ORGANIC LETTERS

2008
Vol. 10, No. 15
3295−3298

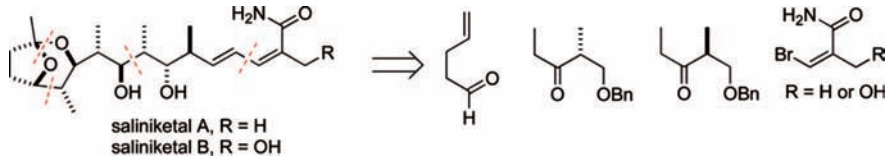
Total Synthesis of (−)-Saliniketals A and B†

Ian Paterson,* Mina Razzak, and Edward A. Anderson

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.
ip100@cam.ac.uk

Received May 20, 2008

ABSTRACT

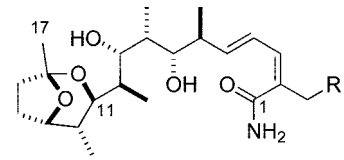


A stereocontrolled total synthesis of the orthinine decarboxylase inhibitors saliniketals A and B is described. Key features of the 17-step route include the use of two boron aldol/reduction sequences to control six of the nine stereocenters, an intramolecular Wacker-type cyclization to install the bicyclic acetal core, and a late-stage Stille coupling to append the requisite (2*Z*,4*E*)-dienamide.

Saliniketals A (**1**) and B (**2**), isolated in 2007 by Fenical and co-workers from the marine actinomycete *Salinispora arenicola*, are inhibitors of ornithine decarboxylase (ODC) induction.[1] ODC hyperactivity is a marker of tumorigenesis and is often seen in epithelial tumors of the colon, skin, prostate, and stomach.[2] As such, ODC inhibitors may potentially be valuable chemotherapeutic or chemopreventative agents.[3]

The novel structures of these unusual bioactive polyketides, comprising a 2,8-dioxabicyclo[3.2.1]octane ring featuring an elaborate side chain at C11 that terminates in an unsaturated primary amide, were determined mainly by 2D-NMR spectroscopic methods, with the absolute configuration assigned by Mosher ester analysis. Intriguingly, the saliniketals show a structural resemblance to the *ansa* chain of the rifamycin antibiotics, which co-occur within the fermentation broth. By employing our versatile boron aldol methodology, we now report the first total synthesis of saliniketals A and B, invoking a late-stage diversification strategy to append the requisite dienamide terminus.

As outlined in Scheme 1, we envisaged that both saliniketal A (**1**) and its more oxygenated congener, saliniketal B



1: R = H, saliniketal A
2: R = OH, saliniketal B

(**2**), may be accessible from the common C4−C17 intermediate **3**. This is primed for a Stille coupling[4] with either vinyl bromide **4** or **5** to install the appropriate (2*E*,4*Z*)-dienamide. Disconnection of the C8−C9 bond in **3** reveals aldehyde **6** and ethyl ketone (*S*)-**7**, where the use of a substrate-controlled *anti*-aldol /reduction sequence[5] would enable installation of the C6−C9 stereotetrad. The dioxabicyclic core present in **6** might then be constructed by an intramolecular Wacker-type cyclization of the olefinic 1,3-diol **8**. This diol would itself be configured using a reagent-controlled *syn*-aldol reaction, now requiring the use of the enantiomeric ethyl ketone (*R*)-**7**.

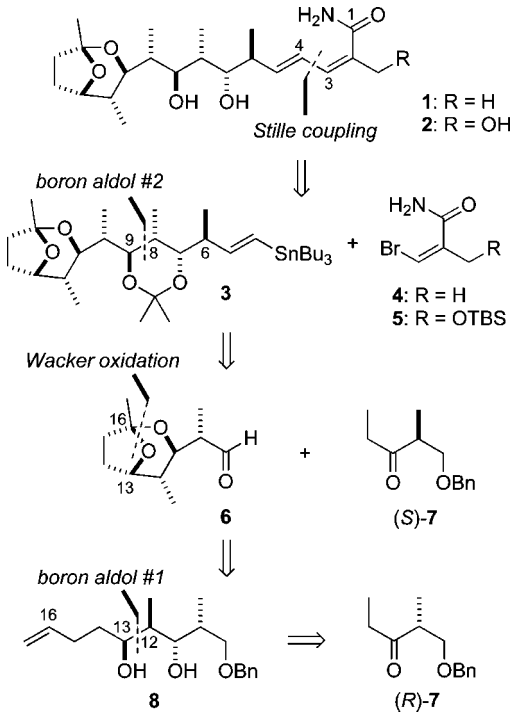
Commencing with the reagent-controlled aldol reaction of (*R*)-**7** (Scheme 2),[5] formation of the (*Z*)-boron enolate[6] **9** ((+)-Ipc_2BOTf, *i*-Pr_2NEt), followed by addition of 4-pentenal,

