Published in final edited form as:

J Am Chem Soc. 2009 September 9; 131(35): 12562–12563. doi:10.1021/ja9061757.

A Concise Total Synthesis of Saliniketal B

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Abstract

We report a concise, enantioselective, and highly efficient synthesis of the marine actinomycete-derived natural product saliniketal B. Our approach was motivated with an eye on future structure-function studies of this inhibitor of phorbol ester-mediated ornithine decarboxylase induction via an unknown mechanism. Our strategy highlights the utility of Pt(II)-mediated cycloisomerization of alkynediols developed in our laboratory to construct the dioxabicyclo[3.2.1]octane ring system, a highly selective aldol fragment coupling of which the stereochemical outcome is influenced by a γ -stereogenic methyl group, and an interesting one-pot desilylation/dihydropyranone fragmentation/amidation sequence. As such, saliniketal B was obtained in 11 steps and 23% overall yield from commercially available starting material via a convergent coupling of two equally complex fragments assembled in 7 and 8 steps (39% and 45%) respectively.

Due to the groundbreaking work of Fenical and coworkers, obligate marine actinomycetes were shown to be a rich source of novel bioactive natural products.¹ In 2007, they reported the isolation of the polyketides saliniketals 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 coworkers.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 due to their ability to inhibit ornithine decarboxylase (ODC) induction. The first enzyme in the polyamine biosynthesis pathway and direct transcriptional target of the oncogene *MYC*, ODC was shown to be a potential target for chemotherapeutic or chemopreventive intervention.⁴ Unlike α -DFMO, saliniketals do not inhibit ODC enzyme activity, but attenuate tumor promoter-mediated induction of ODC.² Herein, we report a concise and flexible synthesis of saliniketal B (**2**) featuring a strategy aimed at enabling future structure-function and mode-of-action studies.

Our synthetic strategy is 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

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

installation of the *E,Z*-dienamide via an interesting but rarely utilized fragmentation of a dihydropyranone.⁵ The 2,8-dioxabicyclo[3.2.1]octane moiety will be assembled via cycloisomerization of alkynediol **5** exploiting methodology developed in our laboratory.⁶

An efficient synthesis of coupling partners **3** and **4** is depicted in Scheme 2. 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% 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, 2 steps) set the stage for a cycloisomerization of alkynediol **5**. Using 5 mol% of Zeise's dimer,⁶ 2,8-dioxabicyclo[3.2.1]octane **10** was obtained in quantitative yield and processed to ketone **3** via Weinreb amide formation and Grignard reaction with EtMgBr (87%, 2 steps).⁸

Dihydropyranone **4** was synthesized from ester **11** (**5**). According to a sequence by Nicolaou and coworkers, *p*-methoxybenzyl ether formation (87%) was followed by semi-reduction to aldehyde **12** (93%) and allylation with Brown's reagent (90%).⁹ The resulting *syn*-homoallylic alcohol **13**,¹⁰ was esterified with acid **14**, a material prepared from methyl acrylate via Baylis-Hillman reaction,¹¹ silylation, and saponification (73%, 3 steps). Dihydropyranone formation ($\rightarrow$ **15**) was accomplished via ring-closing metathesis with Grubbs' second generation catalyst under high dilution conditions in 67% yield (15% starting material was recovered).¹² Final oxidative deprotection (DDQ, 91%) and oxidation with Dess-Martin periodinane¹³ (quantitative) delivered aldehyde **4** in seven steps and 36–39% overall yield.

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-*syn*-1,4-*syn* 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 TTS, whereas the additional γ -Me group disfavors this conformation (**A'**, eq 2) due to 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, combining a fluoride-mediated desilylation and concomitant fragmentation^{5d} of dihydropyranone **16** with an in situ amidation of the liberated carboxylic acid provided saliniketal B (**2**) in 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 of which the selectivity was positively influenced by the ketone γ -stereocenter, and an unusual one-pot desilylation/dihydropyranone fragmentation/amidation sequence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support for was provided by the NIH (CA90349) and the Robert A. Welch Foundation. We thank Christopher F. Bender for helpful suggestions.

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Scheme 1.
Structure of saliniketals and synthetic strategy

Scheme 2. Synthesis of fragments 3 and 4^a

^aReagents and conditions: (a) (COCl)₂, DMSO, Et₃N, CH₂Cl₂, -78 °C, 2 h, 92%; (b) Sn (OTf)₂ (1.05 equiv), Et₃N (1.05 equiv), CH₂Cl₂, -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) [PtCl₂(CH₂CH₂)₂] (5 mol%), THF, 5 min, quantitative; (f) MeONHMe·HCl (3 equiv), AlMe₃ (3 equiv), THF, 0 °C; (g) EtMgBr (3 equiv), THF, 0 °C to rt, 2 h, 87% (2 steps); (h) 4-MeOBnOC(NH)CCl₃, PPTS, CH₂Cl₂, rt, 18 h, 87%; (i) DIBAL-H, CH₂Cl₂, -78 °C, 2 h, 93%; (j) (+)-MeOB(Ipc)₂, allylMgBr, 0 °C, add **12**, -98 °C, then NaOH, 30% H₂O₂, Et₂O, reflux, 90%; (k) para-formaldehyde (10 equiv), DABCO (0.5 equiv), dioxane/H₂O (1/1), 72 h; (l) TIPSCl, imid., DMAP, CH₂Cl₂, 0 °C to rt, 1 h, 79% (2 steps); (m) LiOH, THF/H₂O (1/1), rt, 36 h, 92%; (n) DCC, DMAP, CH₂Cl₂, 0 °C to rt, 12 h, 82%; (o) Grubbs-II (10 mol%), CH₂Cl₂, reflux, 14 h, 67% and 15% recovered starting material; (p) DDQ, CH₂Cl₂/H₂O (20/1), rt, 1 h, 91%; (q) Dess-Martin periodinane, NaHCO₃, CH₂Cl₂, rt, 30 min, quantitative.

Scheme 3. Synthesis of saliniketal B^a

^aReagents and conditions: (a) LiHMDS (1.2 equiv), -78 °C, 1 h, **4** (1.4 equiv), THF, 81%; (b) Me₄N(AcO)₃BH, MeCN/HOAc (1/1), -20 °C, 48 h, 89%; (c) TBAF (10 equiv), THF, 48 h; then NH₃ (gas), HOBT (2 equiv), EDC (2 equiv), rt, 72%; (d) (MeO)₂CMe₂, PPTS, acetone, rt, 87%.