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

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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 microorganisms for compounds possessing activity against lipid peroxidation and for those possessing neuronal cell protecting activity. 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. The syntheses reported to date include carbazoquinocins A, B, C, D, E–F, carquinostatin A, and lavanduquinocin.

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, 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
doubly unsaturated ketene of the type 5 which undergoes
electrocyclic ring closure to give an α-methoxyphenol of type
6 (Scheme 2). In fact, we found that the photolysis of
complex 7 indeed gives the phenol 8 which would be
expected from this process. It was later shown that the yield
of the reaction could be improved if the reaction was
performed under a carbon monoxide atmosphere. In this
paper, we describe the synthesis of carbazoquinocin C with
the α-benzannulation as the key step.

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

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

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

\[ \text{Scheme 2} \]
\[ \text{Scheme 3} \]
\[ \text{Scheme 4} \]
\[ \text{Scheme 5} \]

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 TBSCI 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, 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). All that remains 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 AlCl₃ or with sodium thioethoxide 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 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-dimethoxycarbazole 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 Knöller, this transformation was achieved in two steps beginning with the cleavage of the methyl ethers with boron tribromide. Knöller reported that the resulting hydroquinone would readily undergo oxidation in air to give carbazoquinocin C. 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 ¹H and ¹³C 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. The reaction of carbene complex 21 with tert-

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butylisonitrile in refluxing THF gave the 3-aminocarbazole 30 in 86% yield (Scheme 7). This could be readily debenzyalted 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, KMnO₄, Pb(OAc)₄, Ag₂O, and FeCl₃, 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 BBr₃ 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