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Oxyanionic Sigmatropic Rearrangements Relevant to Cyclooctadienone Formation in Penostatins I and F

Matthew J. Jansma and Thomas R. Hoye*

Department of Chemistry, University of Minnesota, 207 Pleasant Street SE Minneapolis, Minnesota 55455, United States

hoye@umn.edu

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ABSTRACT

The results of several experiments designed to probe the energetic viability of a reaction path for generation of penostatins I (3) and F (4) via spontaneous [3,3]-sigmatropic rearrangement are reported. In particular, the enolate derived from the 2-vinyl-6-acyldihydropyran 8-cis gave cyclooctadienone 12 via facile anionic oxy-Claisen rearrangement, demonstrating the feasibility of such an event.

The penostatins A (**1**), B (**2**), I (**3**), and F (**4**) are four (of nine total) members of a polyketide-derived family of secondary metabolites that have been isolated from the microorganism *Penicillium* sp. OUPS-79, a fungus that was originally separated from the marine alga *Enteromorpha intestinalis*[1,2] (Scheme 1). Each of **1**/**2** and **3**/**4** are tetraepimeric. That is, each member of a given pair possesses the *same* absolute configuration at the C5 carbinol stereogenic center but the *opposite* absolute configurations at the remaining four stereogenic centers. This configurational relationship among members of the same natural product family is certainly rare, if not unprecedented.

We have hypothesized that **3** and **4** are biosynthetically derived from **1** and **2** (or their C9 epimers). This mechanistic thinking is also evident from synthetic studies carried out in the Snider[2a] and Barriault[2c] laboratories. Specifically, **1** or **2** could, via keto−enol tautomerization [KET], generate **5** or **6** (Scheme 1). Embedded within each of these enol tautomers is an allyl vinyl ether (AVE) subunit that bears a donor atom at C1. Spontaneous [3,3]-sigmatropic rearrangement of **5** or **6** would then directly generate the bicyclo[5.3.1]undecenone core of **3** or **4**, respectively. Paquette and co-workers have extensively studied the ring expansion of architecturally similar 2-alkylidene-6-alkenyl pyrans to generate cyclooct-4-enones via thermal Claisen rearrangement.[3]

In 1981 a theoretical treatment of the aliphatic Claisen rearrangement by Carpenter and Burrows qualitatively demonstrated that π-donor substituents positioned at C1 (as well as C2 and C3) of simple AVEs should result in rate enhancement.[4] The prescience of this analysis was soon realized when, in 1985, Koreeda and Luengo reported the discovery of the "anionic oxy-Claisen" rearrangement.[5] These authors demonstrated, among other things, that the [3,3]-sigmatropic rearrangement of the potassium and

(1) Isolation and structure determination of all members of the penostatin family: (a) Takahashi, C.; Numata, A.; Yamada, T.; Minoura, K.; Enomoto, S.; Konishi, K.; Nakai, M.; Matsuda, C.; Nomoto, K. *Tetrahedron Lett.* **1996**, *37*, 655–658. (b) Iwamoto, C.; Minoura, K.; Hagishita, S.; Nomoto, K.; Numata, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 449–456. (c) Iwamoto, C.; Minoura, K.; Oka, T.; Ohta, T.; Hagishita, S.; Numata, A. *Tetrahedron* **1999**, *55*, 14353–14368.

(2) Synthetic studies toward penostatins A, B, and F: (a) Snider, B. B.; Liu, T. *J. Org. Chem.* **1999**, *64*, 1088–1089. (b) Snider, B. B.; Liu, T. *J. Org. Chem.* **2000**, *65*, 8490–8498. (c) Barriault, L.; Ang, P. J. A.; Lavigne, R. M. A. *Org. Lett.* **2004**, *6*, 1317–1319. Total synthesis of penostatin B: (d) Fujioka, K.; Yokoe, H.; Yoshida, M.; Shishido, K. *Org. Lett.* **2012**, *14*, 244–247.

