HETEROCYCLES, Vol. 59, No. 2, 2003, pp. 465 - 472, Received, 6th August, 2002

A SYNTHETIC APPROACH TO BENGAZOLES: A SYNTHESIS OF DEACYLBENGAZOLE

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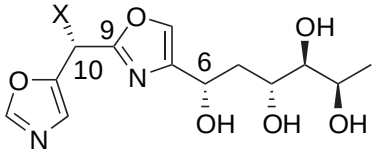
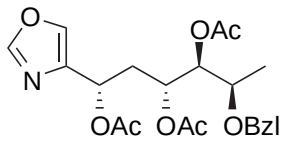
Dedicated to Prof. Yuichi Kanaoka on the occasion of his 75th birthday.

Abstract - The synthesis of deacylbengazole (**3**) and the C1-C9 fragments (**4** and **5**) of bengazoles was accomplished by use of the Thomas $SnCl_4$-assisted coupling of the oxazole aldehydes with δ-alkoxyallylstannanes followed by the Sharpless asymmetric dihydroxylation as key steps.

Bengazoles are a group of bisoxazole containing marine natural products with a carbohydrate-like polyol side chain,[1] and bengazoles A (**1**) and B were first isolated from *Jaspis* sponge by Crews and co-workers in 1988.[1a] Subsequently, bengazole A and their homologues were isolated by Molinski and co-workers who determined their complete absolute configuration to be **1** based on NMR and chiroptical studies.[1e] Bengazoles so far isolated will be classified into two groups: one contains the bis(oxazolyl)methanol as represented by bengazole A (**1**) and the other has no hydroxy function at C10 like bengazole Z (**2**). [1c,1f] Intriguing biological activities such as anthelminthic, cytotoxic, and ergosterol dependent antifungal activities together with the unique bisoxazole array having the polyol side chain have attracted us to devise a novel approach to their synts asn ha an extension of our synthetic efforts on biologically active aquatic natural products.[2] Molinski and co-workers already reported[3a,b] the synthesis of the advanced C1-C9 fragment utilizing the ambident nucleophilicity of 2-lithiooxazoles to couple with a D-galactose derivative, a side chain equivalent, and they succeeded in the total synthesis of bengazole A (**1**) though as



Bengazole A (**1**) : X = O-CO-n-$C_{13}H_{27}$
Bengazole Z (**2**) : X = H
Deacylbengazole (**3**) : X = OH



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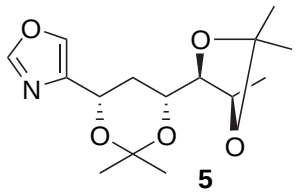

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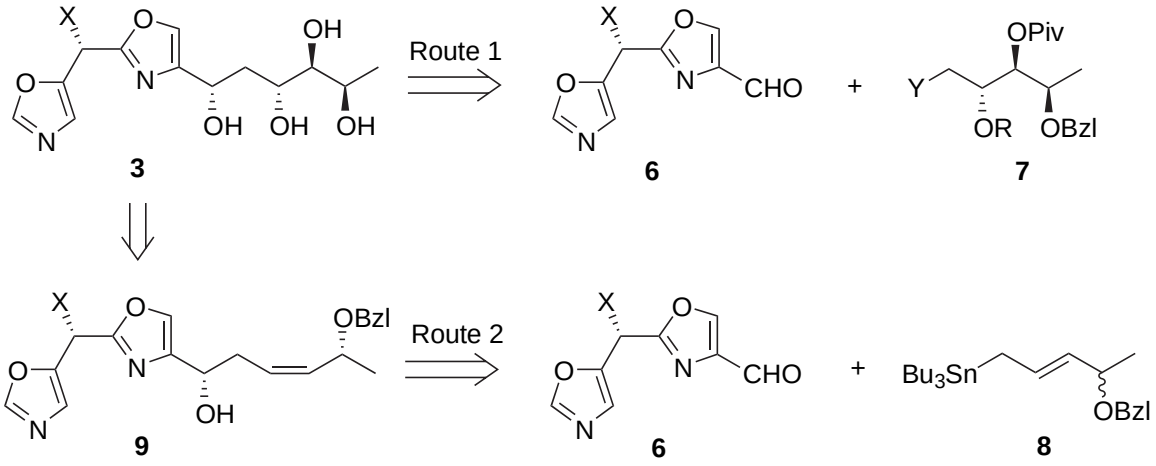
Figure 1

