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SYNTHETIC STUDIES TOWARD DIAZONAMIDE A. PREPARATION OF THE BENZOFURANONE-INDOLYLOXAZOLE FRAGMENT

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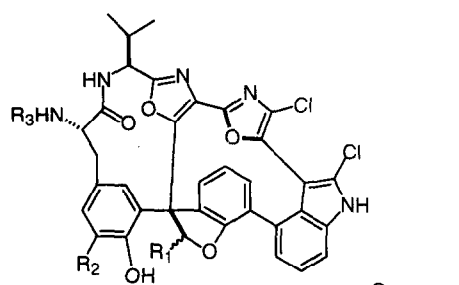
Abstract: The benzofuranone-indolyloxazole fragment of the polycyclic marine natural product diazonamide A was prepared from tryptamine. The oxazole ring was synthesized from an α keto-indole via cyclodehydration with Ph_3P/Cl_3CCCl_3, and after selective Stille biaryl coupling with 2-iodo-6-stannylphenol, the benzofuranone ring was constructed by an intramolecular Heck annulation of an α,β-unsaturated aryl ester. © 1998 Elsevier Science Ltd. All rights reserved.

Diazonamide A (**1**) is a secondary metabolite of the colonial ascidian *Dizona chinensis*, a marine species collected from the ceilings of small caves in the Philippines.[1] It has potent *in vitro* activity against HCT-116 human colon carcinoma and B-16 murine melanoma cancer cell lines, with IC_{50} values <15 ng/mL. The polycyclic diazonamide and its congeners represent an entirely new class of marine natural products. Especially noteworthy is the presence of two directly linked halogenated oxazoles[2] in the polycyclic skeleton which is entrapped as a single atropisomer. Diazonamide A is one of the structurally and biologically most attractive marine natural products isolated in the past few years. As a part of our program toward the synthesis and study of bis-oxazole containing natural products,[3] we have recently embarked on the total synthesis of diazonamide A.[4] In this paper, we describe our progress toward the construction of the benzofuranone-indolyloxazole moiety of diazonamide A.



Diazonamide A, R_1=OH, R_2=H, R_3=

Diazonamide B, R_1=OH, R_2=Br, R_3=H

Selective protection of tryptamine **2** with Cbz-Cl at the primary amine followed by DDQ oxidation under aqueous conditions[5] provided the keto-indole **3** in 73% yield (Scheme 1). Regioselective thallation of the indole C(5)-position with thallium tris-trifluoroacetate followed by treatment with iodine and CuI[6] gave iodoindole **4** in 65% yield. After removal of the Cbz-group with

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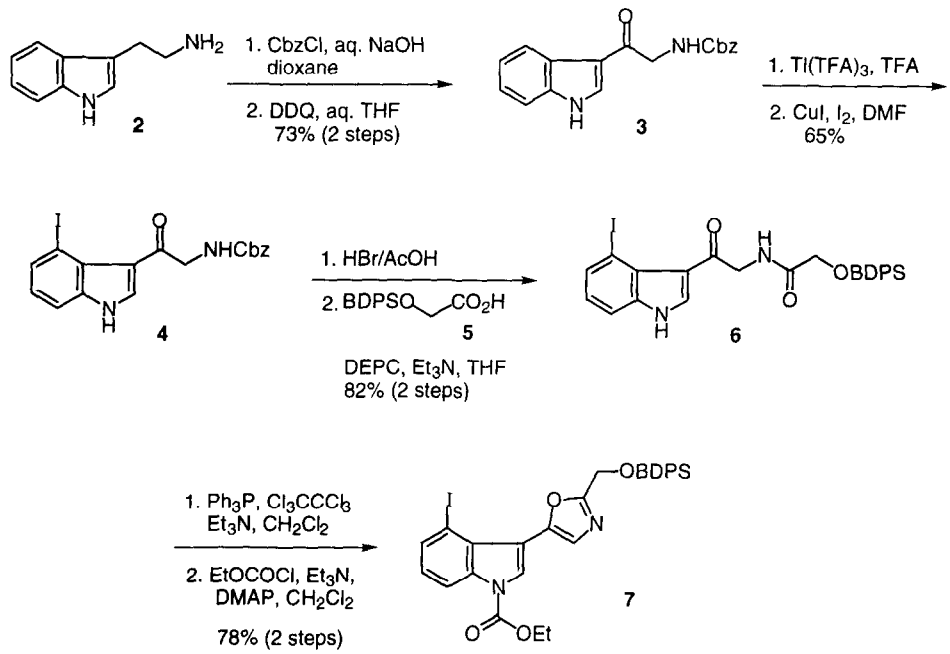
HBr-AcOH, coupling of the resulting HBr salt with BDPS-protected glycolic acid **5** in the presence of diethylphosphoryl cyanide (DEPC)[7] afforded the β-keto amide **6** in 82% yield. According to our oxazole synthesis protocol,[3,8] cyclodehydration of **6** with Ph_3P and Cl_3CCCl_3 in the presence of Et_3N followed by the protection of the indole nitrogen gave indolyloxazole **7** in 78% yield.[9]

Scheme 1.



