Natural Product Synthesis | Hot Paper

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Total Synthesis of Resveratrol-Based Natural Products Using a Palladium-Catalyzed Decarboxylative Arylation and an Oxidative Heck Reaction**

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Abstract: *Controlled access to resveratrol-based natural products is offered by a novel, modular concept. A common building block readily available on a large scale serves as the starting material for the introduction of structurally important aryl groups by a Pd-catalyzed decarboxylative arylation and an oxidative Heck reaction with good yields and high stereoselectivity. The modular approach is convincingly documented by the successful synthesis of three racemic resveratrol-based natural products (quadrangularin A, ampelopsin D, and pallidol).*

Resveratrol (**1**) and its derivatives (e.g. **2**–**6**) belong to the class of natural polyphenols (Figure 1). They are phytoalexines which are produced by various plant species (e.g. grapes) in different amounts in response to external stimuli (e.g. fungal and viral infections).[1] In particular **1** has received great attention due its high in vitro and in vivo activity against a considerable number of diseases.[2] However, the biological activity of resveratrol-based oligomers such as **2**–**6** has so far been little explored. First investigations indicate that the biological activities of these natural products are similar to or even higher than that of **1** and they should therefore find applications as valuable drugs.[3]

Only a few synthetic methods have been described for the preparation of these polyphenolic natural products.[4] First strategies used a biomimetic pathway resulting in a mixture of natural and nonnatural derivatives.[5] In 2007 Snyder et al. published an efficient approach for the synthesis of resveratrol oligomers, like pallidol (**4**; 12 steps; 7%) and ampelopsin F (**6**; 12 steps; 6%).[6] Through the use of readily accessible building blocks other members of the family could be accessed in succeeding work.[7] Alternative synthetic strategies for the preparation of resveratrol-based natural products were published by the research groups led by Sun,[8] Hou,[9] Sarpong,[10] and Flynn.[11] Since these strategies are mostly restricted to the preparation of a single derivative, they are not suitable for synthesis of analogues.

Herein we disclose a novel highly variable approach for the total synthesis of racemic resveratrol-based natural products exemplified by the syntheses of pallidol (**4**), quadrangularin A (**2**), and ampelopsin D (**3**). The retrosynthetic analysis is illustrated in Scheme 1. Resveratrol oligomers such as pallidol (**4**) and ampelopsin F (**6**) are structurally derived from resveratrol dimers containing an indane core. Quadrangularin A (**2**) and ampelopsin D (**3**) differ only in the substitution pattern of the *trans*-configured aryl groups at positions C2 and C3. This connectivity similarity motivated us to develop a modular approach in which the structurally important aryl groups are introduced at a late stage of the total synthesis to gain maximum flexibility. As one of the key steps we chose a novel palladium-catalyzed decarboxylative arylation,[12] which will make it possible to start with the indene carboxylic acid **7** for the introduction of the aryl group at position C3. The so obtained indene derivatives **A** will then be transformed in the second key step to compounds of type **B** with an *E*-configured exocyclic double bond by using our recently developed oxidative Heck coupling process.[13] Deprotection will provide compounds **2** and **3** directly. After oxidation of the double bond in **B**, subsequent

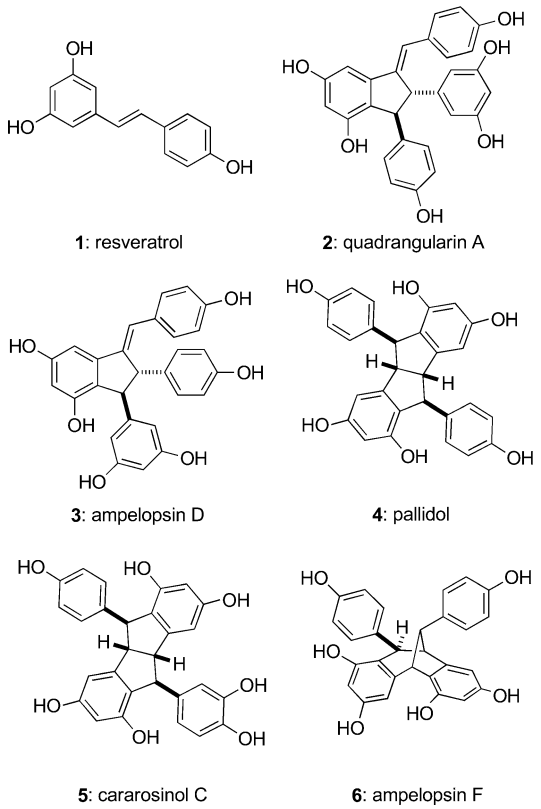

Figure 1. Resveratrol (**1**) and some of its derivatives (**2**–**6**).