a mixture of C10 epimers.[3c] We also reported our preliminary results on the synthesis of the bisoxazoles (**6**) from oxazole-5-aldehyde and 2-lithiooxazole derivatives.[3d] We now wish to report the synthesis of deacylbengazole (**3**) in addition to the advanced C1-C9 fragments (**4** and **5**).

The retrosynthesis for **3** described in Scheme 1 involves two routes, the first of which adopted the coupling of bisoxazole aldehydes (**6**) with the C1-C5 side chain polyol fragments (**7**). The second route involves the substrate induced asymmetric reaction from chiral δ-alkoxyallylstannanes (**8**) according to the Thomas protocol[4] followed by the Sharpless asymmetric dihydroxylation[5] of the (*Z*)-alkene (**9**). The latter route culminated in the successful synthesis of deacylbengazole (**3**), and the advanced C1-C9 fragments (**4** and **5**) were also constructed in the analogous way.



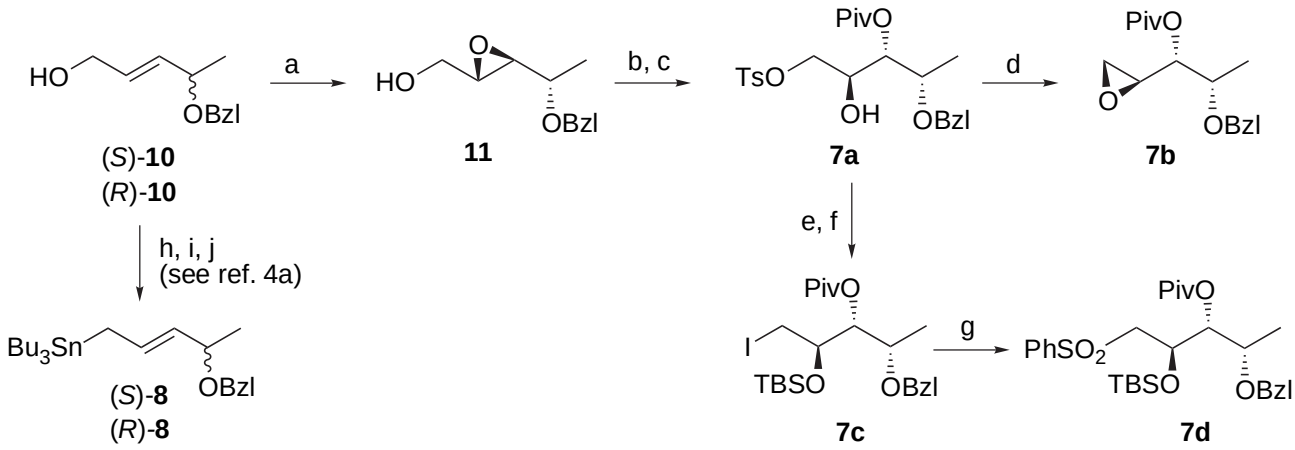
Piv : Bu^{t}CO Bzl : PhCH$_2$

Scheme 1

The synthesis of the requisite side chain fragments (**7a-d**) is outlined in Scheme 2. We first used the easily available (*S*)-allylic alcohol ((*S*)-**10**), which was subjected to the standard conditions of the Sharpless asymmetric epoxidation with (+)-diisopropyl tartrate to provide the *anti*-epoxide (**11**) in 72% yield accompanied with the *syn*-epoxide in 6.5% yield.[6] The critical and selective C3 opening of the chiral *anti* epoxide with pivalic acid was achieved by use of titanium isopropoxide to yield the tetrol derivative[7] in 10:1 selectivity (C-3/C-2). After the conversion of the terminal hydroxy group of the tetrol to the tosyl group, the tosylate (**7a**) was transformed to the epoxide (**7b**) and the O-silyl protected iodide (**7c**), the latter of which was further converted to the sulfone (**7d**). Alternatively, the (*S*)- and (*R*)-allyl alcohols (**10**) were respectively transformed to the corresponding δ-alkoxyallylstannanes (**8**) as a mixture of *E* and *Z* isomers in a 9:1 ratio by the known procedure.[4a]

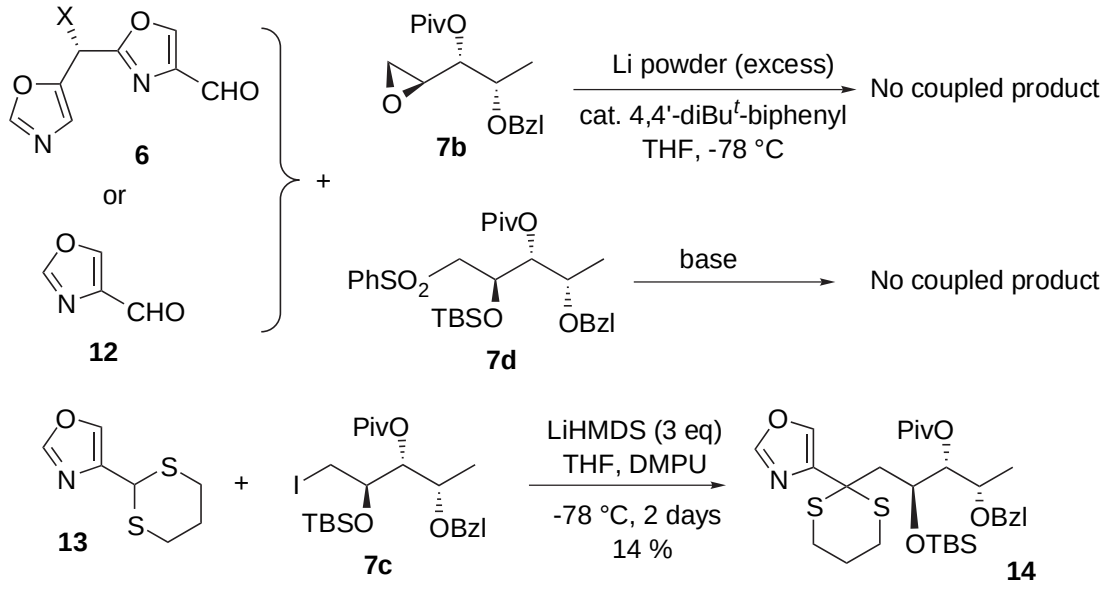
The coupling of the bisoxazole aldehyde (**6**) with the side chain fragments was found to be critical due to the low reactivity of the oxazole aldehydes accompanied by the steric bulk of polyol side chains. As shown in Scheme 3, no coupled products were obtained by use of the epoxide (**7b**) and the sulfone (**7d**) even by use of the arene-catalyzed lithiation reaction.[8] In addition to the bisoxazole aldehyde (**6**), oxazole-4-aldehyde (**12**) proved to be unreactive. However, the corresponding dithiane (**13**) reacted with

the iodide (**7c**) to give the alkylated product (**14**) though in low yield. Further investigations on the coupling of the aldehyde with the side chain fragments proved to be fruitless.



a) cat. $Ti(OiPr)_4$, TBHP, CH_2Cl_2, (+) -diisopropyl tartrate, MS 4A, -20^oC, 4 days, 72%. b) $Ti(OiPr)_4$, pivalic acid, toluene, reflux, C3/C2 = 10/1 (C3-epimer, 64%; C2-isomer, 6.5%). c) tosyl chloride, Et_3N, rt, 48%. d) K_2CO_3, MeOH, 50%. e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 ^oC, 97%. f) NaI, acetone, reflux, 12 h, 97.5%. g) $PhSO_2Na{\cdot}2H_2O$, DMF, 50 ^oC, 12 h, 51%. h) CS_2, MeI, NaH, THF. i) toluene, reflux, 2 h. j) Bu_3SnH, AIBN, benzene, reflux, 3 h.