† Dedicated to the late Jonathan (Joe) Spencer, a greatly missed colleague and friend.

(1) Williams, P. G.; Asolkar, R. N.; Kondratyuk, T.; Pezzuto, J. M.; Jensen, P. R.; Fenical, W. *J. Nat. Prod.* **2007**, *70*, 83.
(2) (a) Saunders, L. R.; Verdin, E. *Mol. Cancer Ther.* **2006**, *5*, 2777. (b) Thomas, T.; Thomas, T. J. *Cell. Mol. Life Sci.* **2001**, *58*, 244.
(3) (a) Basuroy, U. K.; Gerner, E. W. *J. Biochem.* **2006**, *139*, 27. (b) Gerner, E. W., Jr *Nat. Rev. Cancer* **2004**, *4*, 781.
(4) (a) Stille, J. K. *Angew. Chem., Int. Ed.* **1986**, *25*, 508. (b) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1.
(5) (a) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287. (b) Paterson, I.; Cumming, J. G.; Ward, R. A.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9393. (c) Paterson, I.; Perkins, M. V. *Tetrahedron* **1996**, *52*, 1811.

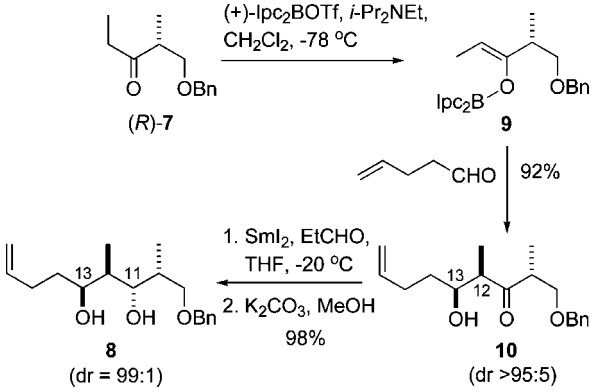
10.1021/ol801148d CCC: $40.75
Published on Web 06/26/2008

Scheme 1



generated the *syn* adduct **10** in 92% yield with the expected high diastereoselectivity (dr >20:1).[7] Installation of the C11

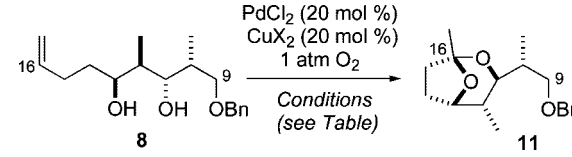
Scheme 2



stereocenter was next achieved by a 1,3-*anti* reduction. Evans−Tischenko[8] conditions (SmI_2, EtCHO) were selected which, following K_2CO_3-mediated solvolysis of the ensuing ester, afforded the 1,3-diol **8** cleanly (98%, dr = 99:1).[7,9]

Formation of the characteristic 2,8-dioxabicyclo-[3.2.1]-octane ring system of the saliniketals was now addressed. In their elegant synthesis of *endo*-brevicomin, Grigg and co-workers[10] first demonstrated that Wacker oxidation conditions (catalytic Pd(II) with Cu(II) as the reoxidant) could be used to convert olefinic 1,3-diols into cyclic acetals.[11] Hence, an intramolecular Wacker-type[12] cyclization of the 1,3-diol **8** was examined, with the aim of installing the C16 oxygenation in a regio- and stereocontrolled manner. After screening several reaction conditions (Table 1, entries 1−3), the use of catalytic

