Pergamon

Tetrahedron Letters 39 (1998) 2223–2226

TETRAHEDRON LETTERS

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

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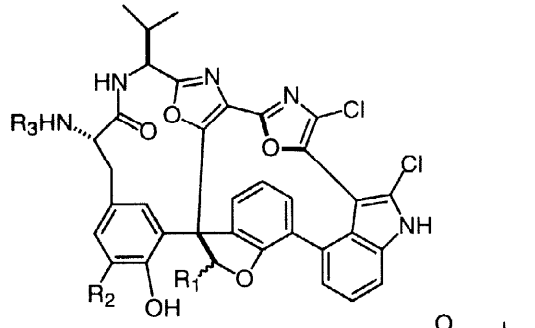
Received 22 December 1997; accepted 15 January 1998

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.

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=

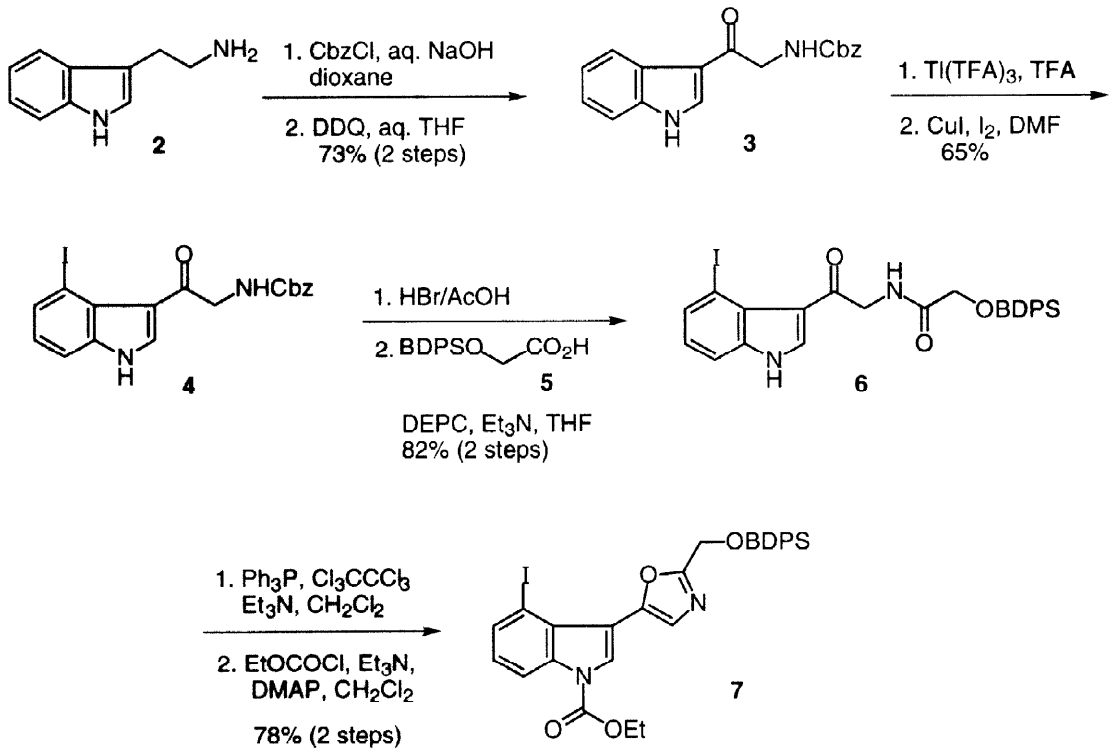
Diazonamide B, R_1=OH, R_2=Br, R_3=H

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

0040-4039/98/$19.00
PII: S0040-4039(98)00231-7

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 quaternary 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.

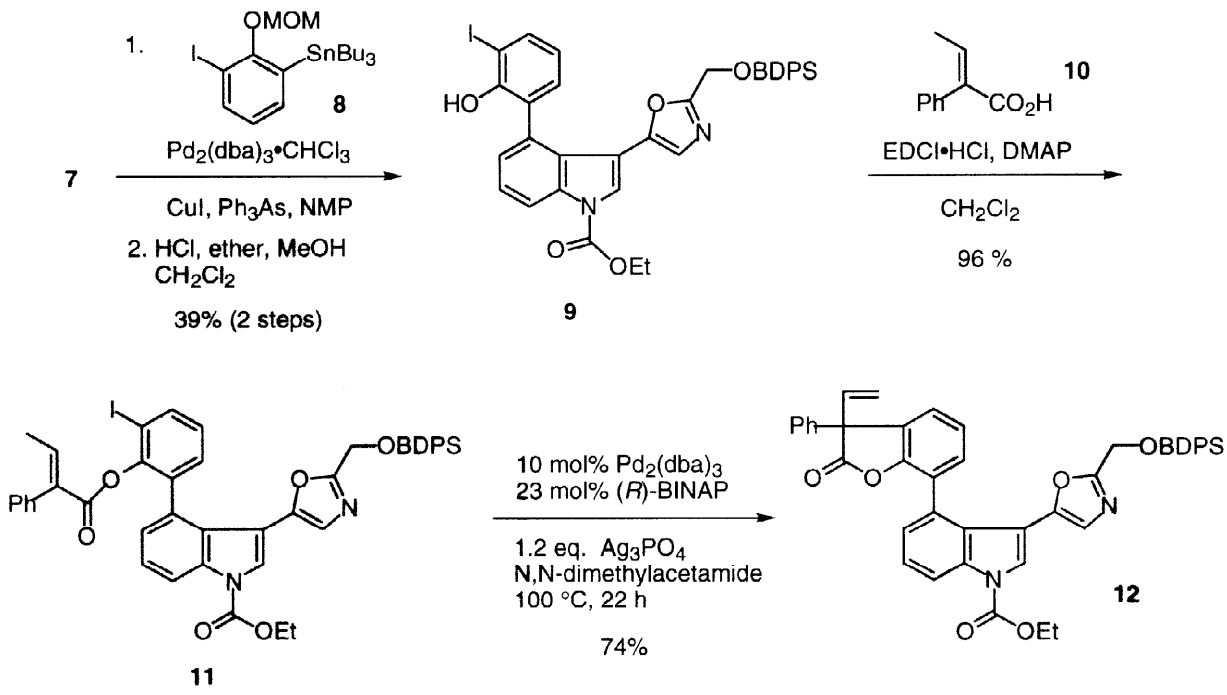


Table 1. Ligand effects in the asymmetric Heck coupling of **11**.

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]

Acknowledgment. This work was supported by the National Institutes of Health (GM 55433). We also acknowledge the Alfred P. Sloan and Camille Dreyfus Foundations for financial support of our program.

References and Notes

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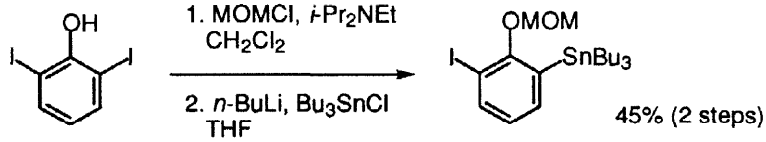

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21. According to our preliminary studies, the chlorination of oxazole and indole rings can be achieved with NCS-benzoylperoxide in CCl_4: