

# A Formal Total Synthesis of (+)-Zincophorin. Observation of an Unusual Urea-Directed Stork–Crabtree Hydrogenation<sup>†</sup>

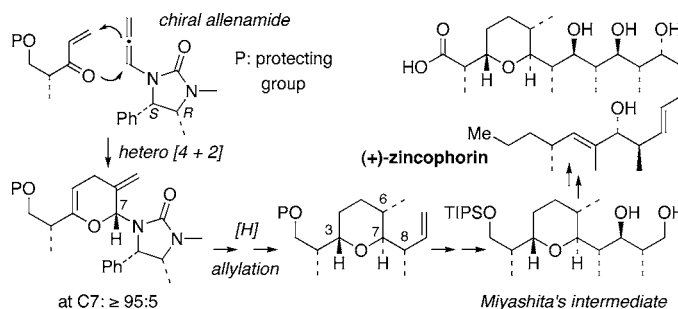
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## ABSTRACT



A formal total synthesis of (+)-zincophorin via interception of Miyashita's advanced intermediates is described here. This effort features the first synthetic application of an inverse demand hetero [4 + 2] cycloaddition of a chiral allenamide, and the observation of an unusual urea directed Stork–Crabtree hydrogenation.

(+)-Zincophorin (**1**), also referred to as M144255 or griseochellin, is a polyoxygenated ionophoric antibiotic that was isolated from *Streptomyces griseus* in 1984.<sup>1</sup> It possesses strong in vivo activity against Gram-positive bacteria and *Clostridium coelchii*. Its methyl ester was reported in a patent<sup>1d</sup> as having strong inhibitory properties against influenza WSN/virus with reduced toxicity for the host cell. Its ability to strongly bind with Zn<sup>2+</sup>, which is also present in its X-ray structure,<sup>1a</sup> is the basis for its name. Over the last two decades, (+)-zincophorin (**1**) has attracted an impressive array of synthetic effort<sup>2</sup> including Danishefsky's<sup>3</sup>

first total synthesis along with two recent elegant total syntheses reported by Cossy<sup>4</sup> and Miyashita.<sup>5</sup>

Our effort some years ago<sup>6,7</sup> in developing a stereoselective inverse electron-demand hetero [4 + 2] cycloaddition of chiral allenamides<sup>8–10</sup> led us to (+)-zincophorin (**1**). Specifically, we envisioned constructing the tetrahydropyran unit

<sup>†</sup> With deepest appreciation and respect, this paper is dedicated to Professor Gilbert Stork on the special occasion of his 85th birthday.

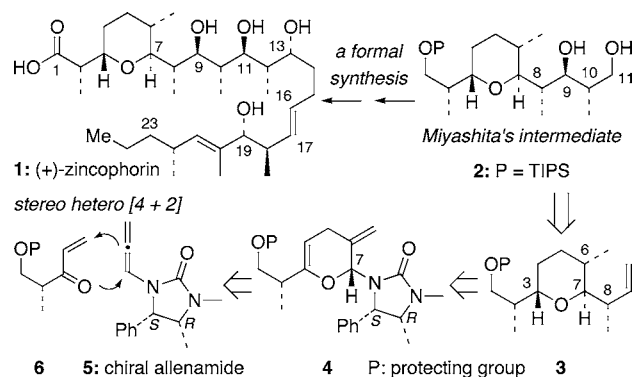
(1) For isolation, see: (a) Brooks, H. A.; Gardner, D.; Poyser, J. P.; King, T. J. *J. Antibiot.* **1984**, *37*, 1501. (b) Grafe, U.; Schade, W.; Roth, M.; Radics, L.; Incze, M.; Ujszaszy, K. *J. Antibiot.* **1984**, *37*, 836. (c) Radics, L. *J. Chem. Soc., Chem. Commun.* **1984**, 599. (d) Grafe, U. German patent [East] DD 231,793.

(2) For approaches, see: (a) Cossy, J.; Blanchard, N.; Defosseux, M.; Meyer, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2144. (b) Guindon, Y.; Murtagh, L.; Caron, V.; Landry, S. R.; Jung, G.; Bencheqroun, M.; Faucher, A.-M.; Guerin, B. *J. Org. Chem.* **2001**, *66*, 5427. (c) Burke, S. D.; Ng, R. A.; Morrison, J. A.; Alberti, M. J. *J. Org. Chem.* **1998**, *63*, 3160. (d) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1998**, *63*, 3701. (e) Chemler, S. R.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 3800. (f) Booyesen, J. F.; Holzapfel, C. W. *Synth. Commun.* **1995**, *25*, 1473. (g) Cywin, C. L.; Kallmerten, J. *Tetrahedron Lett.* **1993**, *34*, 1103. (h) Balestra, M.; Wittman, M. D.; Kallmerten, J. *Tetrahedron Lett.* **1988**, *29*, 6905. (i) Zelle, R. E.; DeNinno, M. P.; Selnick, H. G.; Danishefsky, S. J. *J. Org. Chem.* **1986**, *51*, 5032.

