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Synthesis of resveratrol, DMU-212 and analogues through a novel Wittig-type olefination promoted by nickel nanoparticles

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ABSTRACT

A novel synthesis of resveratrol, DMU-212 and analogues is presented using benzyl alcohols as phosphorus ylide partners in a one-pot Wittig-type olefination reaction promoted by nickel nanoparticles.

Resveratrol [**1**, (*E*)-3,4′,5-trihydroxystilbene] is a naturally occurring phytoalexin present in vine bark, leaves and grapes, as well as in many other plants.[1] In recent years, this polyphenol has attracted the attention of an important part of the scientific community because of its remarkable biological properties and therapeutic potential including chemoprevention of cancer,[1,2] inflammation,[1] aging,[1,3] obesity,[1,4] cardiovascular diseases[1] and neurodegeneration.[1,5] Antioxidant,[1,6] radio-protective,[1] phytoestrogen,[1] antibacterial[1] and antifungal[1] activities have also been attributed to this special molecule. The methoxylated analogues of resveratrol possess increased lipophilicity and a pharmacological profile comparable or even superior to that of resveratrol.[7] Among them, DMU-212 [**2**, (*E*)-3,4,4′,5-tetramethoxystilbene] has recently disclosed a strong anti-cancer activity with higher chemoprotective activity than resveratrol (Chart 1).[8]

Many approaches have been designed in order to prepare this kind of structures primarily through Wittig[7b,9] or Horner–Emmons–Wadsworth[7a] and Heck[10] reactions. Other methodologies involving lithiation–condensation,[11] Perkins,[12] Ramberg–Bäcklund,[13] or Diels–Alder/Wittig[14] reactions have also been reported. In many cases, however, the synthetic sequence is rather long, consequently leading to low product yields, while it can also be difficult to control the stereo- and regiochemistry of the process. Therefore, the development of alternative strategies to synthesise these valuable molecules is welcome.

On the other hand, and due to our ongoing interest on the preparation and reactivity of active metals,[15] we studied a mild and fast methodology for the synthesis of nickel(0) nanoparticles (NiNPs), from different nickel(II) chloride-containing systems in THF, using lithium powder and a catalytic amount of an arene as reducing agent.[16] These nanoparticles were applied to different functional group transformations,[17] and more recently, to the hydrogen-transfer reduction of carbonyl compounds[18] and reductive amination of aldehydes.[19] We also reported for the first time that nickel, in the form of nanoparticles, was a potential alternative to the use of catalysts based on noble metals for the α-alkylation of ketones and indirect aza-Wittig reaction with alcohols.[20] In these reactions, hydrogen transfer from the alcohol to the intermediate α,β-unsaturated ketone or imine, respectively, took place in short reaction times and in the absence of any added ligand, hydrogen acceptor or base, under mild conditions.

Very recently,[21] we have discovered that NiNPs, readily prepared from $NiCl_2$, lithium metal, and a catalytic amount of DTBB (4,4′-di-*tert*-butylbiphenyl) in THF, are able to promote a Wittig-type olefination of benzyl alcohols with benzylidenetriphenylphosphorane. We want to present herein a novel synthesis of resveratrol, DMU-212 and analogues, including a one-pot Wittig-type

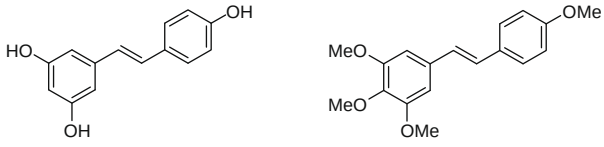

Chart 1. Chemical structures of resveratrol and DMU-212.

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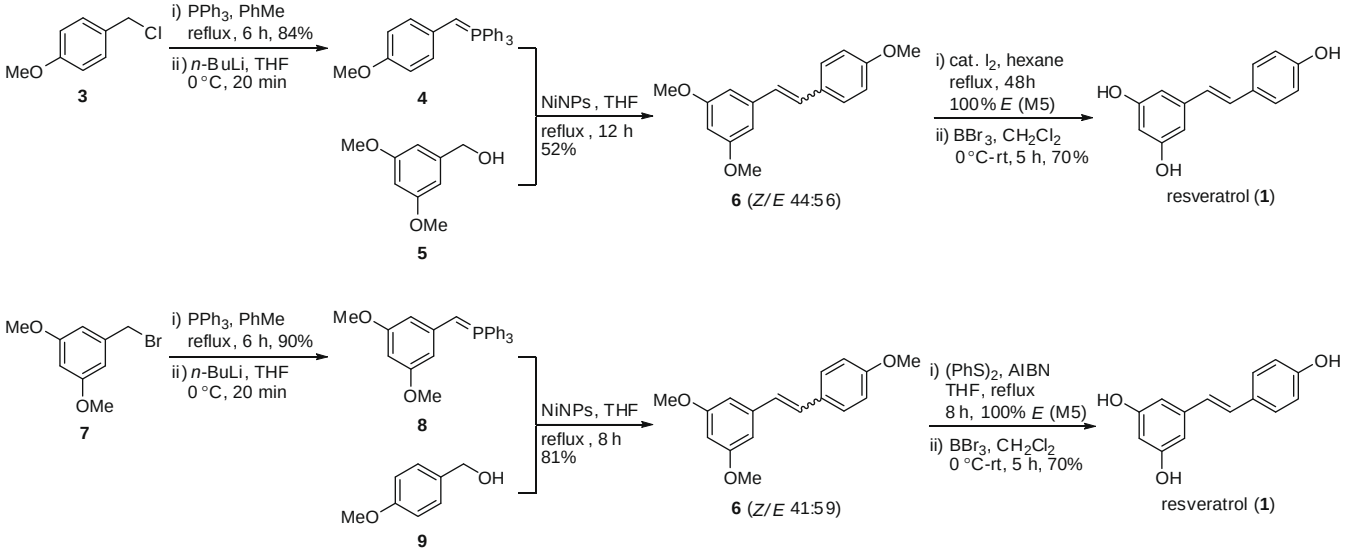


