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Catalytic prenylation of natural polyphenols†

Yi Du,[a] Iman Korchi,[a] Aleksandr E. Rubtsov[ab] and Andrei V. Malkov*[a]

Prenylated polyphenols occur naturally and exhibit biological activity superior to the ubiquitous parent polyphenols. However, their low abundance limits the wider application of these derivatives. In this work, we present an expedient, single-step catalytic protocol for introducing terpene fragments into the aromatic rings of the widely available natural stilbenoids and flavonoids to upgrade their therapeutic potential.

Introduction

Flavonoids and stilbenoids are ubiquitous secondary metabolites in plants, leaves, flowers, fruits and seeds.[1,2] Bioactive flavonoids acquired a proven track record of beneficial effects on human health;[3] the pharmaceutical, medicinal, nutraceutical and cosmetics industries actively use flavonoids in their development.[3,4] However, the most common polyphenols do not reach therapeutic plasma concentration levels due to the low solubility and poor absorption of the compounds. This low bioavailability can be improved through chemical modifications that alter the polarity and lipophilicity of the polyphenols, as well as the biological functions that depend on the structure. Among the chemical modification strategies, prenylation is often considered an essential way to boost the potency of the parent flavonoid.[5–8] Prenylated analogues have been detected for most flavonoids, such as chalcones, stilbenes, flavanones, flavones, flavonols and isoflavones, with some examples shown in Fig. 1. While flavonoids are usually present in reasonable quantities in nature, the levels of prenylated flavonoids are much lower. The low abundance in nature limits their application as medicines and nutraceuticals, therefore it is important to develop facile synthetic approaches.

Chemical synthesis of prenylated flavonoids usually relies on multistep sequences involving the protection of hydroxyls, *O*-prenylation followed by the Claisen rearrangement of the *O*- to *C*-isomer and deprotection.[8–12] Alternative approaches are based on Suzuki–Miyaura cross-coupling, which requires prior synthesis of the respective halides or boronic acid derivatives,[13,14] or the use of chemoenzymatic methods.[15,16]

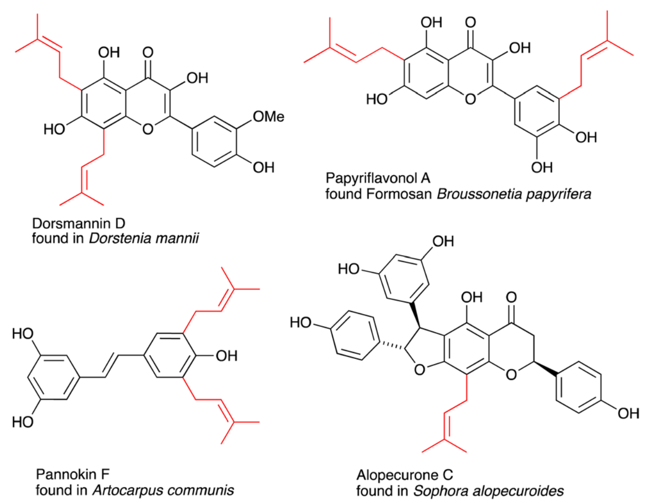

Fig. 1 Selected examples of natural prenylated polyphenols.

Herein, we present the development of a simple, single-step catalytic Friedel–Crafts alkylation of unprotected natural polyphenols using prenyl alcohol and its analogues.

Results and discussion

Optimisation studies

Catalytic C–H allylation of aromatic compounds is a widely used synthetic transformation for the formation of C–C bonds.[17] Of the plethora of methods for the modification of electron-rich arenes, Friedel–Crafts alkylation looks appealing from the practical viewpoint because it can employ unprotected allylic alcohols as the

[a] *Department of Chemistry, Loughborough University, Loughborough, LE11 3TU, UK. E-mail: A.Malkov@lboro.ac.uk*

[b] *Department of Chemistry, Perm State University, Bukireva 15, Perm 614990, Russia*