(3) The first total synthesis, see: (a) Danishefsky, S. J.; Selnick, H. G.; DeNinno, M. P.; Zelle, R. E. *J. Am. Chem. Soc.* **1987**, *109*, 1572. (b) Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368.

in **1** via the hetero cycloadduct **4** derived from a cycloaddition of chiral allenamide **5** with enone **6** (Scheme 1).

**Scheme 1.** A Formal Total Synthesis of (+)-Zincophorin

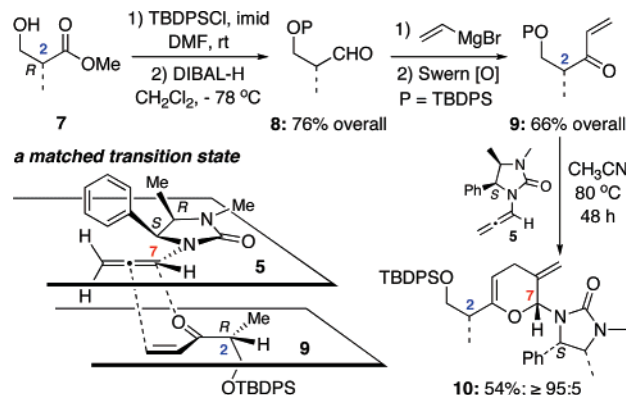


Achieving this exercise would provide the first application of chiral allenamides in natural product synthesis and represent an approach that differs from all other efforts.<sup>13</sup> We report here a formal synthesis of (+)-zincophorin featuring this cycloaddition and a urea-directed Stork–Crabtree hydrogenation.

Our efforts commenced with the synthesis of chiral enone **9**<sup>15</sup> from methyl (*R*)-3-hydroxy-2-methylpropionic ester **7** via

(1) TBDPS-silylation, (2) DIBAL-H reduction,<sup>16</sup> (3) vinyl Grignard addition, and (4) Swern oxidation (Scheme 2). The

**Scheme 2.** A Stereoselective Hetero [4 + 2] Cycloaddition



key [4 + 2] cycloaddition of heterodiene **9** with Close auxiliary<sup>17</sup> substituted allenamide **5** led to pyran **10** as a single isomer. The relative stereochemistry at C7 (the numbering is based on the natural product) was assigned on the basis of our previous work with this cycloaddition.<sup>6,7a</sup> Specifically, the heterodiene (**9** here) with an *s-cis* conformation should approach from the less hindered  $\pi$ -face of the internal olefin of allenamide **5**, which is shown in its lowest energy conformation.<sup>6,7a</sup> It is noteworthy that this was the first time a chiral heterodiene was used, and the high level of diastereoselectivity is a likely result of a matched transition state (Scheme 2).

Our efforts then encountered a serious obstacle at what we had believed to be the most trivial stage: sequential hydrogenations of the two olefins at C6 and C3 (Scheme 3). In short, after much exploration to avoid hydrolysis of the cyclic aminal via cleavage of the C7–O bond, we were delighted to find that hydrogenation of the *exo*-cyclic olefin at C6 could be achieved by using Adam's catalyst along with 3 equiv of NaBH<sub>4</sub>, while the C3 *endo*-cyclic olefin could only be reduced by using Stork–Crabtree conditions.<sup>18,19</sup> Unsuspectingly, we proceeded to remove the silyl group in presumably the desired tetrahydropyran **12**, only to be confronted with a product quite different as established by the X-ray structure of **13**.

While the stereochemistry at C6 is as expected, both stereocenters at C3 and C7 are opposite from what we had expected. These expectations are based on our earlier

(4) For Cossy's total synthesis, see: (a) Cossy, J.; Meyer, C.; Defosseux, M.; Blanchard, N. *Pure Appl. Chem.* **2005**, *77*, 1131. (c) Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *J. Org. Chem.* **2004**, *69*, 4626. (c) Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. *Org. Lett.* **2003**, *5*, 4037.

(5) For Miyashita's total synthesis, see: Komatsu, K.; Tanino, K.; Miyashita, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4341.

