COMMUNICATION

Palladium-catalyzed total synthesis of the antibiotic carbazole alkaloids carbazomycin G and H[1]

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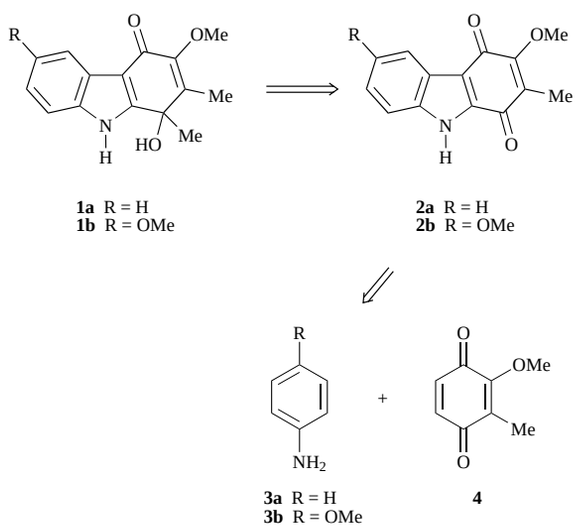
A highly efficient palladium-catalyzed synthesis affords carbazole-1,4-quinones which can be transformed directly into the carbazomycins G and H and are shown to represent precursors for several other biologically active carbazole alkaloids.

The carbazomycin alkaloids isolated by Nakamura and co-workers from *Streptoverticillium ehimense* have become attractive synthetic targets because of their unusual substitution pattern and their useful biological activities.[2] The isolation and structural elucidation of carbazomycin G and H, some further members of this novel class of antibiotics with a characteristic quinol substructure, was reported in 1988.[3] We recently described the first total synthesis of both natural products by construction of the carbazole framework using a consecutive iron-mediated C–C and C–N bond formation. In this approach the electrophilic substitution of a highly substituted arylamine with a tricarbonyliron-complexed cyclohexadienyl cation was followed by oxidative cyclization of the resulting tricarbonyliron–cyclohexadiene complex.[4]

An alternative convergent route to carbazoles involves a palladium-mediated cyclization of *N*,*N*-diarylamines,[5] originally reported by Åkermark *et al*.[6] Furukawa and co-workers first described the application of this method to the synthesis of carbazole-1,4-quinones.[7] The drawback of the palladium-mediated coupling was that stoichiometric amounts of the metal were required due to the reduction of the Pd^{II} in the oxidative cyclization. In a study describing the synthesis of benzo[*b*]carbazole-6,11-diones we showed that a catalytic cyclization is feasible by reoxidation of palladium(0) to palladium(II) with cupric acetate.[1,8] Åkermark *et al*. subsequently reported the use of *tert*-butyl hydroperoxide for reoxidation of the palladium.[9] In the present paper we describe the development of a highly efficient palladium-catalyzed oxidative cyclization to carbazole-1,4-quinones and its application to the total synthesis of carbazomycin G **1a** and carbazomycin H **1b**.

The alkaloids **1a** and **1b** can be prepared directly by addition of methyllithium to the carbazole-1,4-quinones **2**, which previously served as synthetic intermediates in our iron-mediated synthesis.[4] Retrosynthesis of **2** based on the palladium-catalyzed cyclization of the appropriate arylaminobenzo-1,4-quinones as the key-step leads to the corresponding arylamines **3** (**a**: aniline and **b**: *p*-anisidine) and 2-methoxy-3-methylbenzo-1,4-quinone **4** (Scheme 1).