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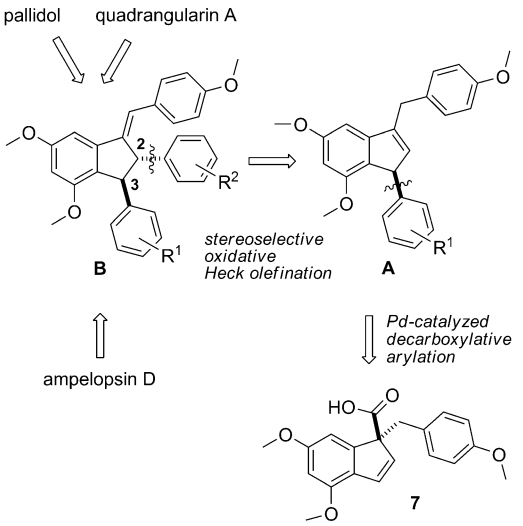


Scheme 1. Retrosynthesis of quadrangularin A (**2**), ampelopsin D (**3**), and pallidol (**4**).

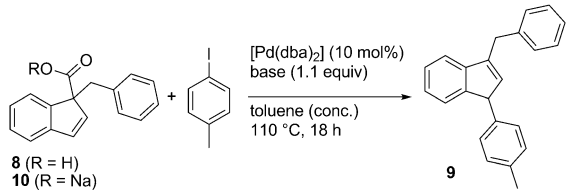
Friedel–Crafts alkylation and deprotection should provide pallidol (**4**).

During the past years decarboxylative reactions have emerged as highly valuable methods for selective formation of C–C and C–heteroatom bonds.[14] In particular in the field of transition-metal catalysis various variants of this approach have been described including decarboxylative Heck reactions,[15] homocouplings,[16] arylations,[17] vinylations,[18] allylations,[19] and decarboxylative C-H arylations.[20]

In view of the total synthesis of resveratrol-based natural products we first investigated the applicability of the highly stereospecific decarboxylative coupling of 2,5-cyclohexadiene-1-carboxylic acids with aryl iodides, which we described recently,[12] to benzyl-1*H*-indene-1-carboxylic acid (**8**). Optimization studies were conducted with 4-iodotoluene as the coupling partner and $[Pd(dba)_2]$ as the catalyst in toluene (Table 1). In initial studies we varied the base. With Cs_2CO_3, Ag_2CO_3, and LiO*t*Bu the arylated product **9** was either not formed or obtained in low yield (entries 1–3). NaO*t*Bu led to a slightly improved result (25%, entry 4). In analogy to our previous studies on the decarboxylative coupling of 2,5-cyclohexadiene-1-carboxylic acids we noted that the addition of ligands leads to lower yield (8%, entry 5). Since protodecarboxylation was the major side reaction, we also tested the Na salt **10** as a substrate and obtained **9** in 31% yield (entry 6). We found that the concentration and also the excess amount of **10** are important factors (entries 7–9). When we used an excess of **10** and also lowered the concentration (0.1M), **9** was obtained in 52% yield (entry 9). Upon further dilution and in situ generation of **10**, the yield was increased to 54% (entry 10). Finally, an increase of the $[Pd(dba)_2]$ loading provided **9** in 66% yield.

