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Dynamic Kinetic Resolution During a Vinylogous Payne Rearrangement: A Concise Synthesis of the Polar Pharmacophoric Subunit of (+)-Scyphostatin

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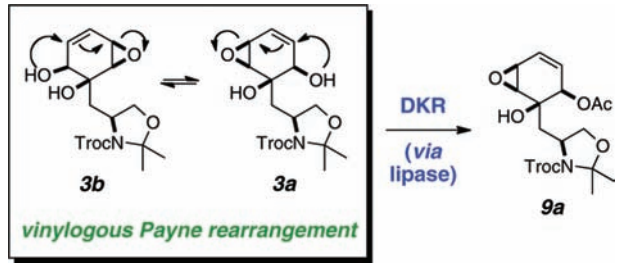
ABSTRACT



The diastereomeric epoxycyclohexenols 3a/b (obtained via a Wharton rearrangement of a bis-epoxycyclohexanone precursor) were shown to undergo interconversion via a facile vinylogous Payne rearrangement. Mechanistic issues were probed; the doubly *O*-deuterated analogues underwent this equilibration more slowly than the parent dihydroxy compounds. It was possible to kinetically resolve the mixture of 3a/b under equilibrating conditions by use of Amano PS. This DKR is additionally noteworthy because it sets four stereocenters in a single event.

Scyphostatin (**1**) is regarded as the most specific and potent inhibitor (IC_{50} = 1.0 μM) of neutral sphingomyelinase, an encouraging pharmacological target for treating inflammation and immunological and neurological disorders.[1] As can be seen from its structure (Figure 1), scyphostatin (**1**) features two principal moieties: a densely functionalized epoxycyclohexenone polar core and an unsaturated fatty acid side chain. The biological activity of scyphostatin is believed to be associated with its epoxyenone headgroup.[2] That fact, coupled with the unusual structure of this pharmacophore, has motivated many synthetic efforts.[3]

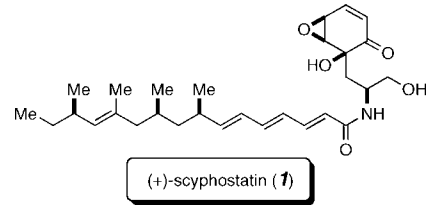


Figure 1. Structure of (+)-scyphostatin (**1**).

(1) Claus, R. A.; Dorer, M. J.; Bunck, A. C.; Deigner, H. P. *Curr. Med. Chem.* **2009**, *16*, 1978–2000.

(2) Waschkowski, V.; Giannis, A.; Pitsinos, E. N. *Chem. Med. Chem.* **2006**, *1*, 718–721.

(3) (a) Inoue, M.; Yokota, W.; Murugesh, M. G.; Izuhara, T.; Katoh, T. *Angew. Chem., Int. Ed.* **2004**, *116*, 4303–4305. (b) Inoue, M.; Yokota, W.; Katoh, T. *Synthesis* **2007**, 622–637. (c) Takagi, R.; Miyanaga, W.; Tojo, K.; Tsuyumine, S.; Ohkata, K. *J. Org. Chem.* **2007**, *72*, 4117–4125. (d) Fujioka, H.; Sawama, Y.; Kotoku, N.; Ohnaka, T.; Okitsu, T.; Murata, N.; Kubo, O.; Li, R.; Kita, Y. *Chem.—Eur. J.* **2007**, *13*, 10225–10238, and references therein to the many studies of fragment synthesis.

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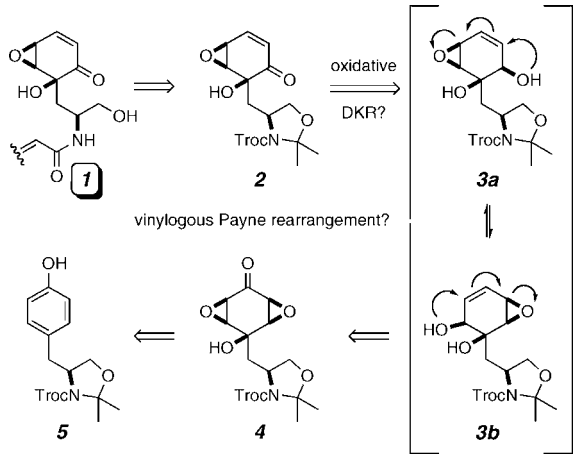
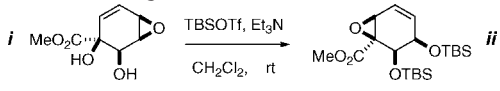
Scheme 1. Plan for Synthesis of the Polar Subunit of (+)-Scyphostatin (**1**)



Here we report a dynamic kinetic resolution (DKR) that is coupled to a reversible (and rare[4]) vinylogous Payne rearrangement (cf. graphical abstract above). The DKR was achieved using a lipase (Amano PS) as the chiral discriminator to generate a product, **9a**, that contains many of the constitutional and configurational features of (+)-scyphostatin (**1**).[5]

Our analysis (Scheme 1) of the scyphostatin core revealed that it might be formed from a protected amino alcohol such as the Troc-acetonide **2** (Troc = Cl_3CCH_2OCO). We hoped to make the epoxycyclohexenone **2** via an oxidative DKR of the pseudoenantiomers **3a** and **3b**, under conditions where the stereoisomers would equilibrate via a vinylogous Payne rearrangement (see curly arrows, Scheme 1). If successful, such a DKR would be significant because it would establish three stereocenters in one step. The mixture of allylic alcohols **3** could arise from the Wharton rearrangement of the diepoxide **4**, another example of a rarely seen transformation.[6] We envisioned that the *syn*-diepoxide **4** could be made by oxidative dearomatization of the L-tyrosine derivative **5** followed by bis-epoxidation *cis* to the tertiary hydroxyl group.[7]

(4) The only example we know of this type of rearrangement (***i*** to ***ii***) occurs under silylative conditions: Myers, A. G.; Siegel, D. R.; Buzard, D. J.; Charest, M. G. *Org. Lett.* **2001**, *3*, 2923–2926.

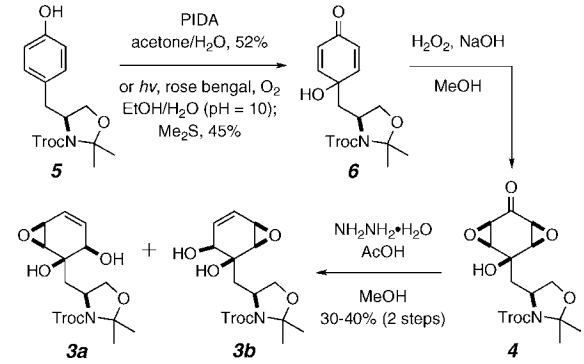


(5) (a) Tanaka, M.; Nara, F.; Suzuki-Konagai, K.; Hosoya, T.; Ogita, T. *J. Am. Chem. Soc.* **1997**, *119*, 7871–7872. (b) Nara, F.; Tanaka, M.; Hosoya, T.; Suzuki-Konagai, K.; Ogita, T. *J. Antibiot.* **1999**, *52*, 525–530. (c) Nara, F.; Tanaka, M.; Masuda-Inoue, S.; Yamasato, Y.; Doi-Yoshioka, H.; Suzuki-Konagai, K.; Kumakura, S.; Ogita, T. *J. Antibiot.* **1999**, *52*, 531–535.

(6) Wharton on a diepoxyketone: (a) Ichihara, A.; Oda, K.; Kobayashi, M.; Sakamura, S. *Tetrahedron* **1980**, *36*, 183–188. (b) Aoyagi, Y.; Hitotsuyanagi, Y.; Hasuda, T.; Fukaya, H.; Takeya, K.; Aiyama, R.; Matsuzaki, T.; Hashimoto, S. *Biorg. Med. Chem. Lett.* **2006**, *16*, 1947–1949.

(7) McKillop, A.; Taylor, R. J. K.; Watson, R. J.; Lewis, N. *Chem. Commun.* **1992**, 1589–1591.

Scheme 2. Synthesis of Allylic Alcohols **3**



The synthesis commenced with oxidative dearomatization of the phenol **5** using phenyliodine diacetate (PIDA) to provide the dienone **6** in 52% yield (Scheme 2). Alternatively, singlet oxygen oxidation of **5** under basic conditions followed by reduction with DMS also gave the dienone **6** in a similar yield (45%).[8]

Epoxidation of the dienone **6** with H_2O_2/NaOH produced the diepoxide **4** as a single diastereomer,[7] and treatment with hydrazine to effect Wharton rearrangement gave a nearly 1:1 ratio of the allylic alcohols **3a** and **3b** (30−40% over two steps). It is noteworthy that sequential application of a set of such elementary reagents as $^1O_2$, H_2O_2/NaOH, and NH_2NH_2 affords a product having the molecular complexity of **3a/b** from a simple phenolic precursor.

The allylic alcohol diastereomers **3a** and **3b** were separated by HPLC (SiO_2). The equilibration of each of these isolated diastereomers back to a mixture of **3a** and **3b** would implicate a vinylogous Payne rearrangement. This equilibration occurred slowly upon heating (80 °C) in deuterated solvents [$CDCl_3$ and d_6-acetone (Scheme 3, top)]. A ca. 1:1 ratio of **3a** and **3b** was reestablished after heating for 3 days (half-life ca. 1 day).

