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Synthesis of the C1-C9 core of Bengazole A: Harnessing the ambident nucleophilicity of 2-lithiooxazole

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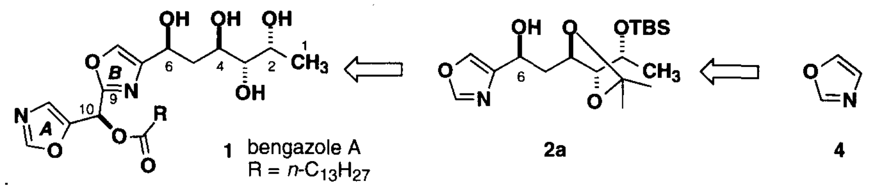
Abstract: *An advanced intermediate for the synthesis of bengazole A (1) was prepared by direct grafting of oxazole to a protected side-chain synthon (prepared from D-galactose) through C-4-directed addition (oxazole numbering) to the ambident nucleophile, 2-lithiooxazole.*

Keywords: *antifungals; natural products; oxazoles; sponges*

Bengazole A (**1**) and related homologs[1] are oxazole-containing heterocycles isolated from marine sponges of the genus *Jaspis*. Bengazole A exhibits potent *in vitro* antifungal activity against *Candida albicans*[2] and Fluconazole®-resistant *Candida* strains[2b] that is dependent upon the presence of the yeast sterol ergosterol. This is a property shared by the polyene antifungal agent, amphotericin B but, presently, it is unclear whether **1**, like amphotericin B, forms ion-permeable pores in yeast cell membranes. The complete configuration of **1** was established in our laboratories by NMR and chiroptical studies,[1b] but no synthesis of any member of the bengazole family has been described. In order to investigate the properties of bengazoles and related derivatives, we embarked on a total synthesis of **1**.



1 bengazole A, R = n-$C_{13}H_{27}$ **2a** **4**

The right hand ring 'B' - a 2,4-disubstituted oxazole - suggests a standard biomimetic synthesis from an appropriate *N*-acylserine amide *via* the corresponding oxazoline.[3] A contentious issue with this strategy is judging the correct point for introduction of the oxazole heterocyclic ring by cyclodehydration-oxidation of an *N*-acylserine amide intermediate which will allow safe propagation of highly functionalized, intact oxazole intermediates through subsequent reactions that are compatible with a π-rich heterocycle. Of more concern is the fact that successful cyclodehydration-oxidation of serine amides are limited to oxazole products bearing 4-carboxy substituents. Here, we demonstrate an alternative to the biomimetic paradigm for 2,4-disubstituted oxazole construction and present a synthesis of an advanced bengazole A intermediate, **2a**. A C-1,6 synthon **3** (bengazole numbering) was grafted *directly* to oxazole (**4**) by exploiting a special property of 2-lithiooxazole; ambident nucleophilicity that directs addition of aldehydes to C-4, rather than C-2.[4] To our knowledge, this is the first

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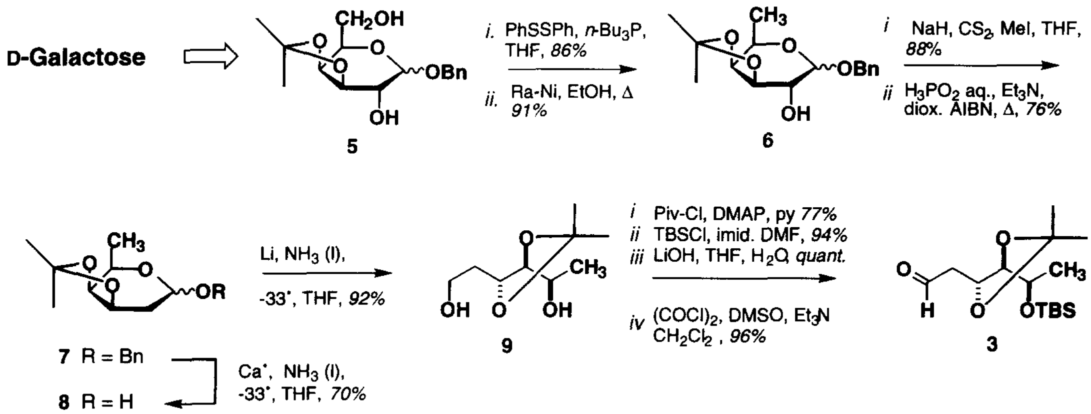
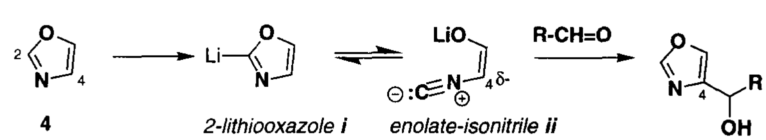
application of C-4-directed oxazole coupling towards natural product synthesis and one that *complements* current synthetic routes to oxazole natural products by allowing introduction of an oxazole ring at a relatively late stage in assembly without the necessity of proceeding through a substituted oxazole-4-carboxylate.

Side-chain synthon **3** was prepared as follows (Scheme 1).[5] D-galactose was converted into the differentially protected 1-*O*-benzyl galactoside **5** (8:1 α:β anomers) in two steps (69%).[6] Stepwise deoxygenation at C-2 and C-6 were achieved as follows. Thiophenyl ether formation at the primary hydroxyl and desulfurization to **6** (Raney Ni, 78% for two steps)[7] was followed by conversion of the C-2 secondary OH to the methyl 2-*O*-xanthate ester and Barton-McCombie deoxygenation with buffered hypophosphorous acid[8] (67% for two steps) which afforded the D-2-deoxyfucose derivative **7**. Selective removal of the 1-*O*-benzyl group proved difficult. Catalytic hydrogenolysis was ineffective in liberating **8**,[9] and Li° or Na° in liquid ammonia (-33° C) gave high yields of over-reduced alditol **9**. To our gratification, the benzyl group was smoothly cleaved by Ca°-NH_3 (*l*, -33°), giving **8** in good yield (70%) with little over-reduction.[10]



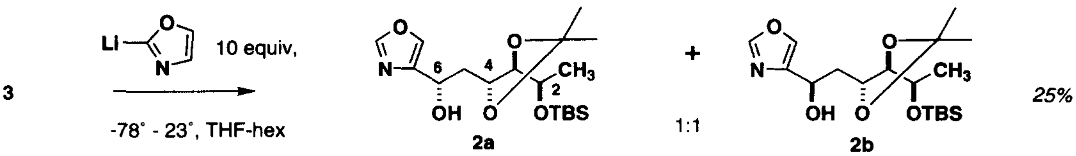
Scheme 1

Aldose **8** embodies a masked carbonyl (C-6 of bengazole A) for coupling to **4**. Earlier model studies confirmed that opening of the pyranose ring takes place in the presence of excess organolithium reagent, followed by 1,2-addition to the unmasked aldehyde.[11] Hodges and others have shown that 2-lithiooxazole ***i*** adds electrophiles at C-2 or C-4 *via* the isomeric ring-opened enolate-isonitrile ***ii*** (Scheme 2),[4] followed by ring closure but addition of aldehydes occurs preferentially at C-4. Unfortunately, 2-lithiooxazole (8 equiv each of **4** and *n*-BuLi, 20 min, -78°, THF-hex, add **8**, 1 equiv, warm to 23°, 16 h) failed to deliver addition products with **8**.



Scheme 2 (see Ref. 4)

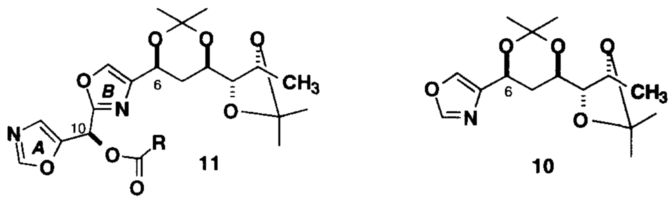
It seemed the liberated 5-alkoxide somehow interfered with 2-lithiooxazole addition to the carbonyl group which indicated the need for protection at C-5. Transformation of **9** to the 5-*O*-TBS aldehyde **3** was carried out in four steps (69%), and addition of 2-lithiooxazole (10 equiv) to **3** under the above conditions now gave a mixture of epimers **2a** and **2b**[12] (1:1, separated by HPLC, total 25% yield).[13]



3 → 2a + 2b (1:1), 25%

The C-4 regioselectivity of substitution in **2a,b** was confirmed by comparison of $^{1}J_{CH}$ of the remaining oxazole protons (H-2,5) with that of **1** and other 2,4-disubstituted oxazoles.[1b,14] No 2-substituted oxazole by-products were detected. The faster-migrating epimer was identified as **2a** by refunctionalization to **10** (*i*. *n*-Bu_4NF, THF, 50°; *ii*. Dowex (H^+), MeOH, 23° C, 2 h; *iii*. dimethoxypropane-acetone, *p*-TSA) and direct stereochemical comparison with the known *bis*-acetonide **11**[1b] by NMR (500 MHz). The ^{1}H chemical shifts and vicinal coupling constants of H-1,6 in **10** and **11** ($CDCl_3$) were essentially identical (eg. for H-6, **10**, δ 5.00, 1H, dd, J = 11.5, 1.5 Hz; **11**, δ 4.97, 1H, dd, J = 11.8, 2.1 Hz[1b]). Studies are underway in our laboratory to improve the diastereoselectivity and yield of **2a** through chelate-controlled addition.

In summary, we have prepared an advanced intermediate **2a** towards the synthesis of bengazole A (**1**) taking advantage of the ambident nucleophilicity of 2-lithiooxazole with preferential C-4 addition to aldehydes. The advantage of this approach is rapid assembly of an oxazole-containing heterocyclic core structure that permits late introduction of the oxazole ring. Whereas 2-lithiooxazole adds to aldehydes at C-4, 2-lithio-4-substituted oxazoles revert the regioselectivity of electrophilic addition to C-2.[4,15] Taking advantage of this fine-tuning of substituted oxazole reactivity, compound **2a** can now be extended at C-2 of ring 'B' for completion of the *bis*-oxazole nucleus of bengazole A. The introduction of ring 'A' in **1** requires appropriate elaboration of a C-5 monosubstituted oxazole, but now the inherent oxazole nucleophilicity at C-2/C-4, which served well in the formation of **2a**, must be diverted to C-5 of ring 'A'. To this end, we are proceeding with deployment of our recently developed C-5 oxazole anion chemistry[16] to address ring 'A' construction, C-10 stereochemical control and completion of the synthesis of **1**.



11 **10**

Acknowledgments: We thank Karl Bailey for 500 MHz ^{1}H NMR measurements on **10**. This research was funded by the National Institutes of Health (AI 31660 and AI 39987). The 500 MHz NMR spectrometer was partially funded through NIH ISIO-RR04795 and NSF BBS88-04739.

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(1) (a) Adamczeski, M.; Quiñoà, E.; Crews, P. *J. Am. Chem. Soc.* **1988**, *110*, 1598-1602; (b) Searle, P. A.; Richter, R. K.; Molinski, T. F. *J. Org. Chem.* **1996**, *61*, 4073-4079; (c) Rodríguez, J.; Nieto, R. M.; Crews, P. *J. Nat. Prod.* **1993**, *56*, 2034-2040; (d) Rudi, A.; Kashman, Y.; Benayahu, Y.; Schleyer, M. *J. Nat. Prod.* **1994**, *57*, 829-832.

(2) (a) Antonio, J.; Molinski, T. F. *J. Nat. Prod.* **1993**, *56*, 54-61; (b) Minimum inhibitory concentration (MIC) against *C. albicans* (ATCC 14503) and certain Fluconazole® resistant strains is ~ 1μg/ml, Molinski, T.F. *et al.*, unpublished results.

(3) Most published syntheses of natural products bearing 2,4-disubstituted oxazole employ the serine amide cyclodehydration-oxidation methodology. Recent examples include total syntheses of calyculin A, (a)

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(4) Hodges, J. C.; Patt, W. C.; Connolly, C. J. *J. Org. Chem.* **1991**, *56*, 449-452 and citations, within. Coupling of **4** with a variety of aldehydes occurs exclusively at C-4 in 20-65% yield.

(5) (a) Full experimental details for preparation of **5-9** will be published elsewhere (Shafer, C.M.; Molinski, T.F. *Carbohydr. Res.*, submitted); (b) All compounds were purified by chromatography (>95%) and gave satisfactory ^{1}H, ^{13}C NMR spectra, and elemental analysis or HRMS.

(6) Catelani, G.; Colonna, F.; Marra, A. *Carbohydr. Res.* **1988**, *182*, 297-300.

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(9) Attempted catalytic hydrogenolysis (Pearlman's catalyst $Pd(OH)_2$-C), EtOH, 1 or 4 atm; Pd-C, EtOH 1-4 atm; Pd-C, NH_4HCOO-MeOH) was sluggish (>4 days) and gave mixtures with incomplete reaction or over-reducted alditol **9**. Pretreating the substrate to remove trace sulfur impurities (Ra-Ni, EtOH, reflux) was only partially successful in improving the yield of **8**.

