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A Concise Total Synthesis of Saliniketal B

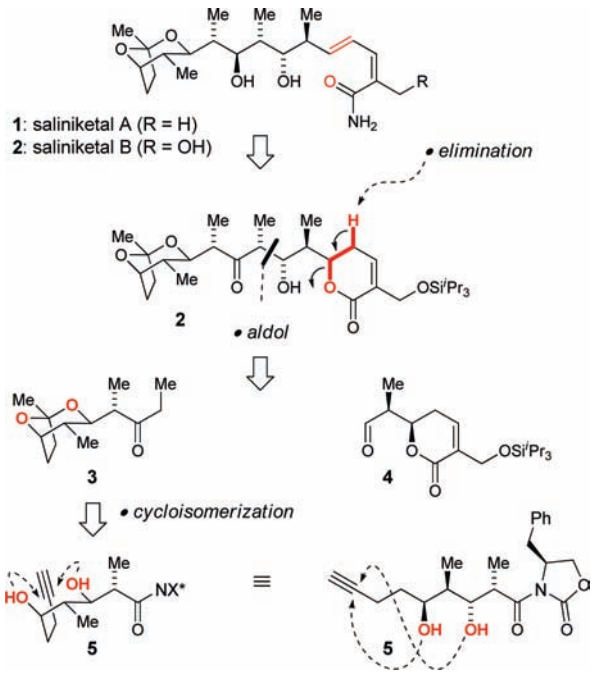
Jun Liu and Jef K. De Brabander*

Department of Biochemistry and Harold C. Simmons Comprehensive Cancer Center, The University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, Texas 75390-9038

Received July 23, 2009; E-mail: jef.debrabander@utsouthwestern.edu

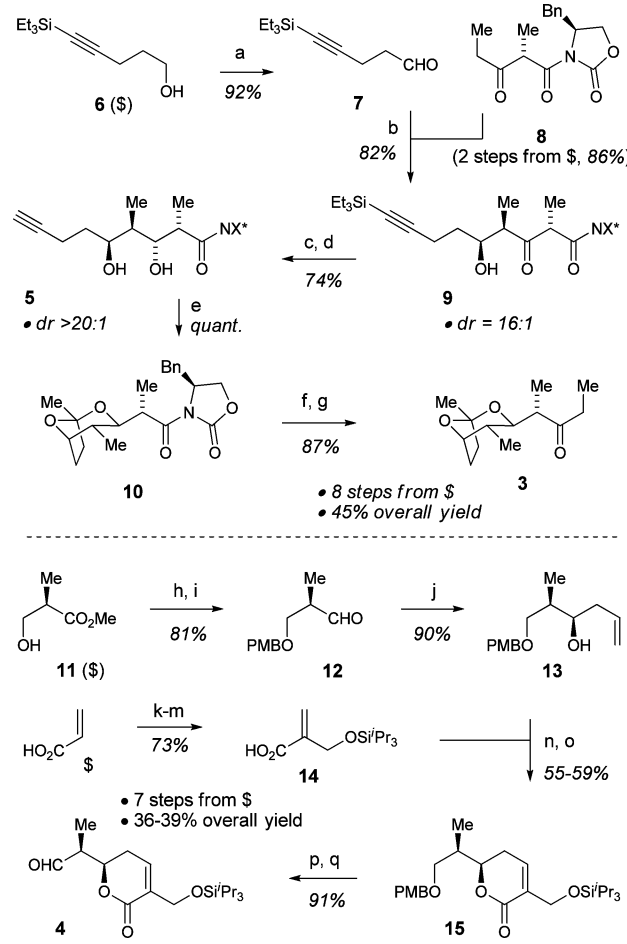
The groundbreaking work of Fenical and co-workers[1] demonstrated that obligate marine actinomycetes are a rich source of novel bioactive natural products. In 2007, they reported the isolation of the polyketides saliniketal A (**1**) and B (**2**) from the marine actinomycete *Salinispora arenicola*,[2] the structure of which was confirmed by a total synthesis of Paterson and co-workers.[3] Besides unusual structural features, including a dioxabicyclo[3.2.1]octane ring system, an *E*,*Z*-dienamide unit reminiscent of the *ansa* chain of rifamycin, and nine stereocenters (eight of which are contiguous), saliniketals are of biological interest because of their ability to inhibit ornithine decarboxylase (ODC) induction. As the first enzyme in the polyamine biosynthesis pathway and the direct transcriptional target of the oncogene *MYC*, ODC has been shown to be a potential target for chemotherapeutic or chemopreventive intervention.[4] Unlike α-DFMO, saliniketals do not inhibit ODC enzyme activity but instead attenuate tumor-promoter-mediated induction of ODC.[2] Herein, we report a concise and flexible synthesis of saliniketal B (**2**) that features a strategy aimed at enabling future structure−function and mode-of-action studies.

Scheme 1. Structure of Saliniketals and Synthetic Strategy



Our synthetic strategy was based on a convergent aldol coupling of fragments **3** and **4** following an anti-selective reduction of β-hydroxyketone **2** (Scheme 1). We envisioned a late-stage installation of the *E*,*Z*-dienamide via an interesting but rarely utilized fragmentation of a dihydropyranone.[5] The 2,8-dioxabicylo[3.2.1]octane moiety was to be assembled via cycloisomerization of alkynediol **5** by exploiting methodology developed in our laboratory.[6]

Scheme 2. Synthesis of Fragments **3** and **4**[a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 2 h, 92%; (b) $Sn(OTf)_2$ (1.05 equiv), Et_3N (1.05 equiv), CH_2Cl_2, −20 °C, then −78 °C, **7** (2 equiv), 82%; (c) $Na(AcO)_3BH$, HOAc, 0 °C to rt, 79%; (d) TBAF, THF, 3 min, 94%; (e) $[PtCl_2(CH_2CH_2)]_2$ (5 mol %), THF, 5 min, quantitative; (f) MeONHMe·HCl (3 equiv), $AlMe_3$ (3 equiv), THF, 0 °C; (g) EtMgBr (3 equiv), THF, 0 °C to rt, 2 h, 87% (two steps); (h) 4-MeOBnOC(NH)CCl_3, PPTS, CH_2Cl_2, rt, 18 h, 87%; (i) DIBAL-H, CH_2Cl_2, −78 °C, 2 h, 93%; (j) (+)-MeOB(Ipc)$_2$, allylMgBr, 0 °C, add **12**, −98 °C, then NaOH, 30% H_2O_2, Et_2O, reflux, 90%; (k) paraformaldehyde (10 equiv), DABCO (0.5 equiv), dioxane/H_2O (1:1), 72 h; (l) TIPSCl, imid., DMAP, CH_2Cl_2, 0 °C to rt, 1 h, 79% (two steps); (m) LiOH, THF/H_2O (1:1), rt, 36 h, 92%; (n) DCC, DMAP, CH_2Cl_2, 0 °C to rt, 12 h, 82%; (o) Grubbs-II (10 mol %), CH_2Cl_2, reflux, 14 h, 67% plus 15% recovered starting material; (p) DDQ, CH_2Cl_2/H_2O (20/1), rt, 1 h, 91%; (q) Dess−Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 30 min, quantitative.

An efficient synthesis of coupling partners **3** and **4** is depicted in Scheme 2. The reagent-controlled aldol reaction of the stannyl enolate derived from known oxazolidinone **8**[7] with aldehyde **7**, obtained from oxidation of commercially available alkynol **6** (92%

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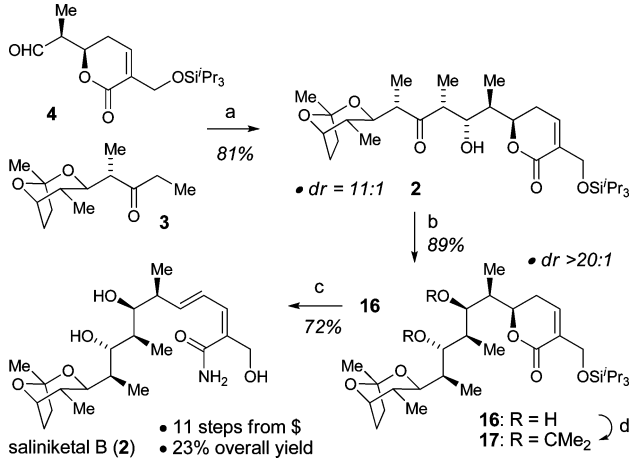
yield), provided aldol product **9** in 82% yield and >16:1 dr. Anti-selective reduction with $Na(OAc)_3BH$ (>20:1 dr)[7a] followed by desilylation (74% yield, two steps) set the stage for a cycloisomerization of alkynediol **5**. Use of 5 mol % Zeise's dimer[6] afforded 2,8-dioxabicyclo[3.2.1]octane **10** in quantitative yield, and this was processed to ketone **3** via Weinreb amide formation and Grignard reaction with EtMgBr (87%, two steps).[8]