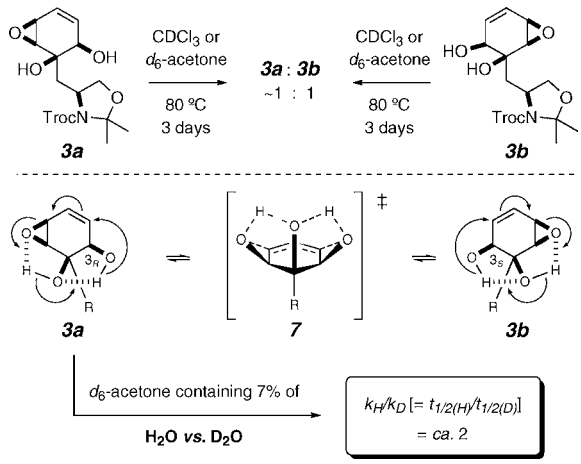
Because this equilibration occurred under such mild (and essentially neutral) conditions, we wondered if the tertiary alcohol could be acting as an intramolecular H-bond donor to the epoxide in **3**,[9] thus lowering the activation barrier of this vinylogous Payne rearrangement. Intramolecular proton-shuttling through a locally symmetrical transition state geometry like **7** (Scheme 3, bottom) was an attractive conceptualization of the process.[10] This mechanistic thinking was probed by comparing the rate of rearrangement of **3a** versus its deuterated analogue. Thus, parallel experiments

(8) Saito, I.; Chujo, Y.; Shimazu, H.; Yamane, M.; Matsuura, T.; Cahnmann, H. J. *J. Am. Chem. Soc.* **1975**, *97*, 5272–5277.

(9) That the degree of hydrogen bonding is substantial in each of **3a** and **3b** is supported by the NMR observation of coupling of both of their hydroxyl protons to, for the secondary hydroxyl, the vicinal/allylic proton at $C3_{R/S}$ ($^3J = \sim$12 Hz) and, for the tertiary hydroxyl, long range coupling ($^4J = \sim$1.5 Hz) to a methylene proton in the sidechain.

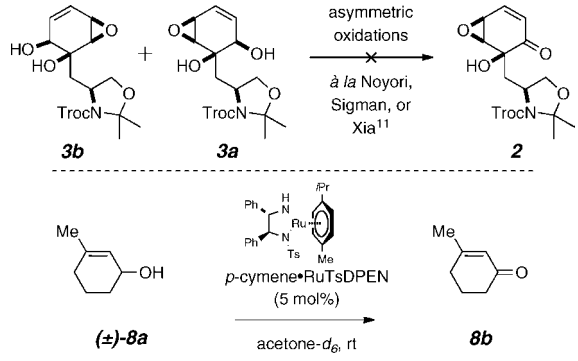
(10) For other examples of internal hydrogen-bond catalysis, see: (a) Choy, W.; Reed, L. A., III; Masamune, S. *J. Org. Chem.* **1983**, *48*, 1137–1139. (b) Cox, C. D.; Siu, T.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5625–5629. (c) Stark, L. M.; Pekari, K.; Sorensen, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12064–12066.

Scheme 3. Vinylogous Payne Rearrangement of **3a/b**



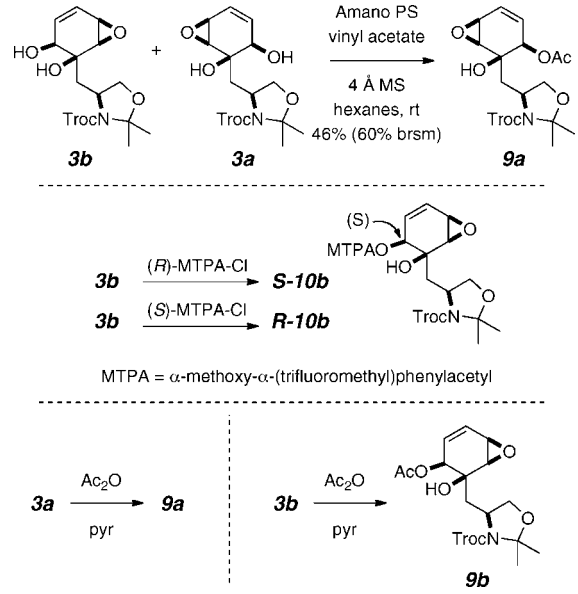
were performed in which diastereomerically pure **3a** was heated in acetone containing ca. 7 vol% H_2O versus D_2O; reaction progress of each was monitored by ^1H NMR spectroscopy. Indeed, the D_2O sample equilibrated at roughly half the rate of the H_2O sample, supporting the view that O−H bond cleavage is involved in the rate-limiting event. Also, the rate of equilibration of the H_2O-spiked acetone reaction mixture was very similar to that when no H_2O was added, suggesting that this change in medium did not appreciably alter the operative mechanism.

