Indoloquinones, Part 6.[13] First Palladium-Mediated Oxidative Cyclization of Arylamino-1,2-benzoquinones to Carbazole-3,4-quinones – Application to the Total Synthesis of Carbazoquinocin C and (±)-Carquinostatin A

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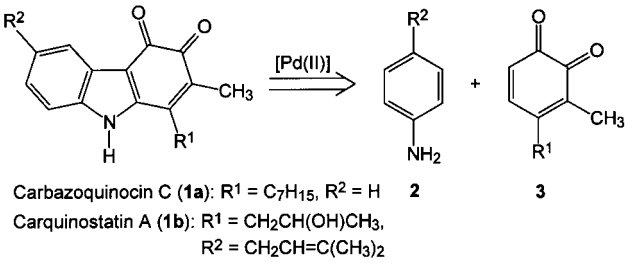
Abstract: A highly convergent synthesis of the carbazole-3,4-quinone alkaloids carbazoquinocin C and (±)-carquinostatin A is reported using a palladium-mediated oxidative coupling of arylamines and substituted 1,2-benzoquinones.

Key words: arylamines, 1,2-benzoquinones, palladium(II) acetate, oxidative cyclization, carbazole alkaloids

Carbazole alkaloids represent an important class of natural products.[1] Therefore, several novel methodologies for the synthesis of carbazoles were developed over the past 10 years.[2,3] Furukawa *et al.* reported the first isolation of carbazole-1,4-quinones from terrestrial plants.[4] Recently, carbazole-3,4-quinone alkaloids, *e.g.* carquinostatin A,[5] the carbazoquinocins,[6] and lavanduquinocin,[7] were isolated from different streptomyces by Seto *et al.* These compounds are structurally unique because they represent the first carbazole alkaloids containing an *ortho*-benzoquinone system. The carbazole-3,4-quinone alkaloids exhibit antioxidative activity and represent potential therapeutic agents for the treatment of a variety of diseases initiated by oxygen-derived free radicals. Due to their useful biological activities the carbazole-3,4-quinones became interesting targets for total synthesis.[8-13] Ogasawara reported the first synthesis of carbazoquinocin A and D.[8] An electrocyclic ring closure was utilized by Hibino to get access to carbazoquinocins.[9] Based on our iron-mediated construction of the carbazole framework,[3] we described the first total syntheses of carbazoquinocin C,[10] carquinostatin A,[11] and lavanduquinocin.[12] Recently, we reported a novel improved route to carbazoquinocin C *via* an efficient palladium(II)-catalyzed oxidative cyclization of an intermediate anilino-1,4-benzoquinone as key-step.[13]

The palladium(II)-mediated oxidative cyclization of *N*,*N*-diarylamines provides carbazole derivatives.[14] The application of this procedure to the cyclization of 2-arylamino-1,4-benzoquinones affords carbazole-1,4-quinones.[15] In the presence of an excess of cupric acetate catalytic amounts of palladium(II) acetate can be used.[16] Alternatively, catalytic reactions were achieved by using *t*-butyl hydroperoxide as oxidant.[17] We applied the palladium(II)-catalyzed oxidative cyclization of arylamino-1,4-quinones in the presence of cupric acetate to the synthesis of benzo[*b*]carbazole-6,11-diones,[16] carbazomycin G and H,[18] and carbazoquinocin C.[13] The palladium(II)-catalyzed oxidative coupling of the anilino-1,4-benzoquinone en route to carbazoquinocin C was very efficient. However, the heptyl side chain at C-1 was introduced subsequent to the cyclization with only moderate regioselectivity.[13] Because of this additional step the synthesis was less convergent compared to our previous iron-mediated route which started from a fully functionalized arylamine.[10] We now devised a novel synthesis of carbazole-3,4-quinone alkaloids which combines the advantages of both previous approaches by using a fully functionalized 1,2-benzoquinone as building block and a palladium(II)-mediated oxidative cyclization as the key-step (Scheme 1).

