ORGANIC LETTERS

2004
Vol. 6, No. 3
329−332

Total Synthesis of Carbazoquinocin C: Application of the *o*-Benzannulation of Fischer Carbene Complexes to Carbazole-3,4-quinone Alkaloids

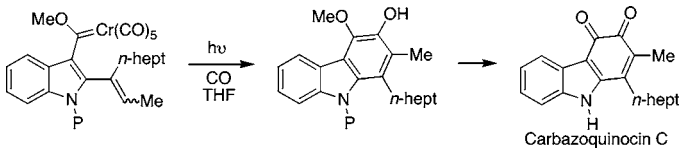
Manish Rawat and William D. Wulff*

Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

wulff@cem.msu.edu

Received October 17, 2003

ABSTRACT

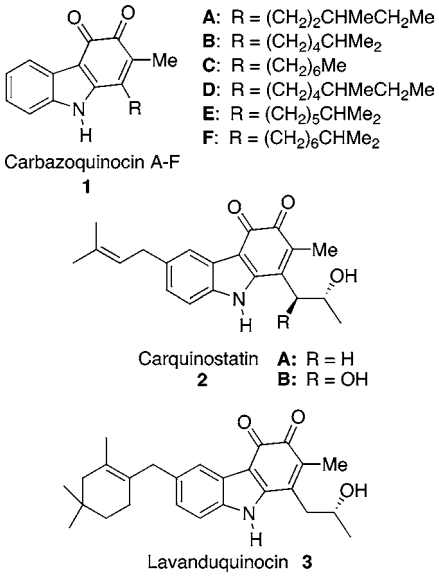


The photoinduced *o*-benzannulation of 3-(2-vinyl)indolylcarbene complexes provides a direct route to carbazole derivatives that are oxygenated in the 3- and 4-positions. This reaction is quite efficient and provides for a unique synthesis of the lipid peroxidation inhibitor carbazoquinocin C.

The carbazole-3,4-quinone unit has been found in a number of molecules which have been discovered largely upon screening several microorganims for compounds possessing activity against lipid peroxidation and for those possessing neuronal cell protecting activity.[1] These molecules include carbazoquinocins A−F, carquinostatins A and B and lavanduquinocin (Scheme 1). The potency of these molecules together with the unique carbazole-3,4-quinone substructure in these molecules have prompted the development of a number of synthetic strategies to this family of natural products.[2] The syntheses reported to date include carbazoquinocins A,[2h] B,[2e] C,[2a−g] D,[2e,h] E−F,[2e] carquinostatin A,[2b,i,j] and lavanduquinocin.[2k,l]

We report a unique approach to the synthesis of the carbazole-3,4-quinone alkaloids in which the *o*-quinone unit is constructed via an *o*-benzannulation reaction of a doubly unsaturated Fischer carbene complex. Inspired by the pioneering work of Hegedus,[3] we envisioned the possibility of such a reaction that involves the photoinduced coupling of a carbon monoxide ligand and a carbene ligand to give a

Scheme 1

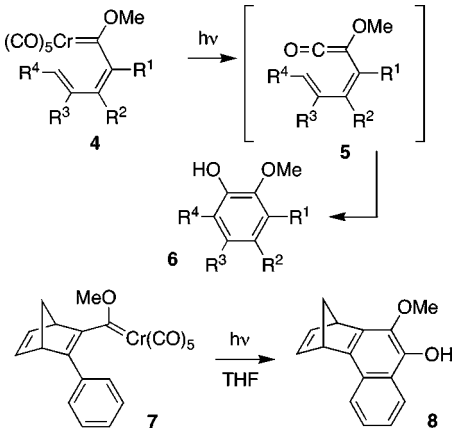


(1) (a) Shin-Ya, K.; Tanaka, M.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1993**, *34*, 4943. (b) Shin-Ya, K.; Shimizu, S.; Kunigami, T.; Furihata, K.; Furihata, K.; Seto, H. *J. Antibiot.* **1995**, *48*, 574. (c) Tanaka, M.; Shin-Ya, K.; Furihata, K.; Seto, H. *J. Antibiot.* **1995**, *48*, 326. (d) Shin-Ya, K.; Kunigami, T.; Kim, J.-S.; Furihata, K.; Hayakawa, Y.; Seto, H. *Biosci. Biotech. Biochem.* **1997**, *61*, 1768. (e) Grammel, H.; Wolf, H.; Gilles, E.-D.; Huth, F.; Laatsch, H. *Z. Naturforsch.* **1998**, *53c*, 325.