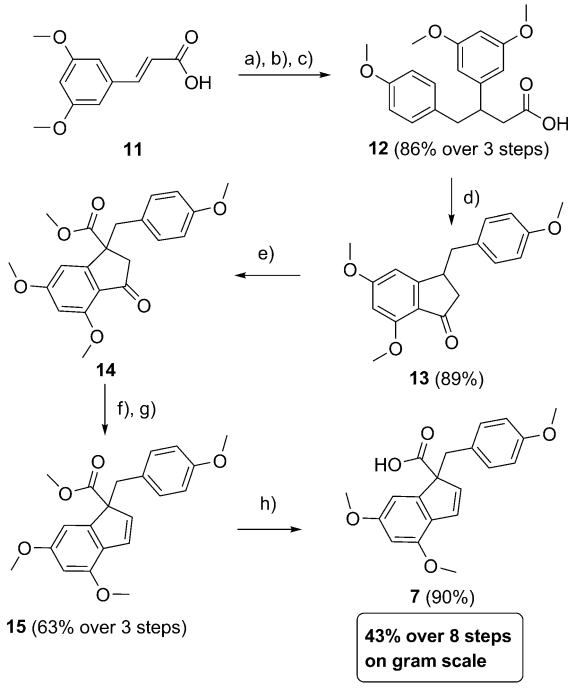
After successful optimization we focused on the total syntheses of quadrangularin A (**2**), ampelopsin D (**3**), and pallidol (**4**). Our first priority was the synthesis of the key building block, indene carboxylic acid **7** (Scheme 2). Commercially available 3,5-dimethoxycinnamic acid (**11**) was readily esterified (>99%) and the 4-methoxybenzyl group

Table 1: Model studies on the decarboxylative arylation of **8**/**10**.



Entry	Indene (equiv)	Equiv of tol-I	Base	Conc. of **8** or **10** [M]	Yield [%][a]
1	**8** (1)	1.1	Cs_2CO_3	0.3	0
2	**8** (1)	1.1	Ag_2CO_3	0.3	10
3	**8** (1)	1.1	LiO*t*Bu	0.3	0
4	**8** (1)	1.1	NaO*t*Bu	0.3	25
5[b]	**8** (1)	1.1	NaO*t*Bu	0.3	8[c]
6	**10** (1)	1.1		0.3	31
7	**10** (2)	1		0.3	57
8	**10** (1.5)	1		0.3	42[c]
9	**10** (1.5)	1		0.1	52[c]
10	**8** (1.5)[d]	1	NaO*t*Bu[e]	0.075	54
11[f]	**8 (1.5)**[d]	**1**	**NaO*t*Bu**[e]	**0.075**	**66**

[a] Yield of isolated product **9**. [b] With $P(OPh)_3$ (20 mol%). [c] Yield determined by ^1H NMR analysis with CH_2Br_2 as the internal standard. [d] Prior to addition of tol-I and Pd the acid was deprotonated with NaO*t*Bu. [e] With 1.6 equiv base. [f] With 20 mol% Pd.



Scheme 2. Reagents and conditions: a) H_2SO_4 (cat.), MeOH, 70°C, 12 h; b) 4-$MeOC_6H_4CH_2MgCl$ (2.0 equiv), CuI (2.0 equiv), TMEDA (2.2 equiv), TMSCl (5.0 equiv), Et_2O/THF, −78°C/−20°C, 3 h; c) NaOH (10%), MeOH, 70°C, 2 h; d) MSA (10 equiv), 70°C, 3 h; e) LDA (2.2 equiv), $ClCO_2Me$ (1.3 equiv), −78°C/RT, 5 h; f) $NaBH_4$ (1.5 equiv), $CeCl_3$ (1.1 equiv), MeOH, 0°C, 0.5 h; g) MsCl (2 equiv), NEt_3 (3 equiv), CH_2Cl_2, 0°C, 17 h; h) NaOH (30%), EtOH/H_2O (5:1), 5°C, 16 h. MSA: methanesulfonic acid, LDA: lithium diisopropylamide, MsCl: methanesulfonyl chloride.

was introduced in a Cu-mediated conjugate addition according to a procedure described by Ferreira et al.[21] Saponification provided carboxylic acid **12** in very good yield (86% over three steps). The indane core in **13** was built up through an intramolecular Friedel–Crafts acylation of **12** using MSA in good yield (89%).

The carboxy functionality was introduced along with a quaternary center (**14**) through the formation of the dianion of **13** by treatment with LDA and subsequent addition of methyl chloroformate. The crude product was used for the next step without any further purification.[22] The keto function in indanone **14** was readily reduced under Luche conditions. Attempts to dehydrate the OH function under acidic conditions (pTSA, silica gel, AcOH, HCl, $Cu(OTf)_2$, or Amberlyst 15) led to oligomerization. However, we found that when we used an excess of MsCl and NEt_3, efficient and clean H_2O elimination could be achieved to give indene ester **15** (63% over 3 steps). Due to the generally high tendency of indene carboxylates to undergo decarboxylation, subsequent saponification was conducted at 5°C (90% yield). The developed eight-step synthesis allowed the preparation of the key building block **7** in a 43% overall yield in gram scale.

