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

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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} labs. 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,

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Supporting Information Available. Experimental procedures, characterization data, and copies of ¹H- and ¹³C NMR spectra for all isolated compounds (44 pages).

that the [3,3]-sigmatropic rearrangement of the potassium and sodium enolates derived from α -(allyloxy)propiophenone occurred with remarkable ease ($t_{1/2} < 0.1$ h and 2.4 h, respectively, at -23 °C).

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 alkoxides 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 simplified 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**) (ca. 1:1 *meso* + *d,l*)⁷ was alkylated with *tert*-butyl bromoacetate ($\text{Bu}_4\text{N}^+\text{Br}^-$, 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 $^3J_{\text{H5,H6}}$ coupling values.⁹

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-sensitive substance required the use of TMS-functionalized silica gel.¹⁵ 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 ($\text{Bu}_4\text{N}^+\text{HO}^-$) in *i*-PrOH/MeOH (entry 2).

We then attempted to trap the silyl enol ether derived from **9** ($\text{M} = \text{Na}$) 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 work-up 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 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*- $\pi\pi$ 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 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, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Isolation and structure determination of all members of the penostatin family: Takahashi C, Numata A, Yamada T, Minoura K, Enomoto S, Konishi K, Nakai M, Matsuda C, Nomoto K. *Tetrahedron Lett.* 1996; 37:655–658. Iwamoto C, Minoura K, Hagishita S, Nomoto K, Numata A. *J Chem Soc, Perkin Trans 1.* 1998:449–456. 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: Snider BB, Liu T. *J Org Chem.* 1999; 64:1088–1089. Snider BB, Liu T. *J Org Chem.* 2000; 65:8490–8498. [PubMed: 11112568] Barriault L, Ang PJA, Lavigne RMA. *Org Lett.* 2004; 6:1317–1319. [PubMed: 15070326] Total synthesis of penostatin B: Fujioka K, Yokoe H, Yoshida M, Shishido K. *Org Lett.* 2012; 14:244–247. [PubMed: 22145647]
3. E.g.: Kinney WA, Coghlan MJ, Paquette LA. *J Am Chem Soc.* 1984; 106:6868–6870. Paquette LA, Philippo CMG, Yo NH. *Can J Chem.* 1992; 70:1356–1365. and references cited therein; Paquette LA, Wang T-Z, Vo NH. *J Am Chem Soc.* 1993; 115:1676–1683.
4. Burrows CJ, Carpenter BK. *J Am Chem Soc.* 1981; 103:6984–6986.
5. Koreeda M, Luengo JJ. *J Am Chem Soc.* 1985; 107:5572–5573.
6. David S, Thieffry A, Veyrières A. *J Chem Soc, Perkin Trans 1.* 1981:1796–1801.
7. (a) Hekmatshoar R, Yavari I, Beheshtiha YS, Heravi MM. *Monatsh Chem.* 2001; 132:689–691. (b) Trost BM, Aponick A. *J Am Chem Soc.* 2006; 128:3931–3933. [PubMed: 16551099]
8. Burke SD, Sametz GM. *Org Lett.* 1999; 1:71–74. [PubMed: 10822536] 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 RE, Mueller RH. *J Am Chem Soc.* 1972; 94:5897–5898.
12. (a) Burke SD, Armistead DM, Schoenen FJ. *J Org Chem.* 1984; 49:4320–4322. (b) Burke SD, Armistead DM, Fevig JM. *Tetrahedron Lett.* 1985; 26:1163–1166. (c) Burke SD, Schoenen FJ, Murtiashaw CW. *Tetrahedron Lett.* 1986; 27:449–452. (d) Burke SD, Armistead DM, Schoenen FJ, Fevig JM. *Tetrahedron Lett.* 1986; 27:2787–2801. (e) Burke SD, Schoenen FJ, Nair MS. *Tetrahedron Lett.* 1987; 28:4143–4146. (f) Burke SD, Lee KC, Santafianos D. *Tetrahedron Lett.* 1991; 32:3957–3960. (g) Burke SD, Buchanan JL, Rovin JD. *Tetrahedron Lett.* 1991; 32:3961–3964. (h) Burke SD, Piscopio AD, Kort ME, Matulenko MA, Parker MH, Armistead DM, Shankaran K. *J Org Chem.* 1994; 59:332–347.
13. (a) Büchi G, Powell JE Jr. *J Am Chem Soc.* 1967; 89:4559–4560. (b) Büchi G, Powell JE Jr. *J Am Chem Soc.* 1970; 92:3126–3133. (c) Danishefsky S, Funk RL, Kerwin JF Jr. *J Am Chem Soc.* 1980; 102:6889–6891.
14. Angle SR, Breitenbucher JG, Arnaiz DO. *J Org Chem.* 1992; 57:5947–5955.
15. E.g., ref 14 and Overman LE, Angle SR. *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).
16. Wissner A, Grudzinskas CV. *J Org Chem.* 1978; 43:3972–3974.
17. Neumann H, Seebach D. *Tetrahedron Lett.* 1976; 17:4839–4842.
18. Thomas AF, Dubini R. *Helv Chim Acta.* 1974; 57:2084–2087.
19. Gentric L, Hanna I, Huboux A, Zaghdoudi R. *Org Lett.* 2003; 5:3631–3634. [PubMed: 14507190]
20. Evans DA, Golob AM. *J Am Chem Soc.* 1975; 97:4765–4766.
21. (a) Lee E, Shin IJ, Kim TS. *J Am Chem Soc.* 1990; 112:260–264. (b) Lee E, Lee YR, Moon B, Kwon O, Shim MS, Yun JS. *J Org Chem.* 1994; 59:1444–1456.
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 JJ, Pratt DV, Hopkins PB. *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 by-product 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 aqueous 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.

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.

Scheme 1. Hypothesis for the biosynthesis of penostatin I (**3**) and penostatin F (**4**).

Scheme 2.
Proposed model study.

Scheme 3.
 Preparation of the model substrates **7-cis** and **8-cis**.