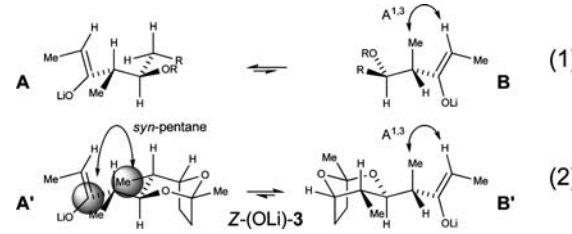
Dihydropyranone **4** was synthesized from ester **11** ($). According to a sequence by Nicolaou and co-workers, *p*-methoxybenzyl ether formation (87%) was followed by semireduction to aldehyde **12** (93%) and allylation with Brown's reagent (90%).[9] The resulting syn-homoallylic alcohol **13**[9,10] was esterified with acid **14**, a material prepared from methyl acrylate via Baylis−Hillman reaction,[11] silylation, and saponification (73%, three steps). Dihydropyranone formation to give **15** was accomplished in 67% yield via ring-closing metathesis with Grubbs' second-generation catalyst under high dilution conditions (15% starting material was recovered).[12] Final oxidative deprotection (DDQ, 91%) and oxidation with Dess−Martin periodinane[13] (quantitative) delivered aldehyde **4** in seven steps and 36−39% overall yield.

Scheme 3. Synthesis of Saliniketal B[a]



[a] Reagents and conditions: (a) LiHMDS (1.2 equiv), −78 °C, 1 h, **4** (1.4 equiv), THF, 81%; (b) $Me_4N(AcO)_3BH$, MeCN/HOAc (1/1), −20 °C, 48 h, 89%; (c) TBAF (10 equiv), THF, 48 h; then NH_3 (gas), HOBt (2 equiv), EDC (2 equiv), rt, 72%; (d) $(MeO)_2CMe_2$, PPTS, acetone, rt, 87%.

The final aldol coupling between ethyl ketone **3** and aldehyde **4** yielded the *anti*-Felkin adduct **2** with high selectivity (>11:1 dr) in 81% yield (Scheme 3). The stereochemical outcome of this reaction deserves some comment. The *Z*(O)-lithium enolates of *syn*-α-Me,*β*-alkoxy-substituted ethyl ketones typically yield the 1,3-*anti*-1,4-*anti*-aldol adducts,[14] a situation that is mismatched with the inherent *anti*-Felkin bias of aldehyde **4**.[10] We surmise that the observed high selectivity for our reaction can be attributed to the presence of the additional *γ*-Me stereocenter. As shown in eq 1, the *Si*-enolate face is normally exposed via conformation **A**, minimizing $A^{1,3}$-strain in the transition state, whereas the additional *γ*-Me group disfavors this conformation (**A′**, eq 2) as a result of unfavorable *syn*-pentane interactions. This exposes the enolate *Re*-face via **B′** for a matched reaction with aldehyde **4**.[15] Next, reduction of *β*-hydroxy ketone **2** delivered *anti*-diol **16** (89%, >20:1 dr).[16,17] Finally, fluoride-mediated desilylation and concomitant fragmentation[5d] of dihydropyranone **16** followed by in situ amidation of the liberated carboxylic acid provided saliniketal B (**2**) with a yield of 72% for this one-pot operation.[18]



In summary, we have achieved a short, highly efficient synthesis of saliniketal B (**2**) in 11 steps (longest linear) and 23% overall yield. Our approach features the utility of our Pt(II)-catalyzed cycloisomerization methodology for the construction of the dioxabicyclo[3.2.1]octane core, a stereoselective aldol coupling whose selectivity was positively influenced by the ketone *γ*-stereocenter, and an unusual one-pot desilylation/dihydropyranone fragmentation/amidation sequence.

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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Oxazolidinone **8** was obtained in two steps from commercially available (4*S*)-*N*-propionyl-4-Bn-2-oxazolidinone. See: (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866. (b) Evans, D. A.; Ng, H. P.; Clark, S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127.
(8) The stereochemistry was confirmed by NMR analysis of the acetonide derived from **5** and comparison of the primary alcohol obtained from reduction of oxazolidinone **10** to the same alcohol prepared independently by Paterson et al.[3] (see the Supporting Information).
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(10) It should be noted that the stereochemical outcome is not important because the resulting stereocenter is destroyed during the final dihydropyranone fragmentation reaction (Scheme 3). However, homogeneous material facilitates characterization, and targeting the syn stereoisomer ensures maximal stereocontrol during the aldol fragment coupling (Scheme 3) in this double-diastereodifferentiating process. See: (a) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151. (b) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. *J. Am. Chem. Soc.* **1996**, *118*, 4322.
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(15) We are currently testing this hypothesis by preparing the corresponding *γ*-desmethyl and *epi*-*γ*-methyl congeners of ketone **3**, which are expected to give lower selectivity in the aldol reaction with aldehyde **4**.
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(18) The spectroscopic data and optical rotation of synthetic saliniketal B (**2**) are in full agreement with literature data reported for natural[2] and synthetic[3] **2**. See the Supporting Information for details.

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