(6) Wei, L.-L.; Hsung, R. P.; Xiong, H.; Mulder, J. A.; Nkansah, N. T. *Org. Lett.* **1999**, *1*, 2145.

(7) Also see: (a) Berry, C. R.; Hsung, R. P. *Tetrahedron* **2004**, *60*, 7629. (b) Wei, L.-L.; Xiong, H.; Douglas, C. J.; Hsung, R. P. *Tetrahedron Lett.* **1999**, *40*, 6903.

(8) For reviews on allenamides, see: (a) Hsung, R. P.; Wei, L.-L.; Xiong, H. *Acc. Chem. Res.* **2003**, *36*, 773. (b) Tracey, M. R.; Hsung, R. P.; Antoline, J.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. In *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*; Weinreb, S. M., Ed.; Georg Thieme Verlag KG: Stuttgart, Germany, 2005; Chapter 21.4.

(9) For a compendium on the chemistry of allenes, see: Krause, N.; Hashmi, A. S. K., *Modern Allene Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004; Vols. 1 and 2.

(10) For an elegant review on the synthesis of allenes, see: (a) Brummond, K. M.; DeForrest, K. M. *Synthesis* **2007**, 795. For an excellent review on the synthetic applications of allenes, see: (b) Ma, S. *Chem. Rev.* **2005**, *105*, 2829.

(11) For recent reports on the allenamide chemistry, see: (a) Parthasarathy, K.; Jegannathan, M.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 621. (b) Fernández, I.; Monterde, M. I.; Plumet, J. *Tetrahedron Lett.* **2005**, *46*, 6029. (c) de los Rios, C.; Hegedus, L. S. *J. Org. Chem.* **2005**, *70*, 6541. (d) Alouane, N.; Bernaud, F.; Marrot, J.; Vrancken, E.; Mangeney, P. *Org. Lett.* **2005**, *7*, 5797.

(12) (a) Antoline, J. E.; Hsung, R. P.; Huang, J.; Song, Z.; Li, G. *Org. Lett.* **2007**, *9*, 1275. (b) Huang, J.; Ianni, J. C.; Antoline, J. E.; Hsung, R. P.; Kozlowski, M. C. *Org. Lett.* **2006**, *8*, 1565. (c) Berry, C. R.; Hsung, R. P.; Antoline, J. E.; Petersen, M. E.; Rameshkumar, C.; Nielson, J. A. *J. Org. Chem.* **2005**, *70*, 4038. (d) Shen, L.; Hsung, R. P.; Zhang, Y.; Antoline, J. E.; Zhang, X. *Org. Lett.* **2005**, *7*, 3081. (e) Huang, J.; Hsung, R. P. *J. Am. Chem. Soc.* **2005**, *127*, 50.

(13) For some recent elegant studies on related inverse demand hetero [4 + 2] cycloaddition of chiral enamides, see: (a) Gohier, F.; Bouhadjara, K.; Faye, D.; Gaulon, C.; Maisonneuve, V.; Dujardin, G.; Dhal, R. *Org. Lett.* **2007**, *9*, 211. (b) Tardy, S.; Tatibouët, A.; Rollin, P.; Dujardin, G. *Synlett* **2006**, 1425 and reference cited therein. Also see: (c) Palasz, A. *Org. Biomol. Chem.* **2005**, *3*, 3207.

(14) Danishefsky's synthesis featured a normal demand hetero [4 + 2] cycloaddition of a diene with aldehyde. See ref 3.

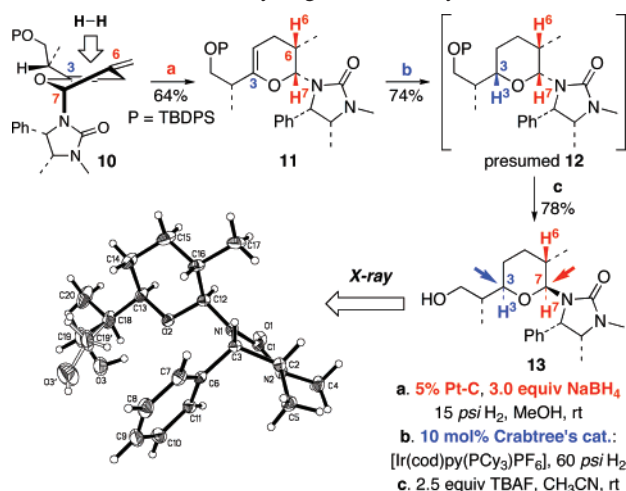
(15) See the Supporting Information.