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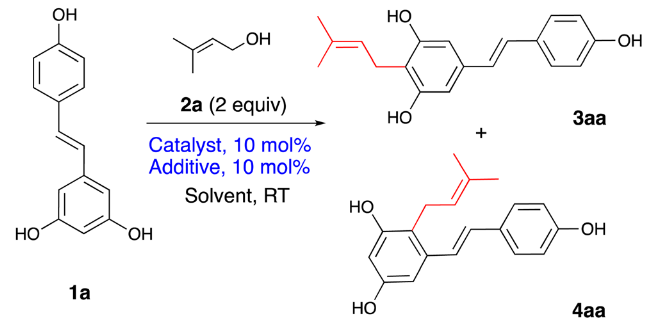
Table 1 Optimisation of prenylation of resveratrol **1a**[a]



Entry	Catalyst	Additive	Solvent	Yield[b] (%)	Ratio 3/4
1	$(acac)_2MoCl_2$	AgOTf	CH_3CN	13	40/60
2	$Fe(OTf)_3$	—	CH_3CN	48	1/99
3	$In(OAc)_3$	—	CH_3CN	nr	—
4	$InCl_3$	—	CH_3CN	nr	—
5	$InCl_3$	AgOTf	CH_3CN	37	1/99
6	$AlCl_3$	—	CH_3CN	42	25/75
7	$AlCl_3$	AgOTf	CH_3CN	65	26/74
8	$AlCl_3$	AgOTf	Et_2O	Trace	—
9	$AlCl_3$	AgOTf	MeOH	nr	—
10	$AlCl_3$	AgOTf	DCM	Trace	—
11	**$AlCl_3$**	**AgOTf**	**Acetone**	**85**	**21/79**
12	$AlCl_3$	AgOTf	EtOAc	81	31/69
13[c]	$AlCl_3$	AgOTf	Acetone	59	24/76
14[d]	$AlCl_3$	AgOTf	Acetone	42	24/76

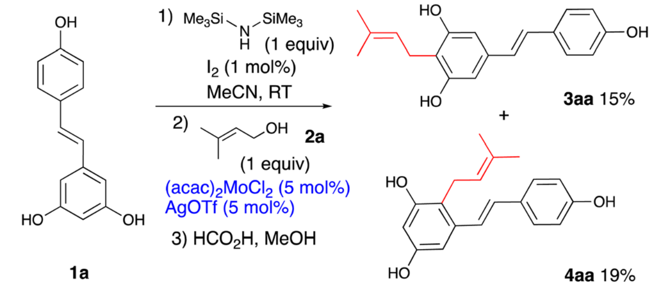
[a] Conditions: **1a** (1mmol), **2a** (2 mmol), catalyst (10 mol%) and additive (10 mol%); in 24 mL solvent under N_2 at RT overnight. [b] Combined isolated yield; nr: no reaction. [c] Catalyst: 10 mol%, additive: 20 mol%. [d] Catalyst: 10 mol%; additive: 30 mol%.

electrophiles.[18,19] The reaction can be performed using catalytic quantities of Lewis or Brønsted acids.[18,20,21]

However, despite the apparent simplicity, there are very few reports of the Friedel–Crafts prenylation of polyphenolic compounds, which mainly focus on the allylation of related resorcinol analogues.[22–24] The reason for this may stem from the inactivation of the Lewis catalysts by binding to the phenolic groups. Therefore, successful examples[22,24,25] usually employ the excess of promoters.

With the aim to develop a catalytic system for the modification of natural polyphenols, prenylation of resveratrol **1a** was selected for optimisation studies (Table 1).

