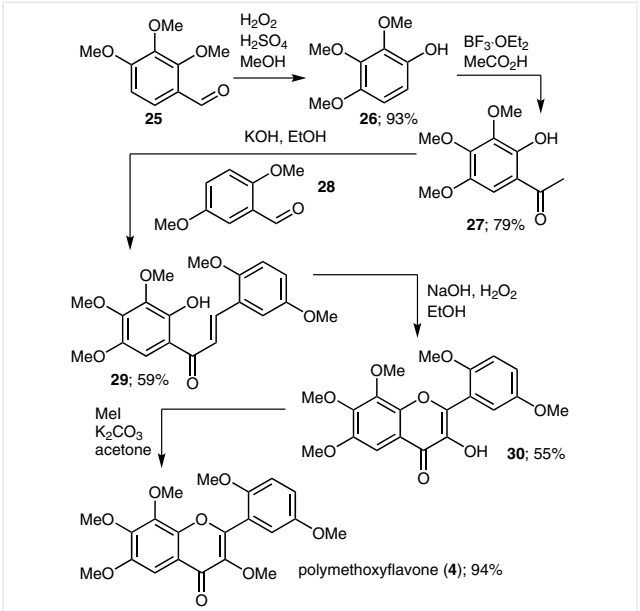
Scheme 2 Synthesis of rugaurone A (**1**)

Rugaurones B (**2**) and C (**3**) were prepared in a similarly efficient manner (Scheme 3). Starting from the commercially available hydroquinone **16**, acetophenone **17** was synthesised in high yield. Regioselective MOM protection of **17** afforded **18**, which was condensed with the corresponding aldehydes **19** and **20** under basic ethanolic conditions to give the required MOM-protected chalcones **21** and **22**, respectively. Subsequent oxidative cyclisation with mercury(II) acetate in pyridine furnished the corresponding aurones **23** and **24** and MOM deprotection yielded the desired natural products, rugaurones B (**2**) and C (**3**)



Scheme 3 Synthesis of rugaurones B (**2**) and (**3**)

Attention was next turned toward the preparation of the polymethoxyflavone **4** (Scheme 4).



Scheme 4 Synthesis of polymethoxyflavone (**4**)

The synthesis commenced with the oxidation of benzaldehyde **25** to give phenol **26**. Subsequent acylation furnished acetophenone **27** in a good yield.[15] A Claisen–

Schmidt aldol condensation between **27** and aldehyde **28** furnished chalcone **29**[2] and Algar–Flynn–Oyamada oxidation[4] yielded the corresponding flavonol scaffold **30**. Methylation of **30** with methyl iodide in acetone under reflux then afforded the desired polymethoxyflavone **4** in an excellent yield.

The divergent strategy employed in the synthesis of natural products **1**–**4** centres on the selective conversion of chalcone intermediates into aurones or flavones through the use of different oxidation procedures. Attempts to rationalise this selectivity are complicated by uncertainties regarding the mechanisms of these oxidations. It has been suggested that Algar–Flynn–Oyamada oxidation to form the flavone scaffold may proceed by direct intramolecular attack of the phenol oxygen on the alkene (presumably a conjugate addition process) or via an intermediate epoxide derivative;[16–18] it is possible that stereoelectronic factors play a role in dictating the regioselectivity in both cases, though these are difficult to delineate.[18,19] The exact mechanistic details of the mercury(II) acetate mediated oxidative cyclisation of chalcones to aurones are also unknown. Most evidence points toward a mechanism which involves formation and cyclisation of an aryloxy–mercury(II) acetate species,[20–23] rather than an electrophilic addition pathway (involving activation of the alkene bond by the mercury species and hydroxy participation).[20] It has been suggested that five-membered ring formation from the aryloxy–mercury(II) acetate species (which leads to the aurone scaffold) is favoured over six-membered ring formation (which leads to the flavone scaffold) due to steric effects.[23]

In conclusion, the first total syntheses of the natural products rugaurones A–C (**1**–**3**) and polymethoxyflavone (**4**) have been achieved. A divergent synthetic strategy was employed,[13] which allowed access to these biologically interesting compounds in an expedient and step-efficient fashion from readily available starting materials. Notably, multi-milligram quantities of all four natural products were generated, which should provide ample material for screening in biological assays. The divergent strategy is currently being applied to the synthesis of unnatural analogues of compounds **1**–**4** to allow the sampling of novel chemical space around these biologically relevant structures. This work, together with the results of biological screening investigations, will be reported in due course.

Acknowledgment

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Supporting Information

Data accessibility: all data supporting this study are included in the paper and provided as Supporting Information accompanying this paper. It is available online at http://dx.doi.org/10.1055/s-0035-1561851.

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