Ester cleavage of the aryl acetate **5**[4] afforded the phenol **6** (Scheme 2). Oxidation of **6** with ceric ammonium nitrate (CAN) provided in high yield the required benzoquinone **4**.[10] Addition of 0.5 equiv. of aniline **3a** or *p*-anisidine **3b** provided the corresponding 5-arylamino-2-methoxy-3-methylbenzo-1,4-quinones **7** with the expected regioselectivity. The benzo-1,4-quinones **7** were cyclized to the carbazole-1,4-quinones **2** by reaction with stoichiometric amounts of palladium(II) acetate under an argon atmosphere in glacial acetic acid at reflux (Table 1). The final step of this oxidative cyclization is a reductive elimination which generates one equivalent of Pd^0. Thus, the overall process can be accomplished using catalytic amounts of the transition metal by reoxidation of Pd^0 to Pd^{II}. We have demonstrated previously,[1] that a catalytic cyclization to carbazolequinones can be realized by using reaction conditions related to those of the Wacker process.[11] In the present study this palladium-catalyzed cyclization has been extensively investigated resulting in a substantial optimization. Finally, cyclization could be achieved with 10 mol% of palladium(II) acetate in the presence of cupric acetate in the air and afforded the two carbazole-1,4-quinones **2a** and **2b** in 71 and 73% yield, respectively (Table 1).



1a R = H
1b R = OMe

2a R = H
2b R = OMe

3a R = H
3b R = OMe

4

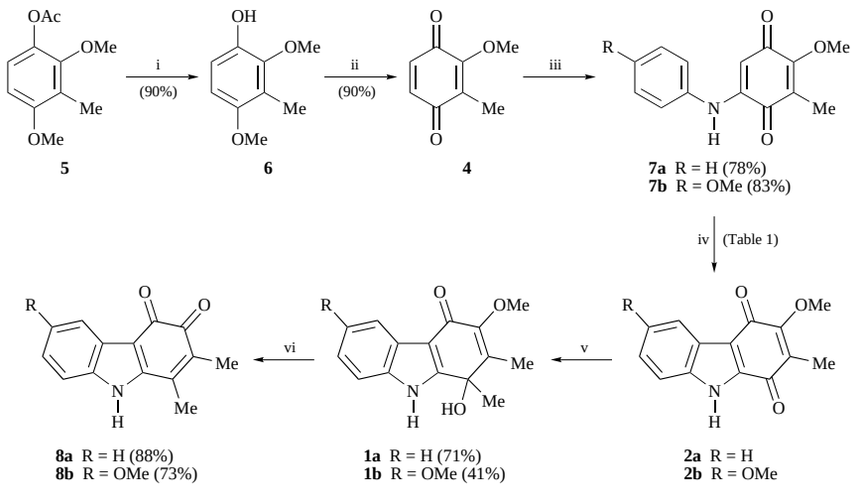
Scheme 1

Regioselective addition of methyllithium to the carbazole-1,4-quinones **2a** and **2b**, as described previously,[4] afforded carbazomycin G **1a** (71% yield)† and carbazomycin H **1b** (41% yield).‡

We envisage the carbazole-1,4-quinones **2a** and **2b** as general precursors for the synthesis of a broad range of biologically active carbazole alkaloids. Thus, we demonstrated that carbazomycin G **1a** is transformed to carbazomycin B on reduction with lithium aluminium hydride followed by elimination of water during work-up.[12,13] Moreover, carbazomycin G **1a** and carbazomycin H **1b** were smoothly converted to the carbazole-

† The present synthesis *via* the palladium-catalyzed cyclization provides carbazomycin G **1a** in three steps and 39% overall yield (46% overall yield *via* the stoichiometric cyclization) based on aniline **3a** as pale yellow crystals, mp 266–268 °C (from ethanol) (decomp.) (lit.,[3] mp 241–243 °C, colourless prisms). All spectral data (UV, IR, ^1H and ^{13}C NMR) are in full agreement with those reported for the natural product.

‡ Carbazomycin H **1b** was obtained in three steps and 25% overall yield based on *p*-anisidine **3b** as pale yellow crystals, mp 208–209 °C (from ethyl acetate) (decomp.) (lit.,[3] mp 228–230 °C, colourless prisms). All spectral data (UV, IR, ^1H and ^{13}C NMR) are in full agreement with those reported for the natural product.