(10) To our knowledge, debenzylation of anomeric *O*-Bn ethers with Ca°-NH_3(*l*) has not been reported,[5a] See Kigoshi, K.; Ojika, M.; Suenaga, K.; Mutou, T.; Hirano, J.; Sakakura, A.; Ogawa, T.; Nisiwaki, M.; Yamada, K. *Tetrahedron Lett.* **1994**, *35*, 1247-1250 for application to a primary *O*-Bn ether.

(11) The addition of phenyllithium to *ent*-**8** proceeded in 86% yield and 1:2.4 diastereoselectivity in favor of the desired 6*R* epimer (bengazole numbering). See Ref. 1b.

(12) Epimer **2a**: retention time 16 min (HPLC, silica, 10 mm × 250 mm, 2:3 ethyl acetate:hexane, 3 ml/min), $[\alpha]_D$ = +10.9° (c 0.34, $CHCl_3$); IR (NaCl, neat) 3440 (OH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (s, 3 H), 0.07 (s, 3 H), 0.87 (s, 9 H), 1.15 (d, 3 H, *J* = 5.9 Hz), 1.35 (s, 3 H), 1.54 (s, 3 H), 1.97 (m, 2 H), 3.88 (m, 2 H), 4.27 (ddd, 1 H, *J* = 10.1, 5.3, 3.5 Hz), 4.96 (dd, 1 H, *J* = 8.6, 4.3 Hz, H-6), 7.65 (d, 1 H, *J* = 0.8 Hz), 7.84 (d, 1 H, *J* = 0.8 Hz); ^{13}C NMR ($CDCl_3$) -4.6 (CH_3), -4.5 (CH_3), 18.3 (C), 20.4 (CH_3), 25.7 (CH_3), 25.8 (CH_3), 28.0 (CH_3), 36.2 (CH_2), 67.0 (CH), 68.1 (CH), 78.0 (CH), 82.4 (CH), 108.8 (C), 135.0 (CH), 143.0 (C), 151.0 (CH); HRCIMS found *m/z* 372.2211 (MH^+), $C_{18}H_{34}NO_5Si$ requires 372.2206. Epimer **2b**: r.t. 18 min, $[\alpha]_D$ = +37.7° (c 0.56, $CHCl_3$); IR (NaCl, neat) 3430 (OH) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.88 (s, 9 H), 1.15 (d, 3 H, *J* = 5.8 Hz, H-1), 1.32 (s, 3 H), 1.50 (s, 3 H), 1.92 (ddd, 1 H, *J* = 14.2, 7.1, 2.5 Hz, H-5), 2.08 (ddd, 1 H, *J* = 14.2, 11.2, 3.3 Hz, H-5), 3.41 (d, 1 H, *J* = 6.3 Hz, OH), 3.88 (m, 2 H), 4.24 (ddd, 1 H, *J* = 11.2, 5.2, 2.5 Hz, H-4), 5.0 (ddd, 1 H, *J* = 7.1, 6.3, 3.3 Hz, H-6), 7.64 (d, 1 H, *J* = 1.0 Hz), 7.85 (d, 1 H, *J* = 1.0 Hz); ^{13}C NMR ($CDCl_3$) -4.6 (CH_3), -4.5 (CH_3), 18.3 (C), 20.3 (CH_3), 25.9 (CH_3), 28.2 (CH_3), 34.5 (CH_2), 65.7 (CH), 67.2 (CH), 74.1 (CH), 82.3 (CH), 108.5 (C), 135.1 (CH), 143.6 (C), 151.3 (CH); HRCIMS found *m/z* 372.2185 (MH^+), $C_{18}H_{34}NO_5Si$ requires 372.2206.

(13) The modest yield appears to be due, in part, to lower reactivity of 2-lithiooxazole compared to PhLi (see note 11) and competing enolization of **3** and β-elimination. Addition of 1.5 equiv of 2-lithiooxazole to **3** gave only ~7% yield of **2**. We are addressing this problem by modifying the preformed 2-lithiooxazole (enolate) prior to addition of **3**, however other reaction pathways may be operative, see Iddon, B. *Heterocycles* **1994**, *37*, 1321-1346.

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