(16) For the synthesis of *ent*-**8**, see: (a) Alois, F.; Egmont, K.; Olivier, Lepage J. *Am. Chem. Soc.* **2006**, *128*, 9194. (b) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1997**, *62*, 4449.

(17) Close, W. J. *J. Org. Chem.* **1950**, *15*, 1131.

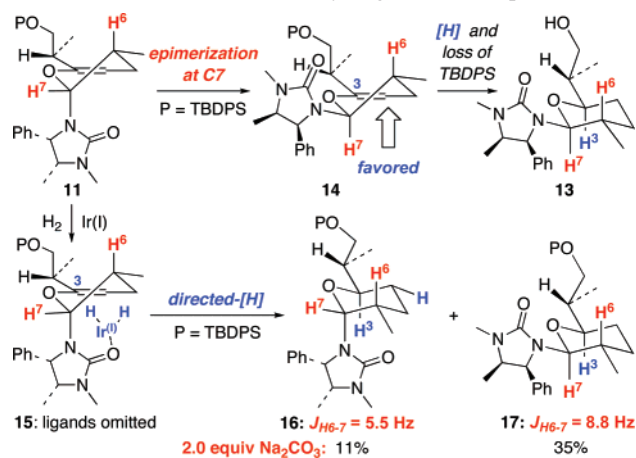
(18) For the first application of directed hydrogenations employing Crabtree's catalyst, see: (a) Stork, G.; Kahne, D. E. *J. Am. Chem. Soc.* **1983**, *105*, 1072. For some leading applications, also see: (b) Evans, D. A.; Morrissey, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3866. (c) Ginn, J. D.; Padwa, A. *Org. Lett.* **2002**, *4*, 1515.

(19) Crabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655.

**Scheme 3.** Hydrogenations of Pyran **10**

analyses<sup>6,7,20</sup> in which these pyran hetero cycloadducts assume a unique conformation as shown for **10** (Scheme 3). Hydrogenations of both the C6 and C3 olefins should show a preference at the top face of a flat pyran ring away from the urea group, which shields the bottom face while being pseudoaxially situated.

This unexpected outcome can imply a number of things including that we had wrongfully assigned the stereochemistry of cycloadduct **10**. However, we considered the following two possibilities illustrated in Scheme 4. First, the

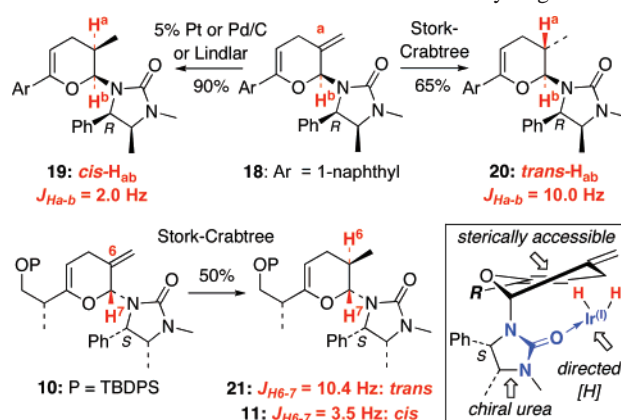
**Scheme 4.** A Urea-Directed Hydrogenation vs Epimerization

monohydrogenation product **11** could epimerize at C7 to give **14** in which hydrogenation could occur at the less congested bottom face, leading to **13** after desilylation. While this pathway is very likely and provides a sound rationale, we suspected a second scenario involving a urea-directed Stork–Crabtree hydrogenation<sup>18,19</sup> via **15** prior to any C7-epimerization.

(20) (a) Berry, C. R.; Rameshkumar, C.; Tracey, M. R.; Wei, L.-L.; Hsung, R. P. *Synlett* **2003**, 791. (b) Rameshkumar, C.; Hsung, R. P. *Synlett* **2003**, 1241.

Toward this end, we carried out the reaction using 2.0 equiv of Na<sub>2</sub>CO<sub>3</sub> to scavenge protic species that could promote the C7-epimerization, and found 11% of **16** along with 35% of **17**. The relative stereochemistry in **16** is assigned on the basis of the  $J$  value between H6 and H7 being in the *equatorial-axial* range (Scheme 4). The relative stereochemistry in **17** was confirmed via silylation of **13**. This result implies that hydrogenation at the hindered bottom face of **11** (shown in its lowest energy conformation<sup>20</sup>) is possible under Stork–Crabtree conditions without a prior C7-epimerization.