Scheme 2



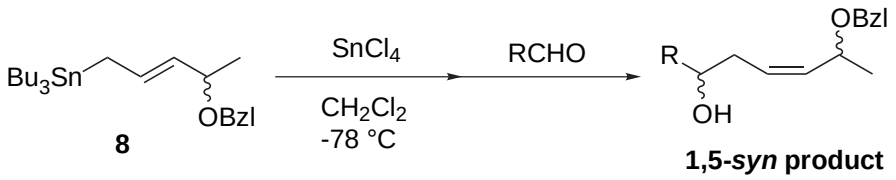
Scheme 3

As an alternative route, 5-benzyloxy-(*E*)-allylstannanes (**8**) was adopted as a side chain precursor because they were expected to couple with oxazole aldehydes through substrate induced remote 1,5-asymmetric induction.[4]

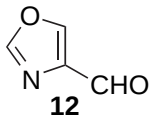
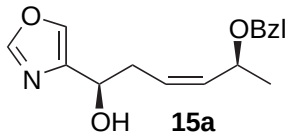
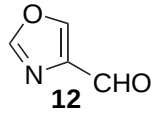
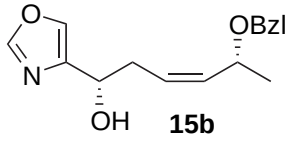
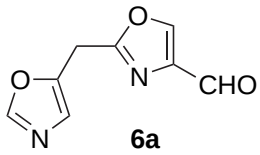
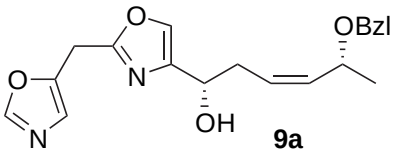
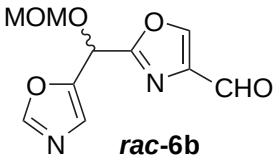
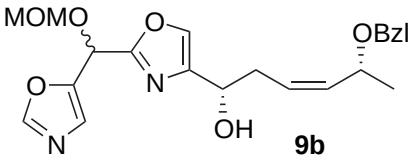
The results using the oxazole aldehydes are summarized in Table 1. Oxazole-4-aldehyde (**12**) reacted with *in situ* prepared allyltin trichloride prepared from the (*S*)-4-benzyloxyallylstannane ((*S*)-**8**) in the presence of $SnCl_4$, giving the coupled product (**15a**) in 91% yield with excellent stereoselectivity (Entry 1). The *cis*

geometry of the double bond was established from the observation of the NOE enhancements between allylic protons of **15a** as reported in the literature.[4] Similarly, the reaction of the (*R*)-isomer of allylstannane ((*R*)-**8**) gave the antipodal (**15b)** in good yield with excellent diastereoselectivity (Entry 2). The configuration of the hydroxy carbon at C6 was assigned by the relative ^{1}H NMR chemical shifts of the corresponding (*R*)- and (*S*)-mandelates.[9] High level of diastereoselectivity together with the desired configurations of the major reaction products (**15**) prompted us to carry on the bisoxazole aldehydes (**6**). The reaction of the (*R*)-4-benzyloxyallylstannane ((*R*)-**8**) with the bisoxazole aldehydes (**6a**) and (*rac*-**6b**) afforded the coupled products (**9a**) and (**9b**), respectively, in good yields with excellent diastereoselectivity.