Table 1. Conditions for Intramolecular Wacker Oxidation of **8**

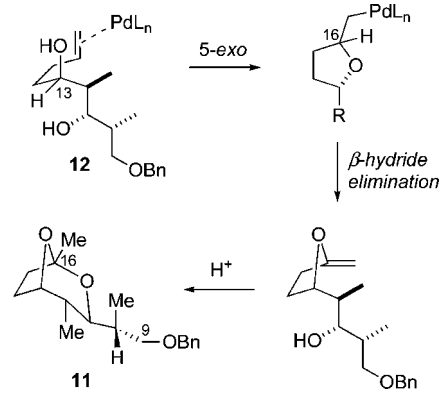


entry	X	solvent	temp. (°C)	yield (%)[a]
1	NO_3	THF	20	48[b]
2	OAc	THF	20	50[b]
3	Cl	DMA/THF/H_2O[c]	20	23[b]
4	Cl	THF	0	88

[a] Isolated yield. [b] Several byproducts were also formed. [c] 7:2:1.

$PdCl_2$ and $CuCl_2$ in THF under an atmosphere of oxygen at 0 °C was found to give a good yield (88%) of the acetal **11** (entry

Scheme 3



4). The desired [3.2.1]-dioxabicycle **11** likely arises from the expected 5-*exo* attack of the C13 hydroxyl onto the palladium−

(6) (a) Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663. (b) Paterson, I.; Lister, M. A. *Tetrahedron Lett.* **1988**, *29*, 585.

(7) See the Supporting Information for details of stereochemical assignments.

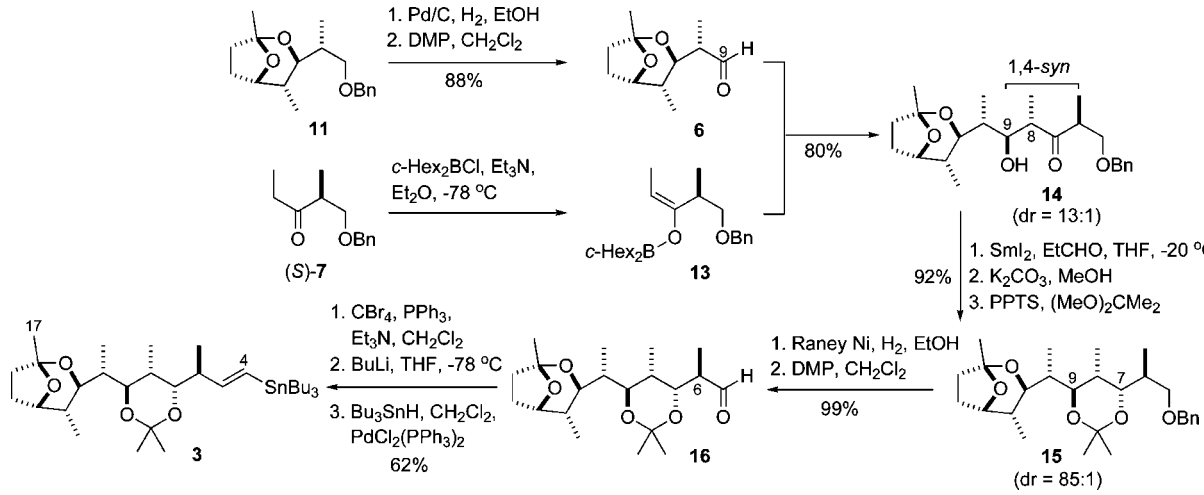
(8) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447.

(9) Confirmation of the desired C11−C13 and C7−C9 stereochemistry was provided by preparation of the acetonides and ^{13}C NMR analysis: (a) Rychnovsky, S. D.; Skalitzky, D. J *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099.

(10) Byrom, N. T.; Grigg, R.; Kongkathip, B. *J. Chem. Soc., Chem. Commun.* **1976**, *6*, 216.

