Synthetic Studies on Bengazoles of Marine Sponge Origin. Synthesis of the Core Bis-oxazole Fragments

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Abstract: The core bis-oxazole fragment **3** was constructed by the coupling of the aldehyde (**6**) with the lithiated oxazoles (**7**), oxidation of the resulting bis-oxazolyl methanol (**11**), followed by the asymmetric reduction with (*R*)-(+)-BINAL-H as key steps. Preparation of another bis-oxazole fragment (**4**) was accomplished by the Barton-McCombie radical deoxygenation reaction of **11**.

Bengazoles are a growing family of natural products isolated from marine sponges and characteristic of bis-oxazoles containing carbohydrate-like polyol side chains,[1] as shown in Fig. 1. They exhibit interesting biological profiles such as anthelminthic, antifungal, or cytotoxicity.[1]

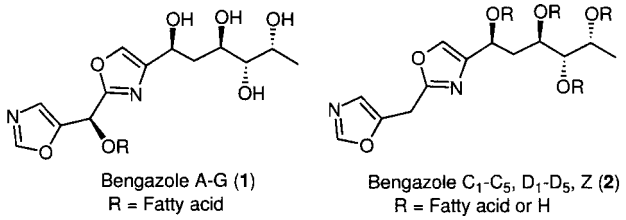
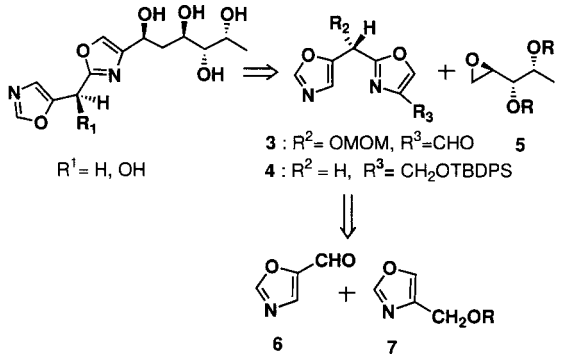


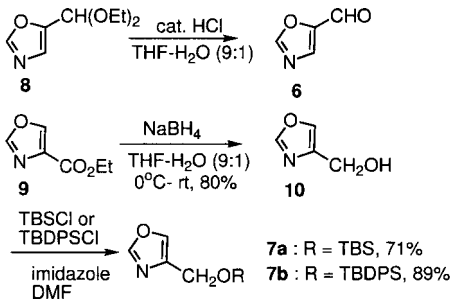
Figure 1

As continuation of our interests on the synthesis of biologically active and structurally interesting marine natural products, we have embarked on the total synthesis of bengazoles (**1** and **2**), the overall strategy of which is shown in Scheme 1. The recent report of Molinski and co-workers[2] prompted us to record our preliminary results on the synthesis of bis-oxazole fragments (**3** and **4**) toward the total synthesis of bengazoles.[3]



Scheme 1

First, 5-formyloxazole (**6**) was quantitatively obtained by acidic hydrolysis of the corresponding acetal (**8**), which was prepared in 86% yield from ethyl diethoxyacetate and lithiated methyl isocyanide.[4a] On the other hand, ethyl oxazole-4-carboxylate (**9**), prepared in 70% yield from ethyl isocyanoacetate and formic acid according to the Schöllkopf's procedure,[4] underwent the reduction with sodium borohydride to give the alcohol (**10**) in 80% yield, which was converted