Table 1



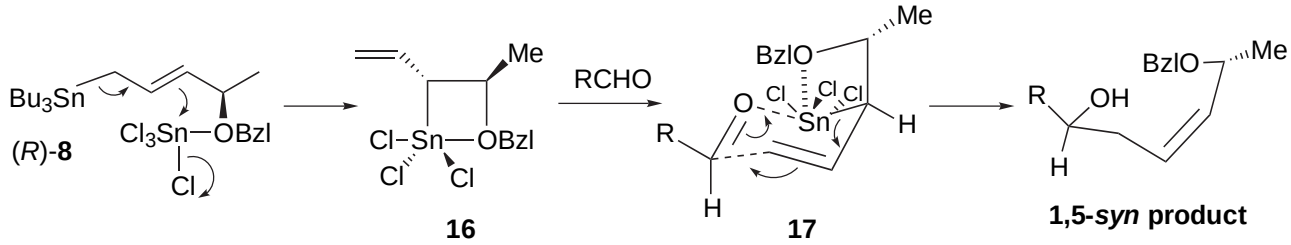
8 **1,5-*syn* product**

Entry	RCHO	Stannane (**8**)	1,5-*syn* product[a]	$[\alpha]_D$ ($CHCl_3$)	dr[b]	Yield (%)
1	 **12**	(*S*)-**8**	 **15a**	+28.4° (c = 1.1)	96 : 4	91
2	 **12**	(*R*)-**8**	 **15b**	-27.1° (c = 1.5)	98 : 2	91
3	 **6a**	(*R*)-**8**	 **9a**	+48.1° (c = 0.1)	99 : 1	68
4	 ***rac*-6b**	(*R*)-**8**	 **9b**	-	>99[c]	80

a) Diastereomers are seperated on silica gel column chromatography.
b) Estimated from the corresponding mandelic acid derivatives.
c) The ratio was 1:1, but dependent on the enantiomeric excess of bisoxazole (**6b**).

The stereochemical outcome will involve the stereoselective formation of the allyltin trichloride (**16**) from the δ-alkoxyallylstannane (**8**) *via* $SnCl_4$ transmetallation at lower temperature, and this intermediate is known for high level of asymmetric induction with aldehydes to provide 1-substituted *syn*-(*Z*)-5-benzyloxyhex-3-en-1-ols *via* the six membered transition state (**17**) comprising the critical chelation of

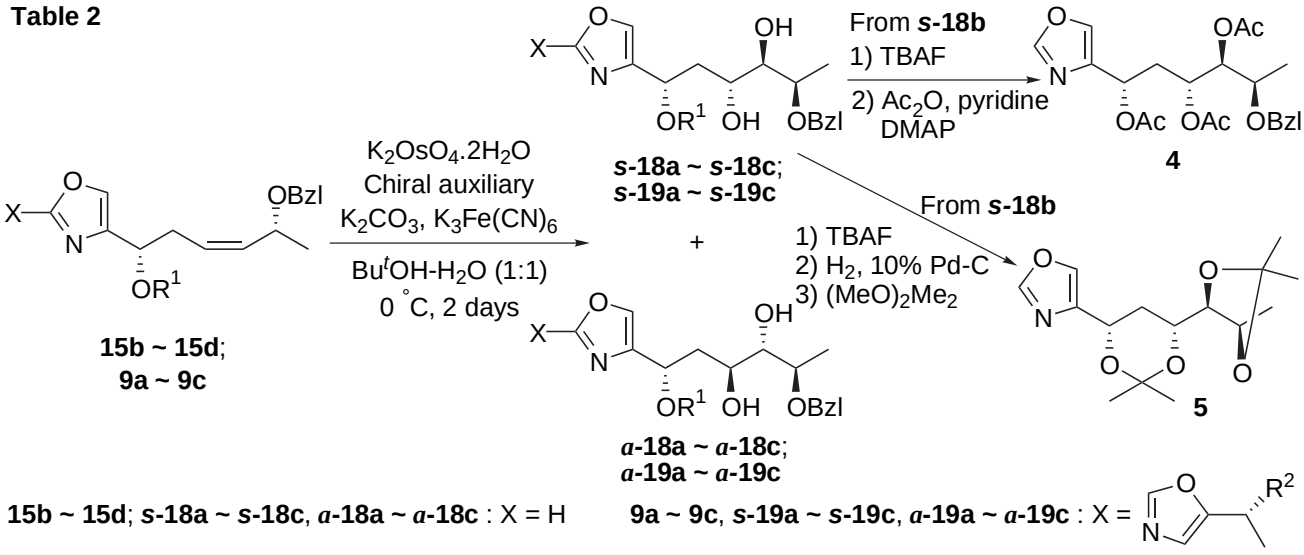
tin with the benzyloxy group, shown in Scheme 4.[4] The higher diastereoselectivities in Entries 3 and 4 might be due to increase in the size of the bisoxazoles.



