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A Tyrosine-Derived Benzofuranone Related to Diazonamide A

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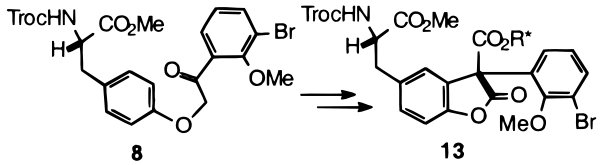
ABSTRACT



Cyclization of 8 with PPA followed by MCPBA oxidation affords the benzofuranone 10. Treatment with a chiral chloroformate in the presence of DMAP affords the target benzofuranone 13 via an enol ester 12.

Diazonamide A (**1**) has attracted attention due to the unprecedented macrocyclic ring system and preliminary indications of biological activity.[1] In vitro, **1** exhibits IC_{50} values of less than 15 ng/mL against HCT-116 human colon carcinoma and B-16 murine melanoma cell lines. Although the structure and activity have been known since 1991, further biological studies have been hampered by the limited availability of natural material.

Several groups have reported progress with some of the structural subunits.[2] Our own work has been directed toward assembly of the lower periphery of the molecule.[3] Here, we describe the synthesis of a benzofuranone of the general structure **2**. The accompanying communication reports the synthesis of the indole subunit of diazonamide A, including methodology for incorporation of the C-24 oxazolyl and C-18 aryl substituents.[4]

The choice of **2** as the generic target was based on the premise that the hemiacetal subunit of diazonamide A is free to equilibrate between the C-7 and C-17 phenolic hydroxyls. Either regioisomeric benzofuranone is therefore a suitable target, assuming selective lactone carbonyl reduction, and **2** was selected because a simple sequence should allow furan annulation via O-alkylation of a protected tyrosine, followed by electrophilic ring closure.

The chloromethyl ketone **6** was prepared from **3** by the addition of the known Grignard reagent **4**[5] to acetaldehyde, followed by Swern oxidation and chlorination. The subsequent O-alkylation of the protected tyrosine methyl ester **7** with **6** was somewhat difficult to control, but an acceptable 71% yield of **8** was obtained using anhydrous two-phase conditions (dichloromethane/K_2CO_3). Phase transfer conditions in the presence of tetrabutylammonium bromide were also tested, but the yield of **8** was lower (50%). Cyclization of **8** to **9** worked well in refluxing benzene with polyphosphoric acid as the catalyst (84% yield), and oxidative conversion to the lactone **10** (81%) occurred upon treatment with peracetic acid.

A related benzofuranone synthesis using dimethyldioxirane as the oxidant[6] has been reported by Adam et al., and the method has been applied to the diazonamide problem by Moody et al.[2c] The latter study had targetted a regioisomeric