First, a catalytic system developed by us previously for the allylation of electron-rich arenes was examined.[21] It employed the Lewis acidic complex $(acac)_2MoCl_2$ activated by silver triflate by replacing the chloride with a non-nucleophilic anion (entry 1), however, the yield and regioselectivity were low. Next, a series of other metal salts were examined. With $Fe(OTf)_3$ (entry 2), 2-prenylresveratrol **4aa** was obtained in a modest yield with only trace quantities of the 4-isomer **3aa**. Indium(III) acetate and chloride were inactive (entries 3 and 4), but $InCl_3$ activated by AgOTf worked similarly to $Fe(OTf)_3$, with a slightly reduced yield (entry 5). The increased yield was obtained with the catalytic system based on the equimolar quantities of $AlCl_3$ and AgOTf (entry 7). $AlCl_3$ worked even without silver triflate (entry 6) but with lower product yield. Notably, $AlCl_3$ produced a 3 : 1 mixture of regioisomers **4aa** and **3aa**. This could be viewed as a disadvantage, however, taking into account that the isomers are readily separable by chromatography and that synthesis of isomer **3aa**, a naturally occurring arachidin-2, requires multistep sequences,[26,27] this reaction can serve as a viable alternative for obtaining practical quantities of **3aa**, in a single step. In this context, the molybdenum catalyst (entry 1) exhibited the highest proportion of the symmetrical **3aa** in the product mixture. To boost the reaction yield, a protection strategy was explored, where the hydroxy groups were protected as silyl ethers (Scheme 1). A nearly equimolar mixture of **3aa** and **4aa** has been achieved, though, despite some improvement in the ratio towards **3aa**, the overall yield remained modest.



Scheme 1 Prenylation of protected resveratrol.

Next, the reaction solvents were briefly assessed (entries 8–12) with a focus on greener solvents with lower environmental impact.[28,29] Ether and methanol were found unsuitable (entries 8 and 9); as was non-green dichloromethane (entry 10). The highest yields were obtained in acetone and ethyl acetate (entries 11 and 12). An increase in the number of equivalents of AgOTf to $AlCl_3$ proved to be detrimental to the reaction yield but the product ratio remained the same (entries 13 and 14). Thus, the conditions of entry 11 were selected as optimal.

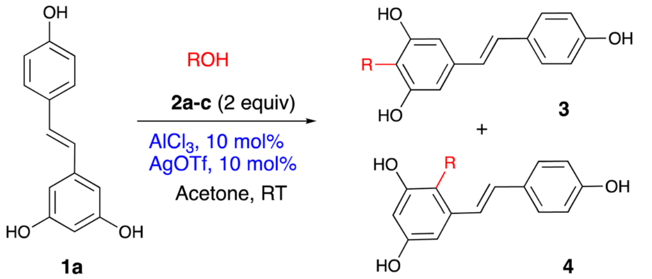
The reaction scope

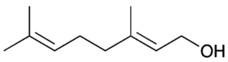
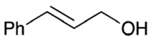
With the optimal protocol in hand, the reaction scope has been investigated using naturally occurring polyphenols. The results are presented according to the polyphenol classes.

Following the optimisation experiments, the allylation of resveratrol was assessed first. Chemical yields of the isolated pure compounds are shown in Table 2. Two entries are shown for the reaction of resveratrol with prenol. Thus, under the optimal conditions (entry 1), the isolated yields of both regioisomers **3aa** and **4aa** are presented. At the same time, this reaction can occur regioselectively, furnishing only **4aa** (entry 2). In this instance, $Fe(OTf)_3$ had been used as a catalyst.

The reaction of resveratrol with geraniol mirrored that of the prenol: a 3 : 1 mixture of products **4ab** and **3ab** was produced in a high overall yield of 92% (entry 3). The two compounds were readily separated by chromatography. The more abundant isomer **4ab** is a bioactive macatrichocarpin F isolated from *Macaranga* plants.[30] This compound previously was synthesised through a sequence involving *O*-alkylation followed by the *O*- to *C*-isomerisation.[31,32] The allylation with cinnamyl alcohol produced an unknown symmetrical isomer **3ac** as a single product in a 60% yield (entry 4). The reason for such a switch in the

Table 2 Allylation of resveratrol **1a**[a]



Entry	Alcohol **2**, R	**3**, Yield (%)	**4**, Yield (%)
1	Prenyl alcohol, **2a**	**3aa**, 18	**4aa**, 67
2	Prenyl alcohol, **2a**[b]	—	**4aa**, 48
3	Geraniol, **2b** 	**3ab**, 22	**4ab**, 70
4	Cinnamyl alcohol, **2c** 	**3ac**, 60	—