Scheme 4

The dihydroxylation was next investigated to construct the C1-C9 fragment of bengazoles, as shown in Table 2. The addition of osmium tetroxide in the presence of *N*-methylmorpholine *N*-oxide to the monooxazole alcohol (**15b**) provided the tetraol product in favor of the *anti* addition product (***a*-18a**) by the presence of the allylic C-2 hydroxy function as expected from the Kishi's empirical rule[10] (Entry 1). Thus we adopted the catalyst controlled dihydroxylation to enhance the desired *syn* selectivity utilizing OsO_4 bound with cinchona alkaloids.[5] First, use of commercially available AD-mix-α and AD-mix-β under standard conditions provided only trace amounts of the products. Then the yields were improved up to 90% by the addition of 8 mol % of OsO_4 along with 10 mol % of chiral auxiliaries. The asymmetric dihydroxylation of the disubstituted *cis* double bond of the compound (**15b**) having the unprotected homoallylic group gave the dihydroxylated products in almost the same ratio of the *syn*- (***s*-18a**) and *anti*-isomers (***a*-18a**) utilizing $(DHQ)_2PHAL$ (Entry 2). Interestingly, use of the pseudoantipodal $(DHQD)_2PHAL$ under the same conditions resulted in the preferential formation of the *anti* isomer (***a*-18a**) (Entry 3). Other chiral auxiliaries such as $(DHQ)_2PYR$, (DHQ)MEQ and monomeric 9-(4-chlorobenzoyl)-DHQ were not effective for the enhancement of the *syn* selectivity (Entries 4-6). We also ruled out the significant effect of the free unprotected allylic hydroxy group in **15b** to increase the *syn* selectivity by the protection with *tert*-butyldimethylsilyl (TBS) and acetyl groups. The reaction of the TBS derivative (**15c**) with $(DHQ)_2PHAL$ and $(DHQD)_2PHAL$ gave the similar results as the hydroxy free derivative (**15b**) (Entries 7, 8). The acetyl derivative (**15c**) favored more towards *anti* addition product with $(DHQ)_2PHAL$ (Entry 9). The dihydroxylated *syn* and *anti* TBS derivatives (***s*-18b** and ***a*-18b**) were separated on conventional silica gel column chromatography, which enabled us to convert them to the corresponding tetraacetyl derivatives (**4**) in pure state. Comparison of the chemical shifts of the *syn* and *anti* isomers with those of natural bengazole Z tetraacetate[1d] established the stereochemistry of each product. Further, the *syn* addition product (***s*-18b**) was transformed to the diacetonide (**5**), shown in Table 2. The diacetonide (**5**) thus obtained had the identical chemical shift values as well as vicinal coupling constants on 500 MHz NMR spectra with those of the diacetonide of natural bengazole A. In the case of the dihydroxylation of the bisoxazole derivatives, the moderate stereoselectivity was observed towards the *syn* addition (Entries 10, 11, and 13) with $(DHQ)_2PHAL$ whereas **9c** gave the *anti* addition product (***a*-19c**) as the major product with $(DHQD)_2PHAL$ (Entry 12).