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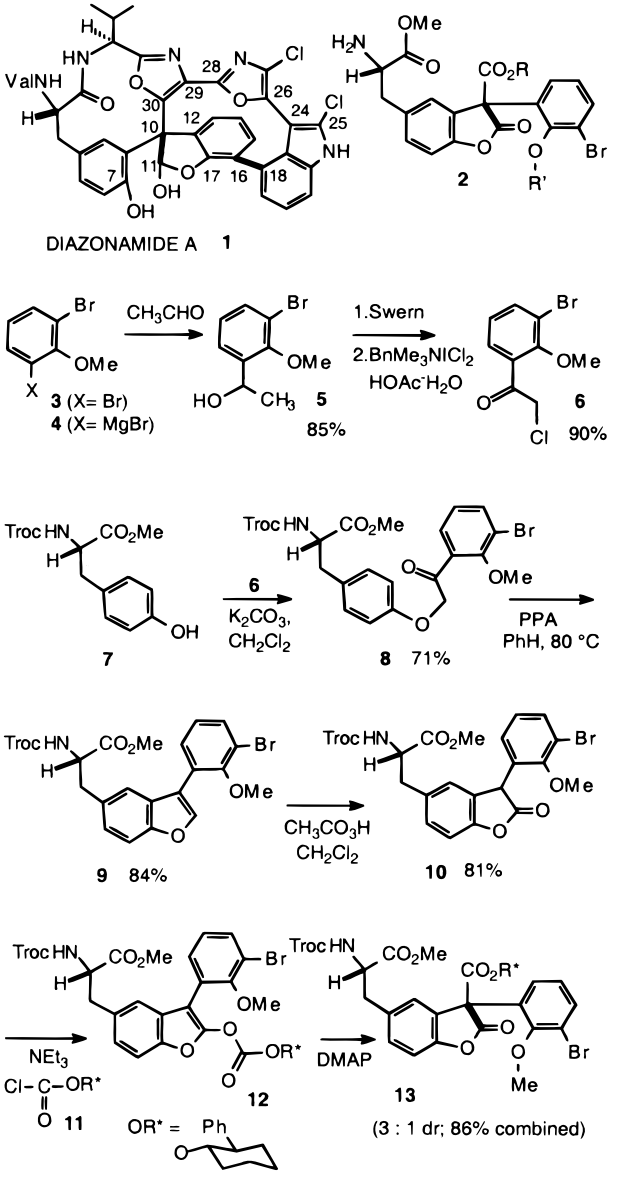
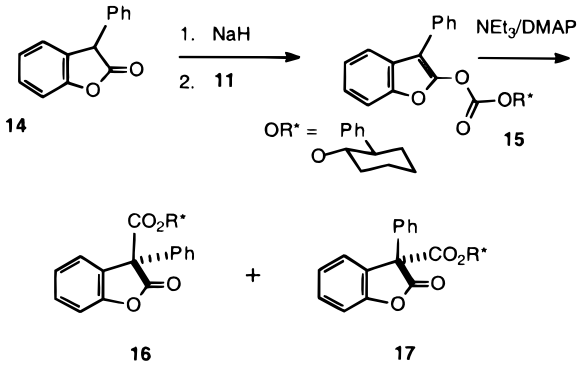
benzofuranone having the lactone ring attached to the C-17 oxygen, as in the hemiacetal ring of **1**, and had used Black's C-acylation method[7] to introduce an additional carbon substituent at C-10. We had also planned to use the Black procedure, but in our case, the substrate was the tyrosine-derived lactone **10**, and a chiral acylating agent **11** was used for acylation.[3] The chloroformate **11** was easily prepared from the Whitesell alcohol, *trans*-(1*R*,2*R*)-2-phenylcyclohexanol,[8] by treatment with phosgene. Subsequent reaction with **10** in the presence of triethylamine gave the enol carbonate **12** in high yield, together with traces of the isomeric **13**. When **12** was treated with DMAP, a blue color was observed, similar to that reported in a simpler case.[7] The color faded on a time scale of hours, and nearly complete conversion to **13** was observed in dichloromethane or in THF. The latter conditions gave the best diastereomer ratio of 3:1. Polar solvents such as acetonitrile produced lower ratios, and so did the use of tributylphosphine as a replacement for the DMAP catalyst. For preparative purposes, it was best to isolate **12** by plug filtration over silica gel and to dry the product over molecular sieves prior to the rearrangement step. Addition of DMAP then gave a mixture of **13** together with the diastereomer (not shown) in a 3:1 ratio, in 86% yield after 12 h at room temperature, and **13** was isolated by preparative HPLC in 60% yield from **10**.

Crystals of **13** were obtained, but the material was not suitable for X-ray structure determination. A similar acylation sequence was therefore carried out from the benzofuranone **14**[7] and the chloroformate **11**. The key rearrangement from the enol carbonate **15** was considerably faster than from **12** (ca. 2 min vs hours; DMAP/THF, rt) and significantly more selective (8:1 **16**:**17**, 82%; major product assigned by X-ray crystallography). On the basis of this evidence, the major diastereomer **13** obtained from **10** was tentatively assigned the same quaternary carbon configuration as in **16**. After the model study was completed, this assignment was confirmed by an X-ray crystal structure of the *minor* diastereomer of **13**.

Scheme 1



Scheme 2



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

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