Scheme 2 *Reagents and conditions*: i, KOH, EtOH–H_2O, 25 °C, 1 h; ii, $(NH_4)_2Ce(NO_3)_6$, MeCN–H_2O, 0 °C, 30 min; iii, 0.5 equiv. aniline **3a** or *p*-anisidine **3b**, MeOH, 25 °C, 1 h; iv, [Pd^{2+}], HOAc, 117 °C (Table 1); v, MeLi, THF, −78 to 25 °C; vi, MeOH–conc. HCl (5:1), 64 to 25 °C, 1 h

Table 1 Results of the palladium-catalyzed oxidative cyclization to **2**

	R	Reaction conditions	Yield (%)
7a	H	1 equiv. $Pd(OAc)_2$, 5 h	83
7b	OMe	1 equiv. $Pd(OAc)_2$, 16 h	71
7a	H	0.1 equiv. $Pd(OAc)_2$, 2.5 equiv. $Cu(OAc)_2$, 17 h	71
7b	OMe	0.1 equiv. $Pd(OAc)_2$, 2.5 equiv. $Cu(OAc)_2$, 19 h	73

3,4-quinones **8a** and **8b**, respectively, by elimination of methanol under acidic reaction conditions.§ Therefore, execution of the same sequence starting with **2a** by addition of 1-heptyl lithium would provide carbazoquinocin C.[14,15]

In conclusion we achieved an efficient palladium-catalyzed synthesis of the carbazole-1,4-quinones **2a** and **2b**, which represent direct precursors not only for carbazomycin G **1a** and H **1b**, but also for the synthesis of the carbazomycins A, B, C and D as well as for the carbazoquinocins. These applications are presently under investigation in our laboratories and will be reported in due course.

Experimental

A solution of the benzo-1,4-quinone **7b** (195 mg, 0.714 mmol), cupric acetate (324 mg, 1.78 mmol) and palladium(II) acetate (15.9 mg, 0.071 mmol) in glacial acetic acid (10 ml) was heated at reflux in the air for 19 h. Silica gel (2 g) was added to the reaction mixture, the glacial acetic acid was evaporated in vacuum, and the residue was purified by filtration over silica gel (EtOAc–MeOH, 10:1). After removal of the solvent the residue was taken up in chloroform (5 ml), heated at reflux, and subsequently cooled to −30 °C. The resulting precipitate was isolated by filtration, washed with chloroform, and dried in vacuum to afford the carbazole-1,4-quinone **2b** (142 mg, 73%) as a black–green solid, mp 270–275 °C (decomp.); λ_{max}(MeOH)/nm 224, 260, 297, 309, 441; ν_{max}(KBr)/cm^{-1} 3244, 2955, 1637, 1601, 1489, 1296, 1263, 1219, 1106, 1029, 835, 810, 753, 643; δ_H(500 MHz; [$^2H_6$]DMSO) 1.88 (3 H, s), 3.80 (3 H, s), 4.01 (3 H, s), 6.97 (1 H, dd, *J* 8.9, 2.6 Hz), 7.38–7.41 (2 H, m), 12.76 (1 H, br s); δ_C(125 MHz; [$^2H_6$]DMSO) 8.50 (CH_3), 55.33 (CH_3), 61.03 (CH_3), 101.47 (CH), 113.41 (C), 114.99 (CH), 117.18 (CH), 124.46 (C), 126.46 (C), 132.71 (C), 135.96 (C), 156.92 (C), 157.75 (C), 178.32 (C=O), 180.22 (C=O); *m*/*z* (EI, 125 °C) 271 (M^+, 100%), 257 (56), 256 (40), 242 (14), 228 (16), 200 (12).

§ The compounds **8a** and **8b** represent the hitherto unknown *ortho*-quinones (carbazomycinones) corresponding to the carbazomycins A–D.[12]

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