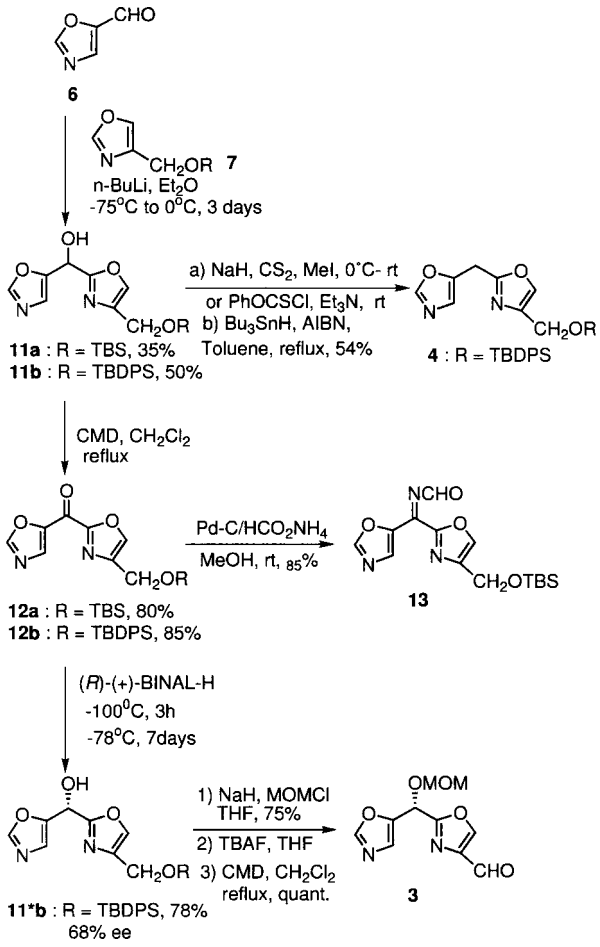


Scheme 2

to the O-silyl derivatives (**7a** : R=TBS (tert-butyldimethylsilyl); **7b** : R=TBDPS (tert-butyldiphenylsilyl)), as shown in Scheme 2.

Formation of the bis-oxazoles (**11a** and **11b**) in their racemic modifications was achieved by the coupling of the aldehyde (**6**) with the lithiated derivatives[5] of the silylated alcohols (**7**) in moderate yield. Attempts to improve the reaction efficiency by the addition of borane as a Lewis acid to complex the oxazole nitrogen[6] failed to increase the yield, and changing bases or addition of co-solvents resulted in either decomposition or recovery of the starting materials. The racemic bis-oxazoles (**11**) were used as the central building block to obtain the chiral oxazoles (**11***) and the de-oxygenated bis-oxazole (**4**), as shown in Scheme 3.

Oxidation of **11** with chemical manganese dioxide (CMD)[7] afforded the bis-oxazolyl ketones (**12**). The asymmetric reduction of the oxazole carbonyl group in **12** was carried out with various reagents, as summarized in Table 1. The initial trial with Brown's (+)-DipCl (diisopinocamphenylchloroborane, **A**)[8] failed to produce the desired product and the reaction mixture turned to black color (run 1). The oxazaborolidine-catalyzed reduction with the Itsuno-Corey reagent (**B**) using catecholborane (CB) as a reducing agent[9] did not give any reduced product (run 2). Similarly, the Lewis acid (boron trifluoride etherate) assisted reduction (hoping to suppress the possible complexation of catechol borane with the oxazole nitrogen[10]) resulted in the recovery of the starting material. Then, we used the methoxy-oxazaborolidines (**C** and **D**) which were developed in our group[11] to increase the reactivity as well as selectivity due to higher Lewis acidity of boron because of the more electron donating methoxy group, which revealed to have a suitable property for coordination with heterocyclic carbonyl group for the asymmetric reduction. As expected, these oxazaborolidine reagents provided better yield and higher selectivity compared to the corresponding B-methyl analog (**B**). Use of a stoichiometric amount of chiral auxiliary **C** with borane dimethyl sulfide (BMS), followed by slow addition of the bis-oxazolyl ketone (**12b**) at 0° C afforded the desired bis-oxazolyl alcohol (**11*b**) in 48% yield with 37% enantiomeric excess (run 5). It might be accompanied by parallel achiral reduction due to proximal arrangement of the complexed borane with the oxazole nitrogen.[12] To overcome the competing achiral reduction, the same reaction was carried out with prior addition of boron trifluoride etherate to suppress the complexation of borane but it resulted in low yields. The oxazaborolidine **D** derived from α-pinene[11]