10.1021/ol0360445 CCC: $27.50
Published on Web 01/06/2004

doubly unsaturated ketene of the type **5** which undergoes electrocyclic ring closure to give an *o*-methoxyphenol of type **6** (Scheme 2). In fact, we found that the photolysis of

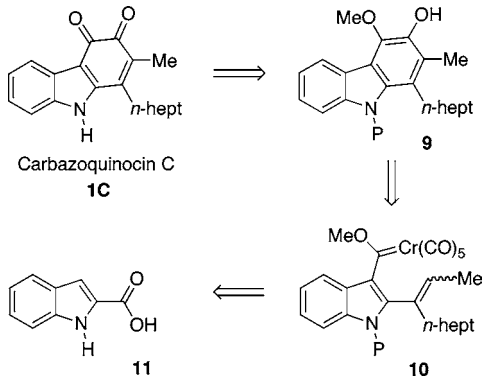
Scheme 2



complex **7** indeed gives the phenol **8** which would be expected from this process.[4] It was later shown that the yield of the reaction could be improved if the reaction was performed under a carbon monoxide atmosphere.[5] In this paper, we describe the synthesis of carbazoquinocin C with the *o*-benzannulation as the key step.

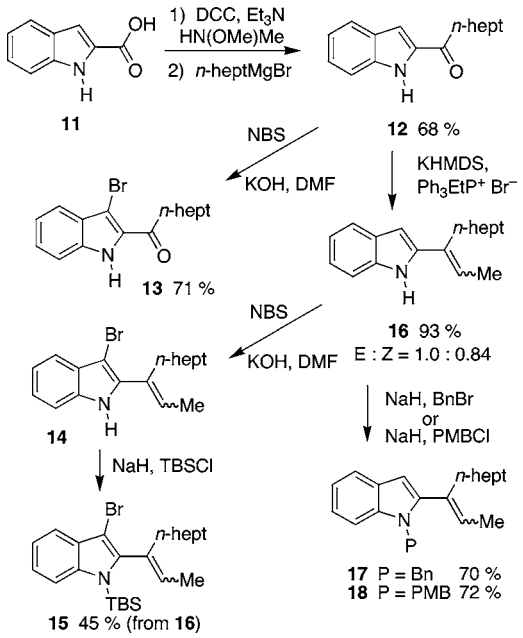
The strategy for the synthesis of carbazoquinocin C involves the intermediacy of the 3-hydroxy-4-methoxycarbazole **9** from which the natural product can be generated by oxidation of the phenol ring (Scheme 3). The key step in

Scheme 3



the synthesis is thus to be the photoinduced CO insertion/cyclization of the α,*β*,*γ*,*δ*-unsaturated carbene complex **10**.

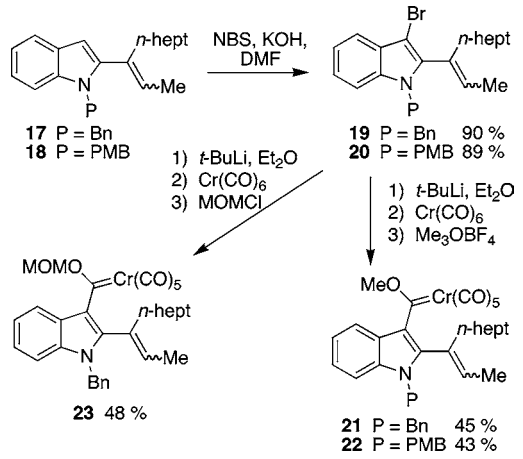
Scheme 4



It was envisioned that this 3-(2-vinyl)indolylcarbene complex could be prepared from the commercially available indole-2-carboxylic acid.