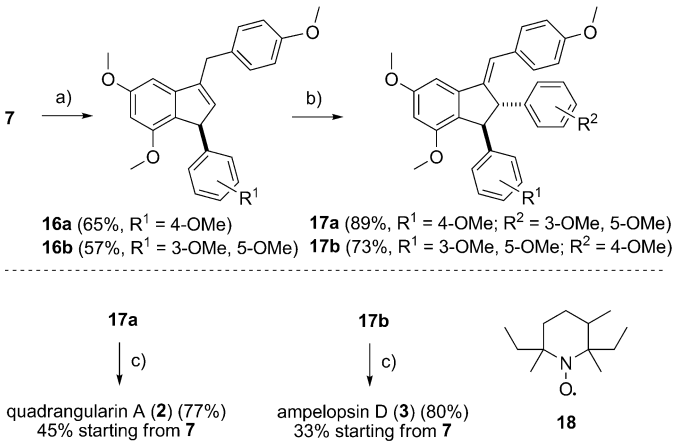
After having established an efficient access to indene carboxylic acid **7**, we turned to the planned key steps (Scheme 3). Pleasingly, the palladium-catalyzed decarboxylative coupling of **7** with aryl iodides proved to be a highly efficient method and the 1,3-disubstituted indene derivatives **16a** and **16b** were obtained in good yields under the optimized conditions. In contrast to the model study the excess of carboxylic acid in these reactions could be reduced to 1.1 and 1.3 equiv, respectively.

We next investigated the applicability of the nitroxide-mediated oxidative Heck reaction[13] for the introduction of the C2 substituent (see Scheme 1). Due to the relative configuration of the aryl groups at positions 2 and 3 in the natural products **2** and **3**, it was essential to introduce the C2 substituent with high *trans*-selectivity. Moreover, the exocyclic double bond of **17a** and **17b** had to be formed stereoselectively in *E* configuration. We were pleased to find that indene **16a** was readily transformed with 3,5-dimethoxyphenylboronic acid and TEMPO as an external oxidant into the protected quadrangularin A **17a** in very good yield and with excellent selectivity (*trans*- and *E*-selective).

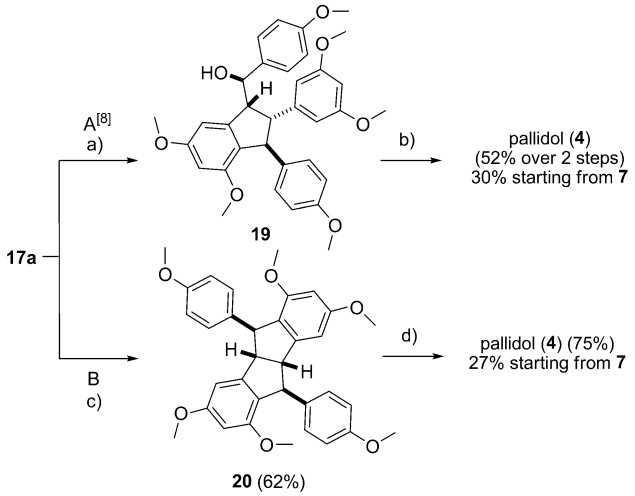
The regioselectivity of the addition to **16a** is controlled by steric and electronic effects. The *E*-selectivity is a result of minimizing allylic $A_{1,3}$ strain during the β-H-elimination reaction, and the *trans*-selectivity is determined by the C3 aryl group. Interestingly, the same reaction with O_2 as the oxidant did not lead to product formation.