[a] Conditions: **1a** (1mmol), **2** (2 mmol), $AlCl_3$ (10 mol%) and AgOTf (10 mol%); in 24 mL solvent under N_2 at RT overnight, unless stated otherwise. The regioisomers were separated by flash chromatography, yields are given for isolated analytically pure compounds. [b] The reaction was performed in CH_3CN using $Fe(OTf)_3$ (10 mol%) as a catalyst.

regioselectivity is unknown but may relate to the formation of a more stabilised cation intermediate.

Prenylation of flavones, chrysin **1b** and luteolin **1c** proved to be more challenging (Fig. 2). Despite good overall yields, mixtures of compounds were produced. Thus, the reaction of chrysin with prenol gave a mixture of mono and di-prenylation products, **3ba** and **5ba**, respectively. The initially formed 6-isomer **3ba** likely undergoes the second alkylation to furnish **5ba**. Nonetheless, the compounds can be readily separated by chromatography. In contrast, luteolin gave a 3 : 1 mixture of monosubstituted isomers **3ca** and **4ca**, which had similar chromatographic mobility and were difficult to separate; only isomer **3ca** was isolated in pure form. Other isomer **4ca** was characterised in the mixture with **3ca**.

Flavonols quercetin **1d** and myricetin **1e** are even more densely substituted with hydroxyl groups and, therefore potentially represented even more challenging targets for the catalytic prenylation. However, they turned out to be good substrates (Scheme 2). Thus, alkylation of quercetin with prenol, geraniol and cinnamyl alcohol occurred uneventfully furnishing good yields of the respective monosubstituted derivatives **3da**, **3db** and **3dc** as single regioisomers. Note that compound **3da** is a natural polyphenol gancaonin P found in liquorice.[33] The reaction of myricetin with geraniol followed the trend to afford **3ab** in a 73% yield. However, the prenylation of myricetin,

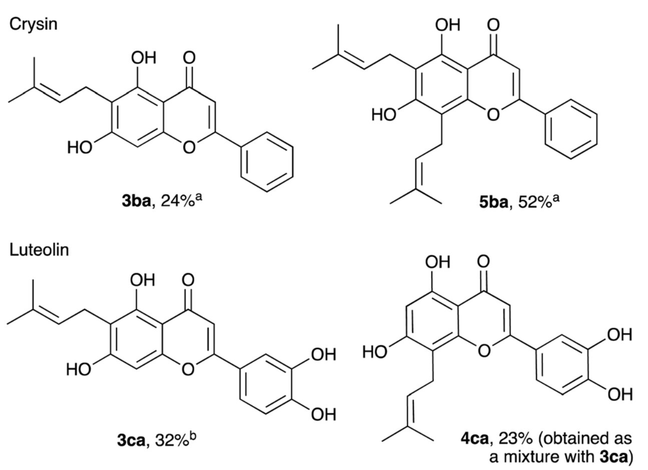
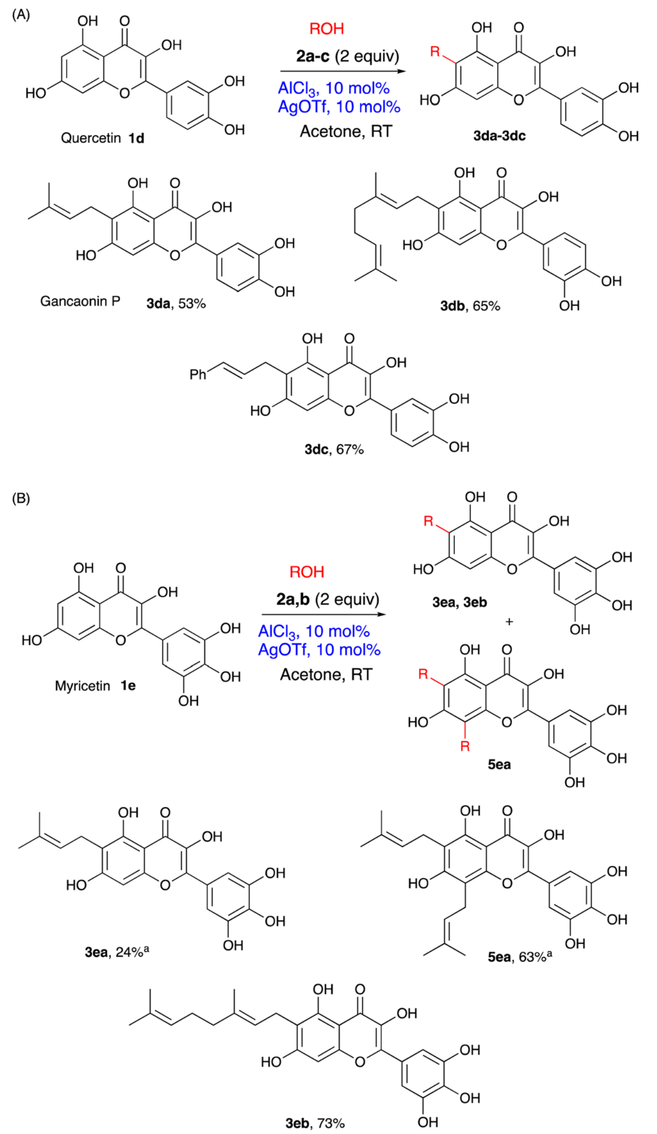