The *n*-heptyl-2-indolyl ketone **12** was efficiently prepared from the acid **11** via Grignard addition to the Weinreb's amide (Scheme 4). The conversion of **12** to intermediates **17** and **18** (Scheme 5), the precursors to the carbene complex

Scheme 5



10, requires N-protection, olefination, and bromination, and some time was spent investigating the optimal order of these steps. Bromination of ketone **12** was successful to give the

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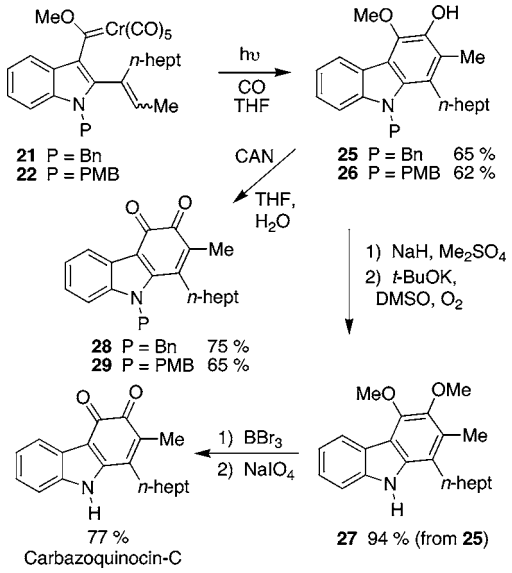
3-bromoindole **13** but all attempts to carry out a Wittig reaction on this substrate failed. In contrast, the olefination of the ketone **12** proceeded smoothly to give the 2-vinylindole **16** in 93% yield as a 1.0:0.84 mixture of *E*/*Z* isomers. The bromination of **16** was successful; however, the resulting 3-bromoindole **14** is not particularly stable. Immediate treatment with TBSCl and NaH gave the stable N-silylated indole **15** in 45% yield for the two steps. Given the instability of bromoindole **14**, the reverse of the bromination/protection sequence was investigated and found to be far more practical. The 2-vinylindole **16** was first protected either as the *N*-benzyl- or *N*-*p*-methoxybenzyl derivatives **17** and **18** in 70% and 72% yield, respectively. Bromination gave the carbene precursors **19** and **20** in excellent yields (Scheme 5). Carbene complexes **21**−**23** were prepared by the standard Fischer procedure in moderate yields. These complexes were usually obtained with a small amount of a side product resulting from reduction of the bromide in the precursors **19** and **20**. These reduced products were not easily separated from the carbene complexes and thus were carried on to the next step where they could be removed. The yields for the carbene complexes **21**−**23** have the amount of the reduced products factored out. We have not been able to prepare a carbene complex from the TBS-protected indole **15**. The only observable product is the 3-unsubstituted indole resulting from reduction of the bromide in **15**.

Although the *o*-benzannulation of certain electron-rich complexes has been reported to fail,[6] the photolysis of the 3-indolylcarbene complexes **21** and **22** under an atmosphere of carbon monoxide gave the carbazoles **25** and **26** in 65% and 62% yield, respectively (Scheme 6).[7] All that remains

Scheme 6



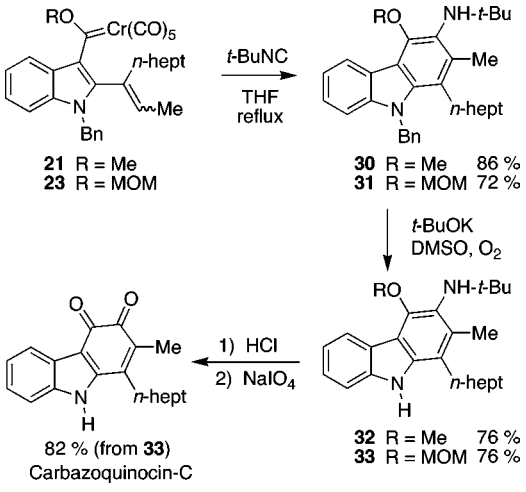
to complete the synthesis of carbazoquinocin C is the adjustment of the oxidation state and deprotection of the indole nitrogen. Deprotection of the *N*-benzylindole **25** was resistant to initial efforts. Hydrogenation with palladium on carbon led to over-reduced products.