(3) For example, see: (a) Kinney, W. A.; Coghlan, M. J.; Paquette, L. A. *J. Am. Chem. Soc.* **1984**, *106*, 6868–6870. (b) Paquette, L. A.; Philippo, C. M. G.; Yo, N. H. *Can. J. Chem.* **1992**, *70*, 1356–1365 and references cited therein. (c) Paquette, L. A.; Wang, T.-Z.; Vo, N. H. *J. Am. Chem. Soc.* **1993**, *115*, 1676–1683.

(4) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6984–6986.

(5) Koreeda, M.; Luengo, J. I. *J. Am. Chem. Soc.* **1985**, *107*, 5572–5573.

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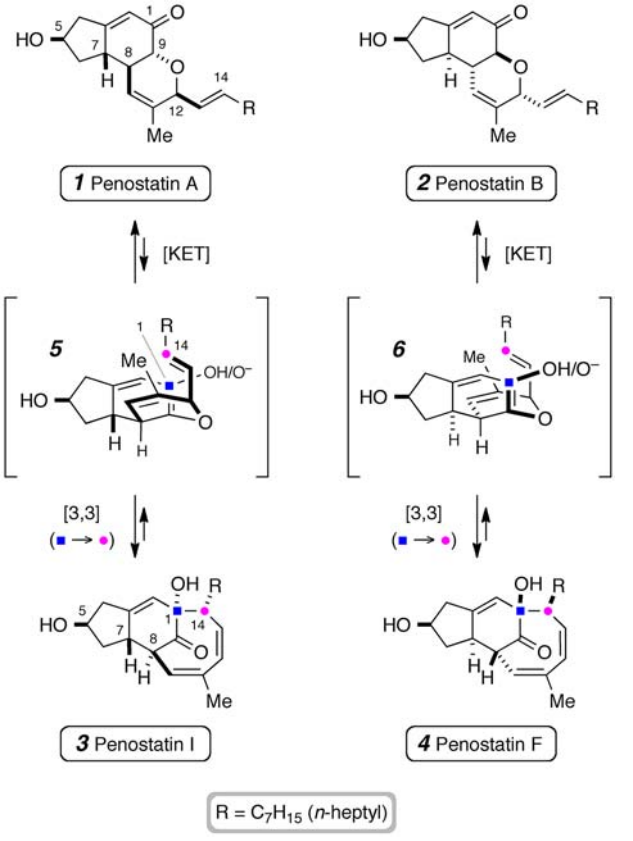
sodium enolates derived from α-(allyloxy)propiophenone occurred with remarkable ease ($t_{1/2}$ < 0.1 and 2.4 h, respectively, at −23 °C).

Scheme 1. Hypothesis for the Biosynthesis of Penostatin I (**3**) and Penostatin F (**4**)

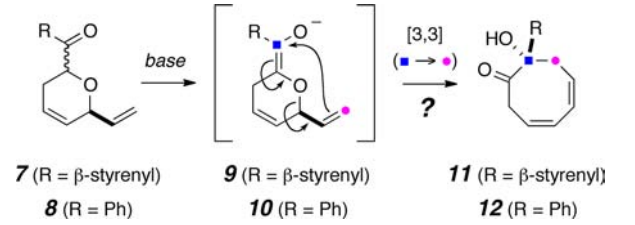


The implications of the Koreeda study vis-à-vis the hypothesis proposed in Scheme 1 were intriguing. Might it be the case that (the enolates corresponding to) **5** and **6**, present at low (but finite) concentration, undergo a pair of biosynthetic, anionic oxy-Claisen rearrangements to give rise to (the alkoxide precursors of) **3** and **4** at ambient temperature? We reasoned that this possibility could be addressed by interrogating the reactivity of the enolates derived from the dihydropyrans **7** and **8** (Scheme 2). These simplied analogs retain many of the key structural attributes of **1** and **2** but have the advantage of being much more readily accessible. The intent was to explore the behavior of **7** or **8** under basic conditions to learn if the enolate **9** or **10** would undergo [3,3]-sigmatropic rearrangement to produce the penostatin-like cyclooctadienone **11** or **12**. We describe here the observations made through this model study.