(11) Subsequently, similar acetals have been installed using slightly modified conditions in syntheses of various insect pheromones and terrestrial natural products. For examples, see: (a) Kongkathip, B.; Kongkathip, N. *Tetrahedron Lett.* **1984**, *25*, 2175. (b) Mori, K.; Seu, Y.-B. *Tetrahedron* **1985**, *41*, 3429. (c) Bulman Page, P. C; Rayner, C. M.; Sutherland, I. O. *Tetrahedron Lett.* **1986**, *27*, 3535. (d) Ploysuk, C.; Kongkathip, B.; Kongkathip, N. *Synth. Commun.* **2007**, *37*, 1463.

Scheme 4



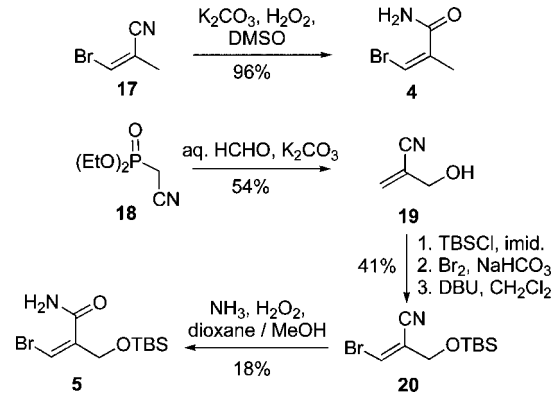
alkene complex **12** (Scheme 3), followed by β-hydride elimination and acid-catalyzed acetal formation. Owing to its skeletal rigidity linked with the avoidance of *syn*-pentane interactions, the ^{1}H and ^{13}C NMR data for the bicyclic acetal **11** matched well with that for the corresponding region of saliniketal A.[7]

With the correctly configured ring system in hand, elaboration of the saliniketal side chain was now required (Scheme 4). Debenzylation of **11** (Pd/C, H_2) and Dess−Martin oxidation gave the aldehyde **6** (88%), primed for a substrate-controlled *anti*-aldol reaction with the ethyl ketone (*S*)-**7**.[4,13] Using our standard conditions (*c*-Hex$_2$BCl, Et$_3$N),[13] enolization of (*S*)-**7** generated the (*E*)-boron enolate **13**, and addition of aldehyde **6** gave the desired *anti*-adduct **14** in 80% yield.[7] Despite the significant steric demands of the aldehyde component, this mismatched aldol coupling proceeded efficiently (dr = 13:1) due to the excellent 1,4-*syn* stereoinduction arising from the enolate **13**.

A sequence of Evans−Tischenko reduction of the β-hydroxy ketone **14**,[8] ester solvolysis, and acetonide formation then gave **15** (92%, dr = 85:1).[7,9] While initial attempts to cleave the benzyl ether in **15** using standard Pd/C hydrogenolysis conditions led to acetonide migration, the use of Raney Ni afforded the desired primary alcohol cleanly. Oxidation with Dess−Martin periodinane then gave aldehyde **16** (99%) which was then progressed to the alkyne, initially using the Ohira−Bestmann conditions.[14] However, this resulted in significant epimerization of the C6 stereocenter. To circumvent this problem, the Corey−Fuchs procedure was employed.[15] By buffering with Et$_3$N, conversion of **16** to the corresponding vinyl dibromide proceeded in good yield (81%) without any epimerization. Treatment with *n*-BuLi afforded the alkyne, Pd-catalyzed *syn*-hydrostannation of which ($PdCl_2(PPh_3)_2$, Bu_3SnH)[16] then provided the vinyl stannane **3** (77%).

With the common C4−C17 stannane **3** in hand, attention now turned to the preparation of the requisite Stille coupling partners **4** and **5** for saliniketal A and B, respectively (Scheme 5). In the former case, this proved relatively straightforward