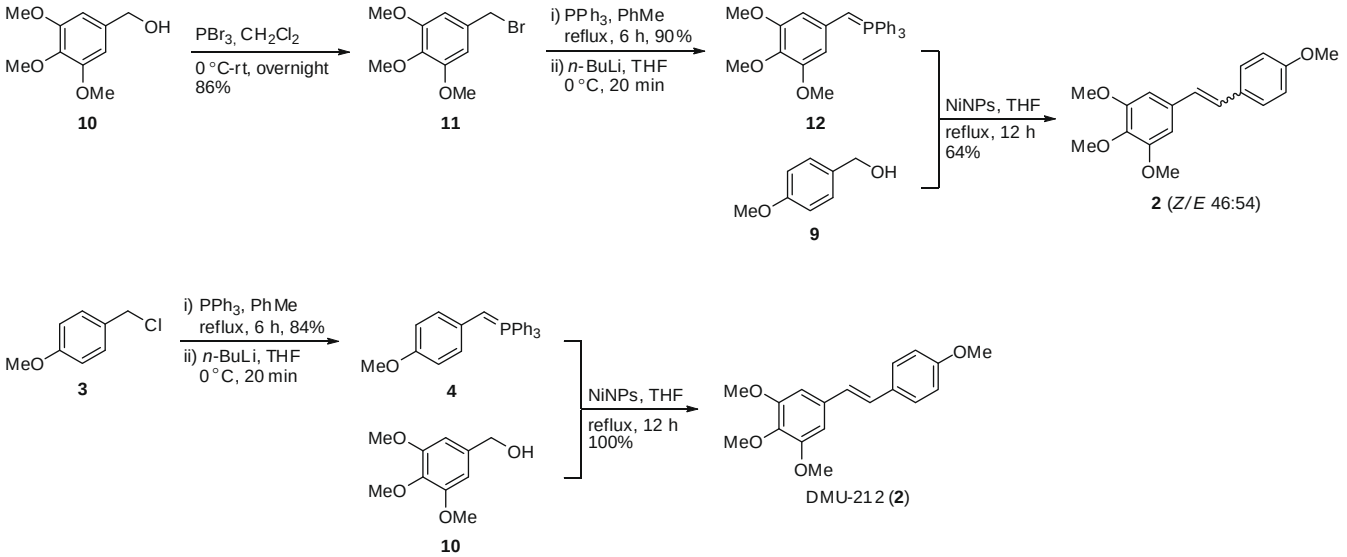
Scheme 1. Two syntheses of resveratrol through a Wittig-type olefination promoted by nickel nanoparticles.

reaction of properly substituted benzyl alcohols and phosphorus ylides, in the presence of nickel nanoparticles as the key step. To the best of our knowledge, this is the first synthesis of resveratrol derivatives through a Wittig-type olefination with alcohols (instead of aldehydes) in which there is no standard redox step.

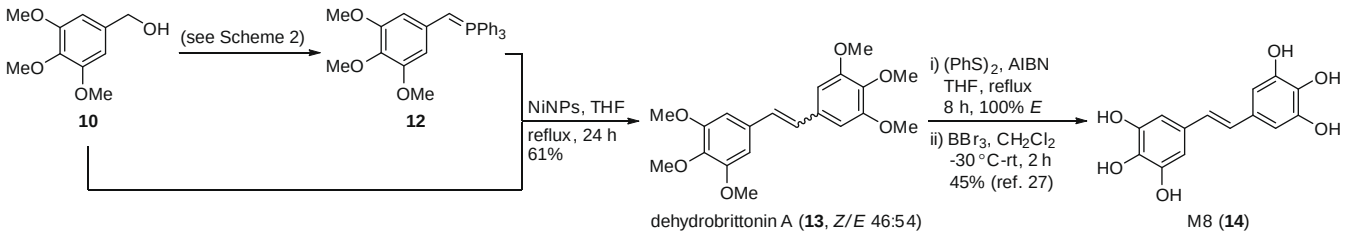
We focused first on the synthesis of resveratrol, for which two approaches were devised from the commercially available starting materials **3** and **7** (Scheme 1). In the first approach, 1-(chloromethyl)-4-methoxybenzene (**3**) was transformed into the corresponding phosphonium salt in good yield, followed by deprotonation with *n*-BuLi. The resulting benzyl phosphorus ylide **4** was reacted with 3,5-dimethoxybenzyl alcohol (**5**) in the presence of 1 equiv NiNPs at reflux for 12 h.[22] Methylated resveratrol (**6**) was obtained as a 44:56 *Z*/*E* mixture of diastereoisomers in moderate yield. It is well known that semi-stabilised ylides, such as benzyl ylides, yield mixtures of *Z* and *E* isomers with practically no selectivity.[23] Fortunately, isomerisation of (*Z*)-**6** to (*E*)-**6** (M5) could be quantitatively accomplished under iodine catalysis.[7b] Final demethylation with BBr_3 furnished resveratrol (**1**) in 31% overall yield.

In the search for a more effective resveratrol synthesis, we decided to change the Wittig-type partners **4** and **5** into **8** and **9**, respectively (Scheme 1). Following the above-described methodology, 3,5-dimethoxybenzyl bromide (**7**) was converted into the corresponding phosphonium salt in higher yield compared to **3**. Wittig-type olefination of **8** and 4-methoxybenzyl alcohol (**9**) proceeded in shorter time and in higher yield in comparison with that in the first approach. Moreover, the reaction time for the *Z* to *E* isomerisation of **6** was substantially reduced by using diphenyl disulfide in the presence of a catalytic amount of AIBN.[24] Final treatment with BBr_3 led to resveratrol in 51% overall yield. This yield is higher than those obtained with previously reported methodologies[9–12] and is comparable to that obtained from resorcylic acid using a decarbonylative Heck approach.[10b]

Following a similar strategy, we focused next on the synthesis of DMU-212 (**2**) (Scheme 2). In the first synthetic variant, 3,4,5-trimethoxybenzyl bromide (**11**), which is not commercially available, had to be prepared by bromination of alcohol **10**. This step, as well as the formation of the corresponding phosphorus ylide (**12**), proceeded in high yield. NiNPs-promoted Wittig-type reaction of **12**



Scheme 2. Two syntheses of DMU-212 through a Wittig-type olefination promoted by nickel nanoparticles.



Scheme 3. Synthesis of dehydrobrittonin A and M8.

with benzyl alcohol **9** led to **2** in 64% yield as a 46:54 *Z*/*E* diastereomeric mixture. A 50% overall yield of **2** was achieved after three synthetic steps. Before trying the *Z* to *E* isomerisation in a fourth synthetic step, however, we decided to study the alternative variant. We were very delighted to discover that by changing **12** and **9** into **4** and **10**, respectively, the Wittig-type olefination reaction proceeded quantitatively. Moreover, DMU-212 (**2**) was obtained as a single diastereoisomer[25] in 84% overall yield after two synthetic steps from commercially available **3**. In view of the results obtained in other Wittig-type olefinations with benzyl ylides and alcohols, the high diastereoselectivity observed in the synthesis of **2** was certainly unexpected. At the moment, we have no explanation for this result, since one would expect the presence of an additional methoxy group in **10**, when compared to the structure **5** (Scheme 1), not to be so essential in driving the diastereoselectivity of the reaction.

In order to study the scope of this methodology, we decided to deal with highly polymethoxylated derivatives. It is worthwhile mentioning that the symmetrically substituted target molecule, dehydrobrittonin A (**13**),[26] could be synthesised from only one starting material (Scheme 3). Thus, benzyl alcohol **10** served both as the precursor of the ylide **12** and as its partner in the Wittig-type olefination. The latter reaction was slower in comparison with the homologues with less methoxy substituents, leading to the expected stilbene in moderate yield as a mixture of diastereoisomers. Quantitative *Z* to *E* isomerisation, followed by demethylation[27] afforded the resveratrol analogue M8 [**14**, (*E*)-3,3′,4,4′,5,5′-hexahydroxystilbene].

The remarkable manifold biological effects of M8 (**14**) have been recently studied and include: (a) highly selective cyclooxygenase-2 inhibition,[27] (b) much higher antioxidant activity than resveratrol in different leukemic cell lines,[28] (c) apoptosis induction at concentrations significantly lower than resveratrol in HL-60 human promyelocytic leukaemia cells[29] and (d) apoptosis induction and cell cycle arrest in prostate cancer [also observed for DMU-212 (**2**)][30] and HT29 human colon cancer cells [also observed for M5, (*E*)-**6**)].[31]

In conclusion, we have reported an alternative synthesis of resveratrol, DMU-212 and analogues, such as M5, dehydrobrittonin A or M8, through a novel Wittig-type olefination promoted by nickel nanoparticles involving benzyl alcohols as phosphorus ylide partners. The polymethoxylated stilbenes were obtained in moderate-to-excellent yields depending on the benzyl alcohol and ylide couple selected. The diastereomeric mixtures of these compounds could be easily transformed into the (*E*)-stilbenes and additionally demethoxylated to give the corresponding polyhydroxylated analogues. Further research to expand the scope of this methodology is under way.

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