Deprotection with $AlCl_3$[8] or with sodium thioethoxide[9] lead to the destruction of the starting material. Deprotection of **25** was only achieved when the phenol function was derivatized as its methyl ether. Benzyl cleavage could then be achieved with potassium *tert*-butoxide in DMSO in the presence of oxygen[10] to give the dimethyl ether **27** in 94% yield for the two steps. The reverse of this sequence did not prove to be viable. Although oxidation of **25** and **26** with CAN gave the corresponding *o*-quinones **28** and **29** in good yields, all attempts to remove the benzyl group in **28** met with failure presumably due to the sensitivity of carbazoquinocin C.

Final conversion of the 3,4-dimethoxylcarbazole **27** to carbazoquinocin C is a two-step process. The direct oxidation of **27** to the natural product with CAN did not give a clean conversion. Following the protocol introduced by Knölker,[2c] this transformation was achieved in two steps beginning with the cleavage of the methyl ethers with boron tribromide. Knölker reported that the resulting hydroquinone would readily undergo oxidation in air to give carbazoquinocin C.[2c] Our finding is that this air oxidation is not clean and gives other products in addition to the natural product. Silver oxide gives a mixture of products that is very similar to that observed upon air oxidation. Carbazoquinocin C binds tightly to silica gel, and attempts to purify the natural product by silica gel chromatography result in substantial loss of material. Thus, we decided to look for oxidizing agents that would give clean conversion of the hydroquinone, and such a condition was found with sodium *meta*-periodate. Simple filtration of the crude reaction mixture through Celite and removal of solvent gave carbazoquinocin C that was pure by ^{1}H and ^{13}C NMR and had a melting point identical to that reported for the natural product.

An alternate synthesis of carbazoquinocin C was achieved by the thermal *ortho*-benzannulation involving isonitrile insertion.[11] The reaction of carbene complex **21** with *tert*-

Scheme 7



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butylisonitrile in refluxing THF gave the 3-aminocarbazole **30** in 86% yield (Scheme 7). This could be readily debenzylated with *tert*-butoxide in DMSO to give **32** in good yield. Considerable effort was extended to directly oxidize **32** to carbazoquinocin C to no avail. Compound **32** was resistant to reaction with sodium *meta*-periodate, and other oxidizing agents, including DDQ, CAN, $KMnO_4$, $Pb(OAc)_4$, Ag_2O, and $FeCl_3$, led to complex mixtures of products.

Given the success in oxidation of the hydroquinone derived from **27** with sodium *m*-periodate (Scheme 6), we attempted to remove the methyl ether in **32** by treatment with BBr_3 but this led to the formation of unidentified products. Final success began with the preparation of the MOM-protected carbene complex **23**. This complex reacted with *tert*-butylisonitrile to give the carbazole **31** in 72% yield, and which could be debenzylated to give **33** in 76% yield. The MOM group could be cleaved in intermediate **33** with HCl, and the resulting *o*-aminophenol could be oxidized with sodium *meta*-periodate to give carbazoquinocin C in 82% yield for the last two steps.

This work describes the successful synthesis of Fischer indole carbene complexes **21** and **23** and their application to the synthesis of carbazoquinocin C via the photochemical *ortho*-benzannulation with carbon monoxide and the thermal *ortho*-benzannulation with isonitriles. An improved method for the oxidation of the hydroquinone of the natural product carbazoquinocin C has also been developed.

Acknowledgment. This work was supported by the National Institutes of Health (Grant No. GM 33589).

Supporting Information Available: Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0360445

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