Scheme 5



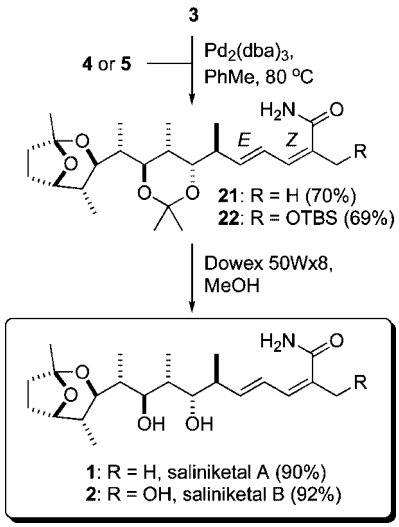
by chromatographic separation of a commercially available mixture of (*E*)- and (*Z*)-3-bromo-2-methylacrylonitrile. The more polar (*Z*)-isomer[17] **17** was then hydrolyzed under oxidative conditions (K_2CO_3, H_2O_2)[18] to give the corresponding primary amide **4**. Owing to the additional oxygenation present in saliniketal B, the synthesis of the required amide **5** proved more involved. Starting from phosphonate **18**, a base-mediated addition to formaldehyde and elimination

(12) Tsuji, J. *Synthesis* **1984**, 369.
(13) (a) Paterson, I.; Scott, J. P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1003. (b) Paterson, I.; Goodman, J. M.; Isaka, M. *Tetrahedron Lett.* **1989**, *30*, 7121.
(14) (a) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett.* **1996**, *6*, 521. (b) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.
(15) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769.
(16) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.
(17) Based on analogous results for a similar system, the desired isomer was assumed to be the major product and was separated from the mixture by flash chromatography: Han, Q.; Wiemer, D. F *J. Am. Chem. Soc.* **1992**, *114*, 7692.
(18) Crowley, B. M.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 2885.

afforded the allylic alcohol **19**.[19] Following TBS ether formation, bromination of the alkene and treatment with DBU then led to the vinyl bromide **20** (2:1 *E*/*Z*).[17] Unexpectedly, the nitrile in (*E*)-**20** proved to be resistant to hydrolysis, and although low yielding, this was achieved using NH_3/H_2O_2 to afford amide **5**.

With the vinyl bromides **4** and **5** both available, it was now an appropriate time to explore the endgame exploiting the Stille coupling reaction[4] of the stannane **3** (Scheme 6).

Scheme 6



For saliniketal A (**1**), this proceeded well with catalytic $Pd_2(dba)_3$ in toluene at 80 °C, leading to cross-coupling with the bromide **4** to produce the (2*Z*,3*E*)-diene **21** in 70% yield. Cleavage of the acetonide was then performed with Dowex 50Wx8 acidic resin in MeOH. Gratifyingly, the spectroscopic data (^{1}H, ^{13}C NMR, and MS) obtained and the measured specific rotation, $[\alpha]_D^{20}$ −10.0 (*c* 0.10, MeOH), cf. −13.7 (*c* 0.133, MeOH), correlated with that reported for natural (−)-saliniketal A (**1**), thus corroborating the stereostructure assigned by the Fenical group.[1] Similarly, Stille coupling between **3** and the bromide **5** also proceeded smoothly to give the (2*Z*,3*E*)-diene **22** (69%), the final intermediate enroute to saliniketal B. This was easily deprotected using the same conditions as before to give **2** (92%) which had spectroscopic data and a specific rotation, $[\alpha]_D^{20}$ −10.8 (*c* 0.12, MeOH), cf. −22.4 (*c* 0.107 MeOH), in accord with that reported for natural (−)-saliniketal B.[1]

In conclusion, we have completed the first total synthesis of saliniketals A and B, novel polyketide inhibitors of ornithine decarboxylase isolated from the marine actinomycete *Salinispora arenicola*, and validated their full configurational assignment. By using our versatile boron aldol methodology, (−)-saliniketal A was prepared in 17 steps (longest linear sequence) from ketone (*R*)-**7** in an overall yield of 18.4%, while (−)-saliniketal B was completed in 18.6% yield. This work should provide a platform for the facile evaluation of side chain analogues of the saliniketals as potential anticancer agents.

Acknowledgment. We thank the EPSRC (EP/C541677/1), the Tertiary Education Commission of New Zealand (M.R.), and Merck Research Laboratories for support.

Supporting Information Available: Experimental details, spectroscopic data, and copies of ^{1}H and ^{13}C NMR spectra for new compounds and synthetic **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801148D

(19) Csuk, R.; Höring, U.; Schaade, M. *Tetrahedron* **1996**, *52*, 9759.