Synthetic pathways towards new antimalarial agents

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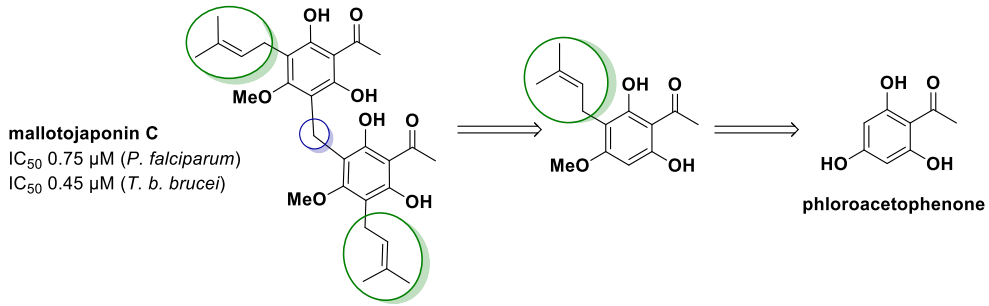
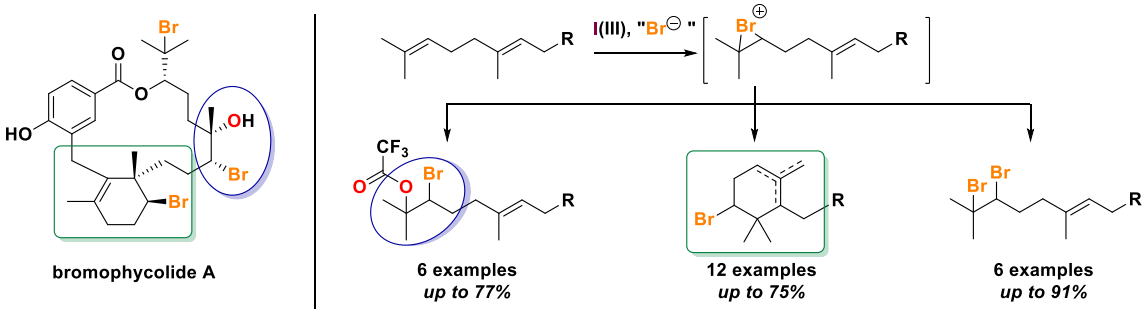
Malaria is a parasitic disease affecting more than 200 million people in the world. The development of new antimalarial drugs is necessary in order to replace the existing treatments that are progressively becoming less efficient due to resistance phenomena. Natural products are an inexhaustible source of inspiration for the discovery of new drugs. In this project, we focused our attention on two natural products families exhibiting antimalarial properties: mallotojaponins and bromophycolides.

In the first part of this project, we carried out the first total synthesis of mallotojaponin C. We also synthesised a library of its analogues. All these compounds were tested against *Plasmodium falciparum* responsible for malaria and against *Trypanosoma brucei* responsible for African sleeping sickness. We have confirmed the antimalarial activity of mallotojaponins and discovered their trypanocidal activity (Scheme 1).[1]



Scheme 1. Retrosynthetic analysis of mallotojaponin C

In the second part of the project, we developed a chemodivergent and selective method of bromination of terpenoids that could later be applied to the synthesis of bromophycolides. Using simple bromides and hypervalent iodine(III) reagents to generate electrophilic bromonium species *in situ*, we have shown that the reaction can be steered selectively towards the bromocarbocyclisation, the oxybromination or the dibromination of terpene chains. In all cases, the reactions are fast and easy to perform (Scheme 2).[2]



Scheme 2. Chemodivergent and selective bromofunctionalisations of polyprenoids

[1] Grayfer, T. D., Grellier, P., Mouray, E., Dodd, R. H., Dubois, J., Cariou, K. *Org. Lett.*, **2016**, *18*, 708–711
[2] Grayfer, T. D., Retailleau, P., Dodd, R. H., Dubois, J., Cariou, K. *Org. Lett.*, **2017**, *19*, 4766–4769