A straightforward, five-step sequence was employed to prepare the substrates **7-cis** and **8-cis** (Scheme 3). The stannylene ketal[6] derived from hexa-1,5-diene-3,4-diol (**13**)

(6) David, S.; Thieffry, A.; Veyrières, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1796–1801.

Scheme 2. Proposed Model Study



(ca. 1:1 *meso* + *d,l*)[7] was alkylated with *tert*-butyl bromoacetate ($Bu_4N^+Br^-$, PhH, reflux) to deliver the isomeric dioxanones **14-trans**/**cis** together with minor amounts of their acyclic, hydroxy ester progenitors. This mixture was driven to the desired products upon treatment with TFA (PhH, reflux).[8] Separation of these isomers (medium pressure liquid chromatography on silica gel) provided **14-trans** (>95% purity) and **14-cis** (ca. 90% purity), the relative configurations of which were assigned by analysis of vicinal $^3J_{H5,H6}$ coupling values.[9]

Lactone **14-trans**[10] was then subjected to Ireland–Claisen[11] rearrangement to effect dioxanone-to-dihydropyran reorganization[12,13] (Scheme 3). In the event, the intermediate silyl enol ether **15-trans** rearranged smoothly (PhMe, 100–110 °C[8,14]) to deliver the TBS ester **16-cis**. It should be noted that isolation of this latter, acid-sensitve substance required the use of TMS-functionalized silica gel.[15]

(7) (a) Hekmatshoar, R.; Yavari, I.; Beheshtiha, Y. S.; Heravi, M. M. *Monatsh. Chem.* **2001**, *132*, 689–691. (b) Trost, B. M.; Aponick, A. *J. Am. Chem. Soc.* **2006**, *128*, 3931–3933.

(8) Burke, S. D.; Sametz, G. M. *Org. Lett.* **1999**, *1*, 71–74. In this report, a single enantiomer of **14-trans** was prepared by a route that commenced with D-mannitol.

(9) The vicinal $^3J_{H5,H6}$ values observed for **14-trans** and **14-cis** (9.0 and 4.5 Hz, respectively) are in good agreement with those reported for related structures by Burke and co-workers; see ref 12d.

(10) As a matter of experimental convenience, the higher purity lactone **14-trans** (which gives **16-cis** upon Ireland–Claisen rearrangement[12,13]) was typically taken forward. Thus the ketones **7-cis** and **8-cis** were used in the majority of the studies described here. However, the analogous series of isomeric intermediates derived from **14-cis** (i.e., **7-trans**, **8-trans**, **16-trans**, and **18-trans**) have also been prepared and fully characterized; see the Supporting Information for full details.

(11) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897–5898.

(12) (a) Burke, S. D.; Armistead, D. M.; Schoenen, F. J. *J. Org. Chem.* **1984**, *49*, 4320–4322. (b) Burke, S. D.; Armistead, D. M.; Fevig, J. M. *Tetrahedron Lett.* **1985**, *26*, 1163–1166. (c) Burke, S. D.; Schoenen, F. J.; Murtiashaw, C. W. *Tetrahedron Lett.* **1986**, *27*, 449–452. (d) Burke, S. D.; Armistead, D. M.; Schoenen, F. J.; Fevig, J. M. *Tetrahedron Lett.* **1986**, *27*, 2787–2801. (e) Burke, S. D.; Schoenen, F. J.; Nair, M. S. *Tetrahedron Lett.* **1987**, *28*, 4143–4146. (f) Burke, S. D.; Lee, K. C.; Santafianos, D. *Tetrahedron Lett.* **1991**, *32*, 3957–3960. (g) Burke, S. D.; Buchanan, J. L.; Rovin, J. D. *Tetrahedron Lett.* **1991**, *32*, 3961–3964. (h) Burke, S. D.; Piscopio, A. D.; Kort, M. E.; Matulenko, M. A.; Parker, M. H.; Armistead, D. M.; Shankaran, K. *J. Org. Chem.* **1994**, *59*, 332–347.

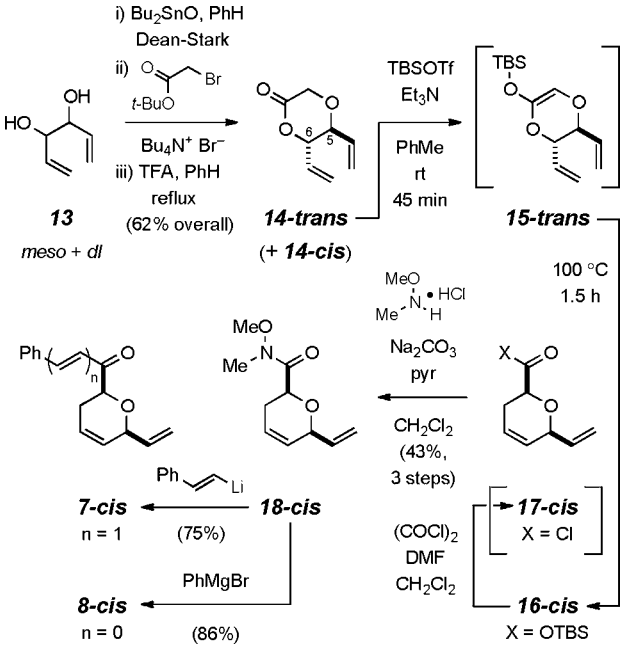
(13) (a) Büchi, G.; Powell, J. E., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 4559–4560. (b) Büchi, G.; Powell, J. E., Jr. *J. Am. Chem. Soc.* **1970**, *92*, 3126–3133. (c) Danishefsky, S.; Funk, R. L.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 6889–6891.

(14) Angle, S. R.; Breitenbucher, J. G.; Arnaiz, D. O. *J. Org. Chem.* **1992**, *57*, 5947–5955.

(15) For example, see ref 14 and Overman, L. E.; Angle, S. R. *J. Org. Chem.* **1985**, *50*, 4021–4028 (the protocol used for the preparation of the TMS-functionalized silica gel used here is described in the Supporting Information).

The Weinreb amide **18-cis** then emerged in moderate overall yield from a two-step procedure that involved (i) exposure of **16-cis** to an excess (3 equiv) of the Vilsmeier reagent[16] and (ii) amidation of the resulting crude acid chloride **17-cis** under standard conditions. Finally, the styrenyl- (**7-cis**) and phenyl- (**8-cis**) ketones were uneventfully produced upon acylation of either β-lithiostyrene[17] or phenylmagnesium bromide with the amide **18-cis**.