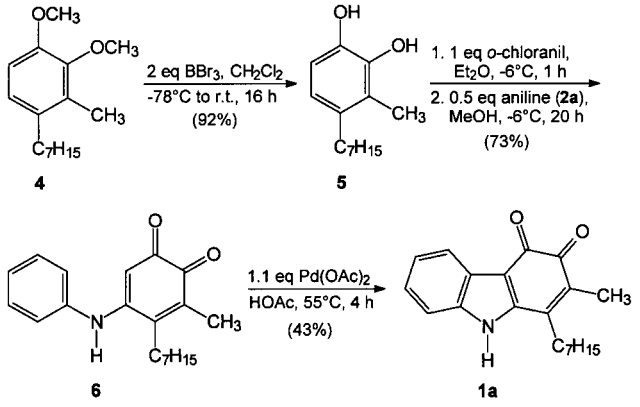


Carbazoquinocin C (**1a**): $R^1 = C_7H_{15}$, R^2 = H **2** **3**
Carquinostatin A (**1b**): $R^1 = CH_2CH(OH)CH_3$,
$R^2 = CH_2CH{=}C(CH_3)_2$

Scheme 1

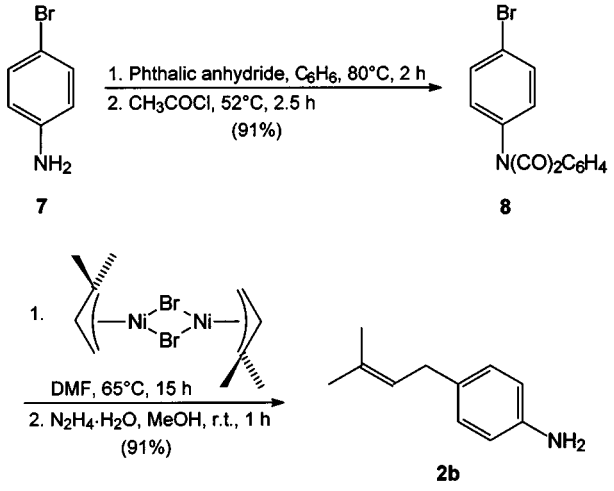
The retrosynthesis of carbazoquinocin C (**1a**) based on this approach provides aniline (**2a**) and 4-heptyl-3-methyl-1,2-benzoquinone (**3a**) as precursors. Carquinostatin A (**1b**) should result from the coupling of 4-prenylaniline (**2b**) and 4-(2-hydroxypropyl)-3-methylbenzo-1,2-quinone (**3b**).

The veratrole **4** was already used as precursor for the iron-mediated synthesis of **1a**.[10] Ether cleavage of **4** using boron tribromide afforded the catechol **5**. Oxidation of **5** with *o*-chloranil led to the required 1,2-benzoquinone **3a**. The 1,2-benzoquinones **3** proved to be very labile. Attempted purification and isolation of **3** resulted to a large extent in decomposition. Therefore, the 1,2-benzoquinone **3a** was immediately transformed to the anilino-1,2-benzoquinone **6** by addition of 0.5 equivalents of aniline (**2a**) in methanol. It is important to note that this reaction was carried out under argon atmosphere and that the second equivalent of the 1,2-benzoquinone had to be used for the reoxidation of the addition product to the quinone. Addition of the arylamine in the air led largely to decomposition. Compound **6** could be isolated and fully characterized. The palladium(II)-mediated oxidative cy-