Fig. 2 Allylation of flavones, chrysin **1b**, and luteolin **1c**. (For conditions, see Table 1, entry 11, yields are given for isolated, analytically pure compounds. [a] Separated chromatographically from the mixture of **3ba** and **5ba**. [b] Separated chromatographically from the mixture of **3ca** and **4ca**).



Scheme 2 Allylation of flavonols, (A) quercetin **1d** and (B) myricetin **1e**. (For conditions, see Table 1, entry 11, yields are given for isolated, analytically pure compounds. [a] Separated chromatographically from the mixture of **3ea** and **5ea**).

along with the expected **3ea** (24%), showed the formation of dialkylated product **5ea** (62%). So far, the attempts at reversing the ratio in favour of monoalkylation have been unsuccessful, but the products are readily separable by simple flash chromatography.

Experimental

General procedure for prenylation of polyphenols

A polyphenol (1 mmol) was added to the solution of $AlCl_3$ (10 mol%) and AgOTf (10 mol%) in acetone (20 mL). The mixture was stirred for 20 min. Then, a solution of prenol or other allylic alcohol (2 mmol) in acetone (4 mL) was added dropwise to this mixture under an inter atmosphere. The resulting solution was stirred at room temperature overnight. The reaction progress was monitored by TLC. The work-up involved dilution with water and extraction with EtOAc. The crude product was purified by chromatography on silica to afford the target compound. For details, see ESI.†

Conclusions

In conclusion, we developed an expedient catalytic method for the introduction of allyl groups, such as prenyl, geranyl and cinnamyl, into the aromatic rings of natural polyphenols under mild reaction conditions. Resveratrol, flavones and flavonols proved to be competent substrates for this reaction furnishing practical yields of the alkylation products, some of the synthesised analogues are occurring in nature. Chemical prenylation can modify the structure of polyphenols, potentially leading to enhanced biological activity and improved pharmacological properties as evidenced by a superior bioactivity of some naturally occurring prenylated analogues compared to the parent polyphenols. Therefore, the developed single-step method may serve as a convenient tool for upgrading the bioactivity of the abundant natural polyphenols.

Author contributions

Conceptualization, A. V. M.; funding acquisition, A. V. M. methodology, Y. D., I. K. and A. V. M. formal analysis, Y. D., I. K. and A. E. R; investigation, Y. D. and I. K.; writing – original draft, A. V. M. and A. E. R.

Conflicts of interest

There are no conflicts to declare.

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