Palladium(0)-catalyzed monocoupling between indolyloxazole **7** and arylstannane **8** derived from 2,6-diiodophenol[10] required considerable optimization and was accomplished in the presence of 40 mol% of Ph_3As and 20 mol% of CuI as a co-catalyst (Scheme 2).[11] Deprotection of the MOM group in an HCl/ether/methanol/CH_2Cl_2 solution gave a 1:1 mixture of **9** and **7**. The desired coupling product **9** was purified in 28% yield by chromatography on SiO_2, and unreacted **7** was recovered in 29% yield. Longer reaction times for the Stille-coupling, or the use of a Me_3Sn-analog of **8** did not lead to any significant yield improvement. Further segment condensation of phenol **9** and acid **10**[12] set the stage for the construction of the benzofuranone ring and the quaternary center of diazonamide A. Under optimized reaction conditions, the intramolecular Heck reaction[13] of **11** in the presence of $Pd_2(dba)_3$•$CHCl_3$ complex (10 mol%), BINAP (23 mol%), and Ag_3PO_4 (1.2 equiv) in *N,N*-dimethylacetamide at 100 °C proceeded cleanly to give benzofuranone **12** in 74% yield. The use of (*R*)-BINAP led to an asymmetric induction of 14% ee at the stereogenic quarternary center in **12**.[14] Other chiral Pd-ligands, including (*R*)-Tol-BINAP,[15] (*R,R*)-DIOP,[16] (*R,S*)-BPPFA,[17] Cl_2Pd-(*R*)-BINAP,[18] and (*S*)-BINAs,[19] gave mostly similar ee's as well as reduced chemical yields (Table 1).

Scheme 2.

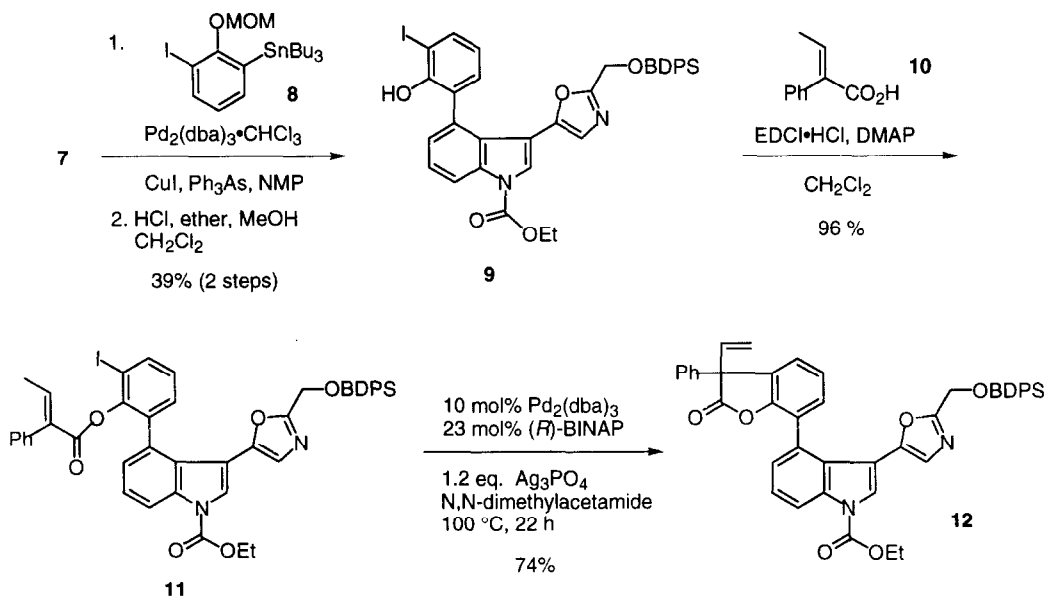


Table 1. Ligand effects in the asymmetric Heck coupling of **11**.

ligand (10 mol%)	T [°C], time [h]	yield of **12** [%]	ee [%][14]
(*R*)-BINAP	100, 22	74	14
(*R*)-BINAP	80, 59	47	19
(*R*)-Tol-BINAP	100, 21	67	19
(*R,R*)-DIOP	100, 21	27	16
(*R,S*)-BPPFA	100, 19	42	3
Cl_2Pd-(*R*)-BINAP	100, 14	72	12
(*S*)-BINAs	100, 20	19	3

In conclusion, we have demonstrated an attractive synthetic strategy for the synthesis of the benzofuranone-indolyloxazole fragment of diazonamide A. Starting from readily available tryptamine, the poly-heterocyclic **12** was obtained by sequential oxazole annulation, Stille coupling, and intramolecular Heck cyclization in 8% overall yield.[20] Further studies toward the total synthesis of this natural product will be reported in due course.[21]

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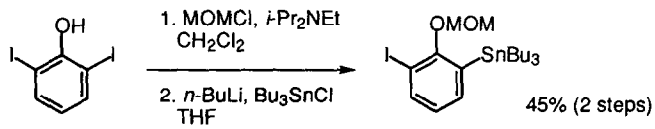

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20. All new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, IR and HRMS.
21. According to our preliminary studies, the chlorination of oxazole and indole rings can be achieved with NCS-benzoylperoxide in CCl_4: