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

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Received July 13, 2012

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 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

ORGANIC LETTERS

2012 Vol. 14, No. 18

4738-4741

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.

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 ketal⁶ derived from hexa-1,5-diene-3,4-diol (13)

Scheme 2. Proposed Model Study



(ca. 1:1 *meso* + d,l)⁷ was alkylated with *tert*-butyl bromoacetate (Bu₄N⁺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–

Lactone **14-trans**¹⁰ was then subjected to Ireland– Claisen¹¹ 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

(9) The vicinal ${}^{3}J_{\rm H5,H6}$ 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.

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(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.

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

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⁽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 p-mannitol.

⁽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 reagent¹⁶ 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 -lithiostyrene¹⁷ or phenylmagnesium bromide with the amide **18-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 rearrangement¹⁸ 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 (Bu₄N⁺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 ¹³C) 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



2	7-cis	Bu₄N ⁺ HO ⁻ , <i>i</i> -PrOH/MeOH rt, ca. 2 min		79	
3	7-cis	NaHMDS, THF, –78 °C; TBSCI, 0 °C, 15 min		58	28
4	8-cis	NaHMDS, THF –78 °C \rightarrow 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 C1¹⁹ 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

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⁽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.

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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 product²³ (Figure 1, Panel B,

(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 (¹H 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.

entry 4). Notably, this rearrangement took place within 10 min at 0 $^{\circ}$ 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.

Acknowledgment. This investigation was supported by a grant awarded by the U.S. Department of Health and Human Services (National Institute of General Medical Sciences, GM-65597).

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

⁽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.

The authors declare no competing financial interest.