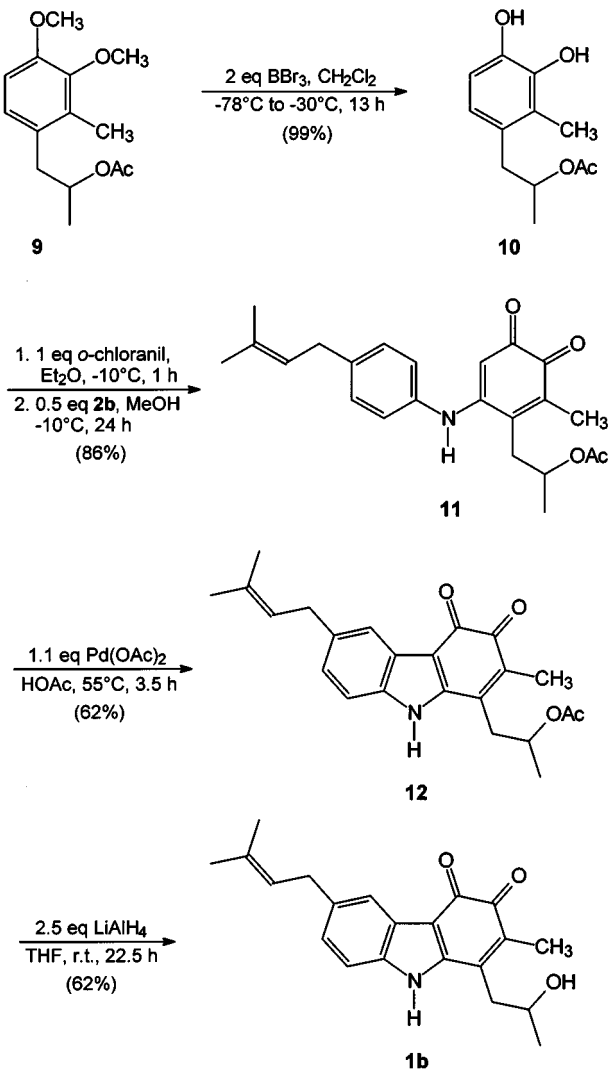
Scheme 2

clization of **6** in glacial acetic acid at 55°C provided directly carbazoquinocin C (**1a**) in 43% yield (Scheme 2). Lower reaction temperatures led to a decreased turnover, while higher reaction temperatures resulted in more decomposition. Carbazoquinocin C is now available in three steps and 29% overall yield based on the veratrole **4**.



Scheme 3

For the synthesis of carquinostatin A (**1b**) by the route indicated in Scheme 1 we required an efficient access to 4-prenylaniline (**2b**). The acid-catalyzed amino-Claisen rearrangement of *N*-prenylaniline affords **2b** only as a by-product.[19] A selective synthesis of **2b** was developed by prenylation of a protected 4-bromoaniline with bis[μ-bromo(η³-prenyl)nickel][20] (Scheme 3). This procedure for the regioselective introduction of the prenyl group was already used in our iron-mediated syntheses of carquinostatin A[11] and neocarazostatin B.[21] By a modified procedure 4-bromoaniline (**7**) was converted to the known phthaloyl imide **8**.[22] The nickel-mediated prenylation of **8** followed by cleavage of the imide with hydrazine in methanol at room temperature provided 4-prenylaniline (**2b**).



Scheme 4

Ether cleavage of the veratrole **9**[11] afforded the catechol **10**. Oxidation of **10** using *o*-chloranil provided the *O*-acetyl derivative of the 1,2-benzoquinone **3b**, which led to the arylamino-1,2-benzoquinone **11** by addition of 4-prenylaniline (**2b**). The palladium(II)-mediated cyclization of **11** using the reaction conditions as described above provided *O*-acetylcarquinostatin A (**12**) in 62% yield (see Experimental Procedure). Removal of the acetyl protecting group by reduction with lithium aluminum hydride transformed **12** to (±)-carquinostatin A (**1b**) (Scheme 4). The present synthesis affords (±)-carquinostatin A in four steps and 33% overall yield based on the veratrole **9**.

In conclusion we developed a palladium-mediated oxidative coupling of arylamines and appropriately functionalized 1,2-benzoquinones. This novel methodology opens up new avenues for highly convergent, short-step syntheses of carbazole-3,4-quinone alkaloids.

Experimental Procedure

O-Acetylcarquinostatin A (**12**): A mixture of **11** (80 mg, 0.21 mmol) and palladium(II) acetate (52 mg, 0.23 mmol) in glacial acetic acid (10 ml) was heated at 55°C for 3.5 h under argon. The reaction mixture was cooled to room temperature, silica gel (1g) was added, the glacial acetic acid was evaporated in vacuum, and the residue was purified by filtration over a short path of silica gel (EtOAc/MeOH, 10:1). After removal of the solvent, hexane/EtOAc (1:1) was added to the residue. The resulting precipitate was separated by filtration, washed with hexane/EtOAc (1:2), and dried *in vacuo* to afford **12** (49 mg, 62%) as a brown solid, mp 210-211°C. UV (MeOH): λ = 231, 267, 429 nm; IR (drift): υ = 3217, 1733, 1656, 1639, 1620, 1599, 1588, 1475, 1373, 1251 cm^{-1}; ^{13}C NMR and DEPT (125 MHz, DMSO-d_6): δ = 12.13 (CH_3), 17.71 (CH_3), 20.08 (CH_3), 20.76 (CH_3), 25.54 (CH_3), 33.86 (CH_2), 34.08 (CH_2), 69.12 (CH), 110.84 (C), 113.13 (CH), 119.32 (CH), 123.73 (CH), 125.11 (CH), 125.99 (C), 131.53 (C), 135.20 (C), 135.53 (C), 137.54 (C), 137.70 (C), 145.68 (C), 169.73 (C=O), 172.52 (C=O), 183.53 (C=O). Analysis calcd. for $C_{23}H_{25}NO_4$: C 72.80, H 6.64, N 3.69; found: C 72.33, H 6.68, N 3.51.

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