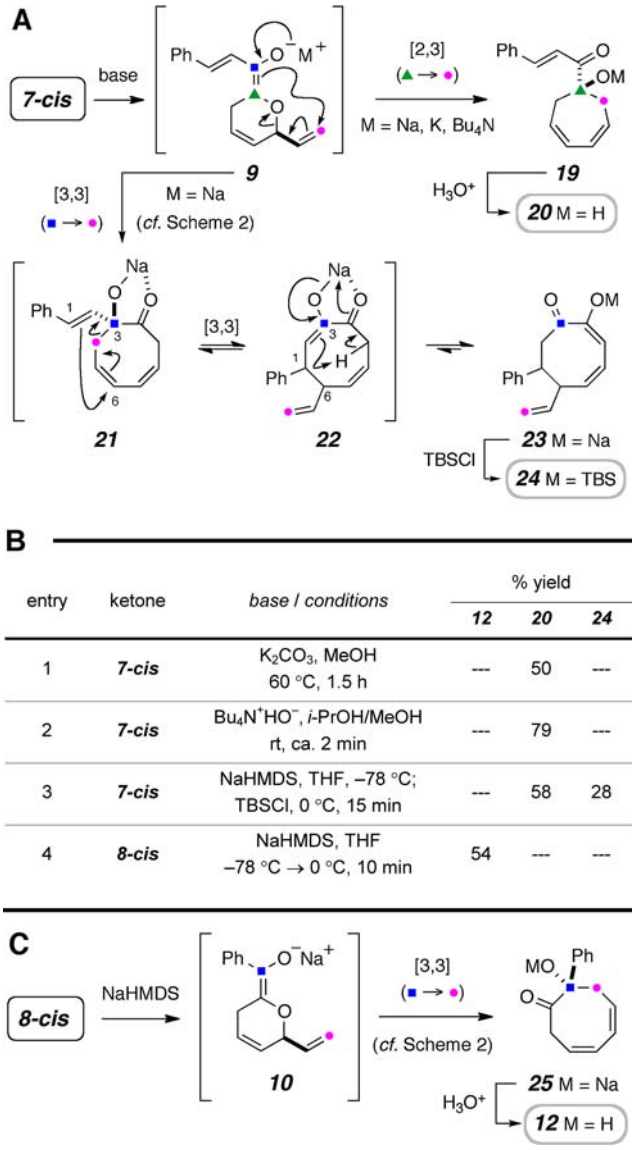
Scheme 3. Preparation of the Model Substrates **7-cis** and **8-cis**



When ketone **7-cis** was exposed to K_2CO_3 in MeOH for 90 min at 60 °C, the only isolable product was the symmetric cycloheptadiene derivative **20** (Figure 1, Panel A), derived from [2,3]-Wittig rearrangement[18] of the enolate **9** (Panel B, entry 1). This product was again formed, this time within minutes at room temperature, upon addition of **7-cis** to a solution of tetra-*n*-butylammonium hydroxide ($Bu_4N^+HO^-$) in *i*-PrOH/MeOH (entry 2).

We then attempted to trap the silyl enol ether derived from **9** (M = Na) with the intent of subsequently examining its thermal reactivity. Deprotonation of **7-cis** with NaHMDS in THF at −78 °C followed by treatment with TBSCl prior to workup again gave rise to **20**, but now along with a second unexpected product, the conjugated cyclooctadienone **24** (Figure 1, Panel B, entry 3). Its structure was established through extensive 1-D (^1H and ^{13}C) and 2-D ($^1H-^1H$ COSY, HMQC, and HMBC) NMR experiments and analysis. Although this product was formed as essentially a single diastereomer, we have not unambiguously established its relative configuration.

Formation of **24** can be explained by the following sequence, which is a pathway that is a consequence of



entry	ketone	*base / conditions*	% yield		
			12	***20***	***24***
1	***7-cis***	K_2CO_3, MeOH 60 °C, 1.5 h	---	50	---
2	***7-cis***	$Bu_4N^+HO^-$, *i*-PrOH/MeOH rt, ca. 2 min	---	79	---
3	***7-cis***	NaHMDS, THF, −78 °C; TBSCl, 0 °C, 15 min	---	58	28
4	***8-cis***	NaHMDS, THF −78 °C → 0 °C, 10 min	54	---	---

Figure 1. Oxyanionic rearrangements of enolates **9** and **10**, derived from **7-cis** and **8-cis**, respectively. (A) Rearrangement of **9** via competitive [2,3]-Wittig (to **19**) vs Claisen/Cope (to **23**) pathways. (B) Table of results. (C) Rearrangement of **10** via a Claisen pathway.

the fortuitous positioning of the (*E*)-styrenyl appendage in **7-cis** (Figure 1, Panel A). The cyclooctadienone **21** arising from anionic oxy-Claisen rearrangement of **9** contains yet another (all-carbon) *vic*-π,π subunit. It bears an aromatic substituent at C1[19] and an electron-donating oxido at C3.[20] [3,3]-Sigmatropic (anionic oxy-Cope[20,21]) rearrangement of **21** gives the isomeric cyclooctadienone **22**. The prototropic

(16) Wissner, A.; Grudzinskas, C. V. *J. Org. Chem.* **1978**, *43*, 3972–3974.
(17) Neumann, H.; Seebach, D. *Tetrahedron Lett.* **1976**, *17*, 4839–4842.
(18) Thomas, A. F.; Dubini, R. *Helv. Chim. Acta* **1974**, *57*, 2084–2087.
(19) Gentric, L.; Hanna, I.; Huboux, A.; Zaghdoudi, R. *Org. Lett.* **2003**, *5*, 3631–3634.
(20) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765–4766.
(21) (a) Lee, E.; Shin, I.-J.; Kim, T.-S. *J. Am. Chem. Soc.* **1990**, *112*, 260–264. (b) Lee, E.; Lee, Y. R.; Moon, B.; Kwon, O.; Shim, M. S.; Yun, J. S. *J. Org. Chem.* **1994**, *59*, 1444–1456.

shift indicated within **22** produces the isomeric and presumably more stable dienolate **23**. Silylative quenching then gives rise to the observed dienol ether **24**.[22]

In light of this proposed mechanism, we judged that the product derived from anionic oxy-Claisen rearrangement might be isolable if the styrenyl unsaturation were removed from **7-cis**. Thus, the phenyl ketone **8-cis** was subsequently studied (Figure 1, Panel C). Indeed, deprotonation of this compound with NaHMDS in THF at −78 °C followed by warming gave rise to the cyclooctadienone **12** as the major product[23] (Figure 1, Panel B, entry 4). Notably, this rearrangement took place within 10 min at 0 °C.

In summary, as part of our studies designed to probe the hypothesis that penostatin F (**3**) and penostatin I (**4**) arise via spontaneous [3,3]-sigmatropic rearrangements of their progenitors **1** and **2**, respectively (Scheme 1), the homologous 2,6-disubstituted dihydropyran model substrates **7-cis** and **8-cis** were prepared by five-step synthetic sequences emanating from the dioxanone **14-trans**. The rearrangements of each were studied under a variety of basic conditions. The observed formation of cyclooctadienone **12** via a rapid [3,3]-sigmatropic (anionic oxy-Claisen) rearrangement serves as evidence that the pathways shown in Scheme 1 that interconnect **1** with **3** and **2** with **4** are energetically viable.

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Supporting Information Available. Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all isolated compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(22) We considered an alternative mechanism wherein **21** would arise by [1,2]-migration of a C−C bond within **19**. This type of reorganization has been considered previously; see: Kirchner, J. J.; Pratt, D. V.; Hopkins, P. B. *Tetrahedron Lett*. **1988**, *29*, 4229–4232. A control experiment was performed in which **20** was reexposed to NaHMDS under the conditions used to generate **24** from **7-cis**. Following reaction quench with TBSCl, none of **24** was observed, ca. 20% of **20** was recovered, and a byproduct that was shown to be a monosilylated dimer was isolated in ca. 19% yield, the structure of which was not fully delineated.

(23) The β,γ-unsaturated cyclooctadienone **12** was also seen to form slowly upon exposure of **8-cis** to aqeuous base (i.e., 0.1 M NaOH, THF, rt, 20 d, ca. 7% conversion to **12**). Under these conditions, the epimers **8-cis** and **8-trans**[10] (ca. 0.9:1) were observed (^{1}H NMR analysis) as the major components of the crude mixture in addition to the rearrangement product **12**. This implies that enolate **10** was reprotonated (from both diastereotopic faces) more rapidly than it underwent [3,3]-sigmatropic rearrangement to **25**. Moreover it suggests that **12** is more stable than one of its isomeric α,β-unsaturated cyclooctadienone isomers under these apparently equilibrating conditions.