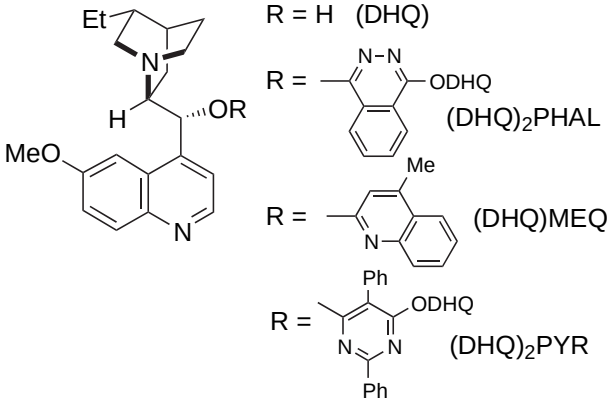
Table 2

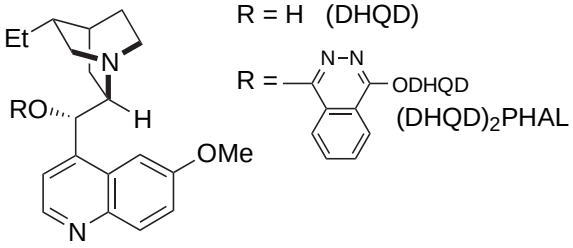


15b ~ 15d; ***s*-18a ~ *s*-18c**, ***a*-18a ~ *a*-18c** : X = H **9a ~ 9c**, ***s*-19a ~ *s*-19c**, ***a*-19a ~ *a*-19c** : X =

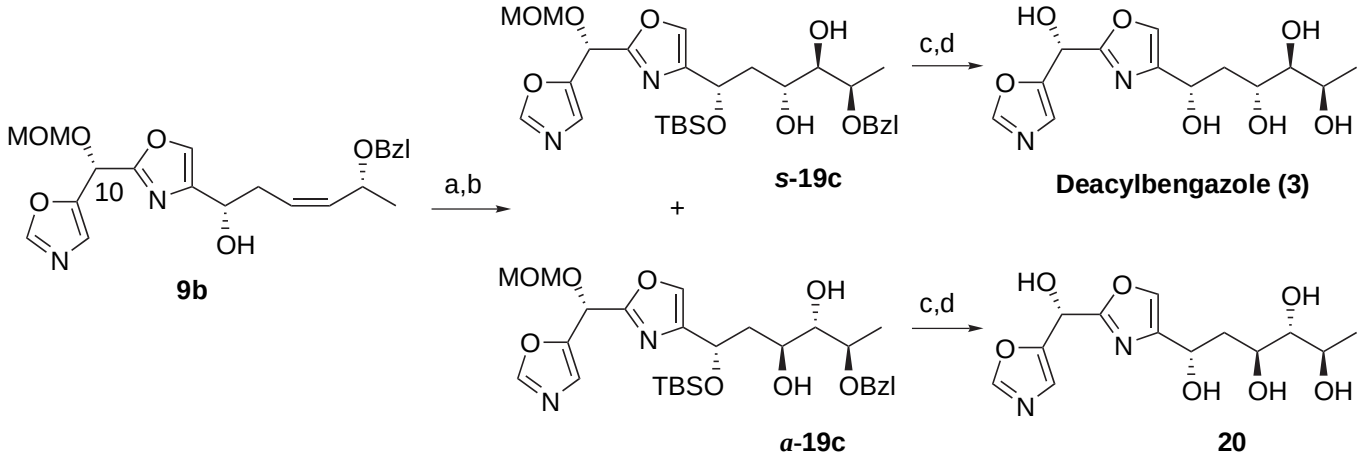
Entry	Substrate	Chiral auxiliary	Product	Yield (%)	*Syn*/*Anti* [a]
1	**15b** (R^1 = H)	none	***s*-18a/*a*-18a**	75	1 / 4.5
2	**15b** (R^1 = H)	$(DHQ)_2PHAL$	***s*-18a/*a*-18a**	80	1 / 1
3	**15b** (R^1 = H)	$(DHQD)_2PHAL$	***s*-18a/*a*-18a**	80	1 / 25
4	**15b** (R^1 = H)	9-(4-chlorobenzoyl)-DHQ	***s*-18a/*a*-18a**	trace	-
5	**15b** (R^1 = H)	(DHQ)MEQ	***s*-18a/*a*-18a**	65	1 / 3
6	**15b** (R^1 = H)	$(DHQ)_2PYR$	***s*-18a/*a*-18a**	83	1 / 2
7	**15c** (R^1 = TBS)	$(DHQ)_2PHAL$	***s*-18b/*a*-18b**	71	1.3 / 1
8	**15c** (R^1 = TBS)	$(DHQD)_2PHAL$	***s*-18b/*a*-18b**	75	1 / 24
9	**15d** (R^1 = Ac)	$(DHQ)_2PHAL$	***s*-18c/*a*-18c**	80	1 / 1.4
10	**9a** (R^1 = H, R^2 =OH)	$(DHQ)_2PHAL$	***s*-19a/*a*-19a**	60	1 / 1
11	**9b** (R^1 = H, R^2 =OMOM)	$(DHQ)_2PHAL$	***s*-19b/*a*-19b**	90	1 / 1.8
12	**9c** (R^1 = TBS, R^2 =OMOM)	$(DHQD)_2PHAL$	***s*-19c/*a*-19c**	87	1 / 49
13	**9c** (R^1 = TBS, R^2 =OMOM)	$(DHQ)_2PHAL$	***s*-19c/*a*-19c**	85	6 / 7