For the construction of the ampelopsin D structure 4-methoxyphenylboronic acid was used as the aryl source. Under analogous conditions with TEMPO as oxidant product **17b** was obtained as a mixture containing an inseparable compound. However, using the bulky TEMPO derivative **18** formation of the unwanted side product was largely suppressed and indane **17b** was obtained from **16b** in 73% yield with excellent *trans* and *E*-selectivity.[23] Lewis acid mediated demethylation of all phenolic methyl ethers in **17a** and **17b** eventually provided the natural products quadrangularin A (**2**, 45% yield starting from **7**) and ampelopsin D (**3**, 33% yield starting from **7**), respectively.[24]

To complete the synthesis of the hexacyclic natural product pallidol (**4**) starting with indane **17a** we chose a known two-step reaction sequence comprising a hydroboration and a Friedel–Crafts alkylation with concomitant phenol deprotection (Scheme 4).[8] This sequence led to the biologically active compound **4** via alcohol **19** (method A).[25] During the studies on the hydroboration of **17a** we noted formation of trace amounts of a protected pallidol (**20**) during



Scheme 3. Key steps in the modular approach to the natural products starting with *rac*-**7** (only one enantiomer drawn). Reagents and conditions: a) **7** (1.1 equiv for **16a**, 1.3 equiv for **16b**), $[Pd(dba)_2]$ (20 mol%), NaO*t*Bu (1.1 and 1.3 equiv, respectively), ArI (1.0 equiv), toluene (0.075 M), 110°C, 18 h; b) $Pd(OAc)_2$ (5 mol%), $ArB(OH)_2$ (4 equiv), TEMPO (4 equiv) for **17a** (TEMPO derivative **18** (4 equiv) for **17b**), KF (4 equiv), propionic acid, RT, 18 h for **17a**, 13 h for **17b**: 89% **17a**, 73% **17b**;[23] c) BBr_3 (12 equiv), CH_2Cl_2, 0°C/RT, 6 h: 77% **2**, 80% **3**.[24]



Scheme 4. Total synthesis of pallidol (**4**). Reagents und conditions: a) BH_3·THF (10 equiv), THF, RT, 18 h, NaOH (0.25 M)/H_2O_2 (30%) [3:1], 1 h, basic workup; b) BBr_3 (30 equiv), CH_2Cl_2, 0°C/RT, 8 h, 52% over 2 steps (HPLC purification); c) BH_3·THF (10 equiv), THF, RT, 18 h, NaOH (0.25 M)/H_2O_2 (30%) (3:2), 3 h, aqueous workup, 62%; d) BBr_3 (30 equiv), H_2O (1 equiv), CH_2Cl_2, 0°C/RT, 8 h, 75% (FC purification).

aqueous workup when a slight excess of H_2O_2 was used. After further experimentation we were able to isolate **20** in 62% yield when we used an excess of H_2O_2 (method B). We believe that with excess H_2O_2 an acidic boron compound is generated which induces a spontaneous and clean cyclization during workup. Phenol deprotection from **20** finally afforded the targeted natural product pallidol (**4**).

In conclusion we have described a novel modular approach for the synthesis of racemic resveratrol-based natural products. The strategy involves a novel type of decarboxylative coupling followed by a nitroxide-mediated oxidative Heck reaction. Using this approach structurally relevant aryl groups could be variably introduced. The concept was first applied to the synthesis of the resveratrol-dimers quadrangularin A (**2**) and ampelopsin D (**3**). An optimized reaction sequence afforded pallidol (**4**) in 12 steps and 13% overall yield (Ref.: 7% over 12 steps;[6] 5% over 8 steps).[8] Importantly, our strategy can be used to prepare other natural and nonnatural derivatives which should be interesting for biological studies.

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[22] After purification by colum chromatography, **14** was obtained along with inseparable starting material **13** (^{1}H NMR: **14**/**13** = 11:1; see the Supporting Information).

[23] An inseparable side product was formed (overall yield: 77%; ^{1}H NMR: **17b**/side product = 17:1). We believe that this side product is an isomer containing an internal double bond (see the Supporting Information).

[24] Along with the product an isomer containing an internal double bond was formed in small amounts (see the Supporting Information). Yield: 84% (^{1}H NMR: **2**/isomer = 11:1); 90% (^{1}H NMR: **3**/isomer = 8:1). Final purification was conducted by preparative HPLC.

[25] An additional isomer was formed in 10% yield. It is an isomer of quadrangularin A (**2**) containing an internal double bond, which is likely formed in the reaction of **19** with BBr_3 through an elimination and rearrangement sequence (see the Supporting Information). Surprisingly, alcohol **19** was formed as diastereomeric mixture (in Scheme 4 only the major product is depicted).