Scheme 4. Attempted Oxidative DKR



With the viability of the vinylogous Payne rearrangement established, we proceeded to study a DKR that would selectively drain one of **3a** or **3b** from the equilibrating mixture. We first examined an oxidative resolution strategy, which would have provided the epoxycyclohexenone core of scyphostatin (cf. **2**, Scheme 4) directly. Unfortunately, none of the asymmetric oxidative methods of Noyori,[11a] Sigman,[11b] or Xia[11c] proved effective. We successfully used the Noyori conditions to oxidize the simple allylic alcohol (±)-**8a** to enone **8b** [5 mol % *p*-cymene•RuTsDPEN; progress slowed substantially at ca. 50% conversion (^1H NMR analysis)]. When we repeated this experiment, now with a mixture of substrates (±)-**8a** and **3a/b**, we observed that (±)-**8a** did not turn over. This suggested that vicinal diol **3** (or initially oxidized products derived therefrom) might be inhibiting this catalytic system.

Scheme 5. Lipase-Mediated DKR



We then turned attention to a lipase-mediated DKR (Scheme 5).[12] Exposure of the mixture of **3a/b** to Amano PS in hexanes containing 5 equiv of vinyl acetate at ambient temperature resulted in slow but steady conversion. A single, diasteromerically pure acetate was produced [46% yield following a 14-day reaction time and HPLC purification (SiO_2)]. This acetate was assigned structure **9a** on the following basis. The more polar alcohol, which turned out to have the configurations depicted in **3b**, was converted to its *R*- and *S*-Mosher ester *R*-**10b** and *S*-**10b** (via treatment with *S*- and *R*-MTPA-Cl, respectively). Analysis[13] showed that the configuration of the carbinol center in **3b** was *S*, thereby establishing our structure assignment for both **3a** and **3b**.

Each of **3a** and **3b** was then independently converted to its acetate ester **9a** and **9b**, respectively (Scheme 5). The former was identical to the acetate generated by lipase-catalyzed acetylation (see above), an outcome that, incidentally, is consistent with the model of Kazlauskas for the

(11) (a) Hashiguchi, S.; Fujii, S.; Haack, K.-J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 288–290. (b) Jensen, D. R.; Pugsley, J. S.; Sigman, M. S. *J. Am. Chem. Soc.* **2001**, *123*, 7475–7476. (c) Sun, W.; Wang, H.; Xia, C.; Li, J.; Zhao, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 1042–1044.

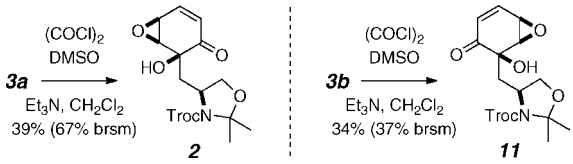
(12) Ghanem, A.; Aboul-Enein, H. Y. *Tetrahedron: Asymmetry* **2004**, *15*, 3331–3351.

(13) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451–2458.

(14) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.

kinetic selectivity of lipases.[14] To establish that a DKR was operative, the lipase experiment was repeated starting with pure **3b** as the substrate. After 14 days (and at ca. 50% conversion), a ca. 2:1:1 ratio of **9a**:**3a**:**3b** had been established, unambiguously demonstrating that the vinylogous Payne rearrangement-based DKR was indeed taking place.

Scheme 6. Oxidation to Epoxycyclohexenones **2** and **11**



Each pure allylic alcohol **3a** and **3b** was oxidized under Swern conditions to furnish both the epoxycyclohexenone **2** found in (+)-scyphostatin and its tris-epimer **11** (Scheme 6). Selective removal of the Troc group proved to be problematic; but this was not surprising given the known sensitivity of the epoxy-alkenols, -alkenyl acetates, and -enones of this family.[3]

In conclusion, a new strategy for synthesis of the epoxycyclohexenone core of (+)-scyphostatin (**1**) has been established. It allows concise and stereoselective access to molecules containing the pharmacophoric core of **1** that could be of biological interest. An example of the rare, vinylogous Payne rearrangement, which likely proceeds via a unimolecular (and an unusual type of) prototropic shift, has been uncovered. Furthermore, this transformation was shown to be a viable basis for a DKR. Finally, this DKR is additionally noteworthy because it sets four stereocenters in a single event (cf. **3a** + **3b** to **9a**, Scheme 5).

Acknowledgment. These studies were supported by the National Institute of General Medical Sciences (GM-65597) and the National Cancer Institute (CA-76497) of the United States National Institutes of Health.

Supporting Information Available: Detailed experimental procedures and spectroscopic characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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