a) The *syn*/*anti* ratio was determined from the proton NMR spectra of acetyl derivatives.





We now extended our studies towards the total synthesis of deacylbengazole (**3**) that was a common structural unit of bengazoles. The requisite bisoxazole aldehyde (**6b**) was prepared according to our earlier report[3d] as a mixture of (*S*)- and (*R*)-isomers in a ratio of 84:16. The tin catalyzed δ-alkoxyallylation of **6b** with (*R*)-**8**, as described in Table 1 (Entry 4), afforded the coupled product (**9b**) in 85% yield. After its conversion to the TBS derivative (**9c**), the Sharpless asymmetric dihydroxylation with $(DHQ)_2PHAL$ afforded the *syn*/*anti* addition products (***s*-19c** and ***a*-19c**) in 6:7 ratio, which were separated on conventional silica gel column chromatography, as shown in Scheme 5. The deprotection of the benzyl group from the *syn*- and *anti*-isomers with catalytic hydrogenolysis over 10 % Pd-C quantitatively afforded the respective alcohols. Finally, the both methoxymethyl and TBS groups of *syn*- and *anti*-isomers were respectively deprotected in one step using 5 equivalents of TMSBr to give deacylbengazole (**3**) ($[\alpha]_D$ +1.12° (c=0.1, MeOH)) and its isomer (**20**) ($[\alpha]_D$ -1.88° (c=0.15, MeOH)) in 95% yield. Deacylbengazole (**3**) was found to be exactly identical with that derived from the natural product on its NMR spectra, which revealed the presence of a small amount of the minor C10 epimer. The spectral data of isomer (**20**) were clearly distinct from those of the natural product.



a) TBSCl, 2,6-lutidine, CH_2Cl_2. b) $K_2OsO_4{\cdot}2H_2O$, $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, Bu^tOH-H_2O (1:1), 2 days, 0 C, 85% (2 steps), *syn* / *anti* = 6 / 7. c) H_2, 10% Pd/C, EtOH, rt, 12 h, quantitative. d) Me_3SiBr, CH_2Cl_2, 0 °C, 2 h, 95 %. **Scheme 5**

In conclusion, we have demonstrated our studies towards total synthesis of the bengazole family, which also provides other isomers in tunable way by the choice of catalysts. This will become a novel route to synthesize various isomers of bengazoles to investigate the studies of structure-activity relationship of the bengazole family.

ACKNOWLEDGMENTS

This work was financially supported in part by Grant-in-Aids from the Ministry of Education, Culture, Sports, Science and Technology, Japan and the Japan Society for the Promotion of Science. One of the authors (P. C.) is grateful to the Japan Society for the Promotion of Science and the Japan Science and Technology Corporation for postdoctoral fellowship.

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2. For our synthesis of hennoxazole A having a bisoxazole moiety, see F. Yokokawa, T. Asano, and T. Shioiri, *Tetrahedron*, 2001, **57**, 6311. See a review: T. Shioiri and Y. Hamada, *Synlett*, 2001, 184.
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