Scheme 3

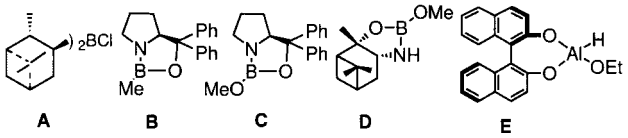
did not give any good results (run 4) compared to the proline based chiral auxiliary (**C**). Our attention now focused the use of the aluminum complex (**E**) of binaphthol, (*R*)-(+)-BINAL-H.[13] When 5 equivalents of **E** was used for the reduction, the best result (78% yield with 68% ee) was obtained. The configuration of the major isomer (**11*b**) was found to be (S) by the modified Mosher method.[14] The asymmetric reduction with (*R*)-(+)-BINAL-H will proceed via the six-membered chair transition state by the chelation between the oxazole nitrogen and the BINAL oxygen atom.[15] The synthesis of the required aldehyde **3** was accomplished by the reactions, outlined in Scheme 3. The hydroxyl function in **11*b** was protected with methoxymethyl (MOM) chloride, followed by deprotection of the TBDPS group with tetrabutylammonium fluoride (TBAF) to give the alcohol. The resulting alcohol was oxidized with CMD[7] afforded the aldehyde (**3**).[16a]

For the construction of another bis-oxazole fragment (**4**), the Clemmensen reduction of the bis-oxazole ketone (**12**) or catalytic hydrogenation over palladium-carbon resulted in the partial reduction to give the oxazole alcohol (**11**). Transfer hydrogenation of the ketone (**12a**) with palladium carbon-ammonium formate gave the formyl imino derivative (**13**). The successful formation of **4** was finally achieved by the Barton-McCombie radical deoxygenation reaction of **11b**,[17] involving the xanthate formation either with carbon disulfide-methyl iodide-sodium hydride or phenyl thionochloroformate. Surprisingly, the xanthate intermediate was accompanied by the deoxygenated product (**4**). This might be due to the active benzylic carbon of the bis-oxazole xanthate leading to the generation of free radical species in the presence of light. Thus, the reaction mixture was subjected to radical catalyzed

Table 1. Asymmetric Reduction of the Oxazolyl Ketone (**12**)

Run	Ketone	Chiral Reagent	Temp, h	Yield, %	%ee[a]
1	**12b**	(+)-DipCl (**A**) (1.2eq)	-78°C-rt	-	-
2	**12b**	**B** (1.0 eq), CB	0°C-rt	-	-
3	**12a**	**C** (0.1 eq), BMS (1.2 eq)	0°C-rt, 2 h	42	12[b]
4	**12b**	**D** (0.1 eq), BMS (1.2 eq)	0°C-rt, 20 h	38	2
5	**12b**	**C** (1.0 eq), BMS (1.2 eq)	0°C, 24 h	48	37[c]
6	**12b**	**E** (5.0 eq)	-100°C (3 h) -75°C (7 days)	78	68

a) Enantiomeric excess was determined from Chiralpak AS column.
b) The corresponding 4-nitrobenzoate was used for ee measurement.
c) The ketone **12b** was added by syringe pump for 2h.



conditions by use of tributyltin hydride-azobisisobutyronitrile (AIBN) to ensure complete deoxygenation, giving the desired bis-oxazole (**4**)[16b] in 54% yield, as shown in Scheme 3.

In summary, we have achieved the synthesis of the core bis-oxazole fragments (**3** and **4**) of the bengazole family. Further coupling of the side chain and generalization of the novel synthetic route for bengazoles are actively under investigation in our laboratories.

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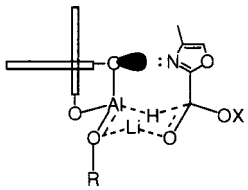
15. Possible transition state will be as follows:[13]



16. a) **3**: oil; $[\alpha]_D$ = +1.4^o (c 0.3, $CHCl_3$); IR ($CHCl_3$): 1700, 1585, 1558, 1506, 1471, 1396, 1330, 1213, 1151, 1103, 1028 cm^{-1} ; ^1H NMR ($CDCl_3$, 270 MHz): 3.41(s, 3H, CH_3), 4.77 (s, 2H, CH_2), 6.05 (s, 1H, CH), 7.27 S, 1H, CH), 7.93 (s, 1H, CH), 8.31 (s, 1H, CH), 9.96 (s, 1H, CHO). b) **4**: oil, IR ($CHCl_3$): 1587, 1576, 1487, 1471, 1427, 1361, 1213 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz): 1.07 (s, 9H, $3CH_3$), 4.17 (s, 2H, CH_2), 4.66 (s, 2H, CH_2), 6.99 (s, 1H, CH), 7.34-7.43 (m, 6H, ArH), 7.47 (s, 1H, CH), 7.65 (m, 4H, ArH), 7.83 (s, 1H, CH).
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