To be more definitive, we employed the model pyran **18** (with the (*R*)-Close auxiliary) because we had unambiguously established the stereochemical outcome of its hydrogenations (Scheme 5).<sup>6,20a</sup> Specifically, the monohydrogenated product

**Scheme 5.** A Urea-Directed Stork–Crabtree Hydrogenation

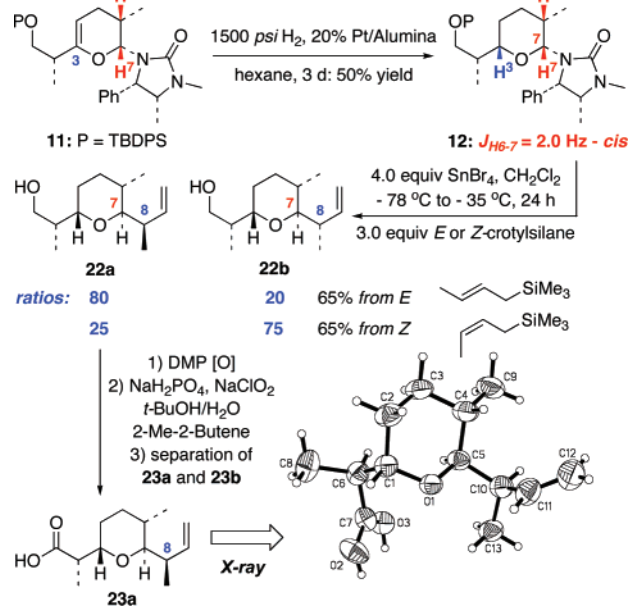
**19** obtained from standard hydrogenations contains exclusively a *cis* relationship for H<sup>a</sup> and H<sup>b</sup> with a small  $J$  value. When hydrogenating pyran **18** with Crabtree's catalyst, we isolated **20** with a large  $J$  constant, distinctly suggesting a *trans* relationship between H<sup>a</sup> and H<sup>b</sup>. Stork–Crabtree hydrogenation of **10** afforded the monohydrogenated product **21** also with a large  $J$  value in contrast to that of **11** (from standard hydrogenations of **10**: see Scheme 3), indicating again a *trans* relationship between H6 and H7 in **21**. Given the unique conformational preference of **10** or **18**,<sup>6,7,20</sup> these studies unequivocally support a urea-directed<sup>21,22</sup> Stork–Crabtree hydrogenation (see the box in Scheme 5).

The ultimate solution to this dilemma was high-pressure hydrogenation. At 1500 psi of H<sub>2</sub> and with Pt–Alumina in hexane, the desired pyran **12** was isolated and stereochemically confirmed by using NOE<sup>15</sup> (Scheme 6). Epimerization at C7 was still an issue for **12** but no longer relevant because the next step involved the C7-crotylation with concomitant removal of the urea group with SnBr<sub>4</sub>.<sup>20,23</sup> Addition of *E*- or

(21) For a review on directed reactions, see: (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, 93, 1307. (b) For a spotlight related to Crabtree's catalyst, see: Nell, P. G. *Synlett* **2001**, 160.

(22) For an amide directed hydroboration using Crabtree's catalyst, see: (a) Evans, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1991**, 113, 4042. (b) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, 114, 6671.

### Scheme 6. Key Hydrogenation and Crotylations

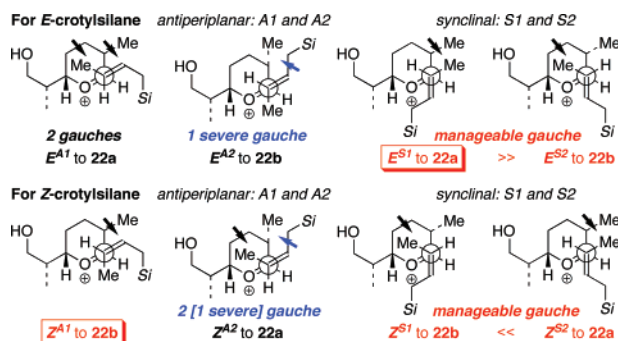


Z-crotylsilane to the oxocarbenium intermediate generated in situ (not shown) gave the crotylation products **22a** and **22b** in opposing ratios, and the TBDPS group was also lost in the process.

Successive oxidation of **22a/b** (as a 4:1 mixture) led to acids **23a** and **23b**, which could be separated. The X-ray structure of **23a** unambiguously confirmed all relative stereochemistry. The assignment of C8 in **23a** suggests that **22b** would be the desired crotylation product for the synthesis. The rationale for the stereochemical outcome in

(23) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168.

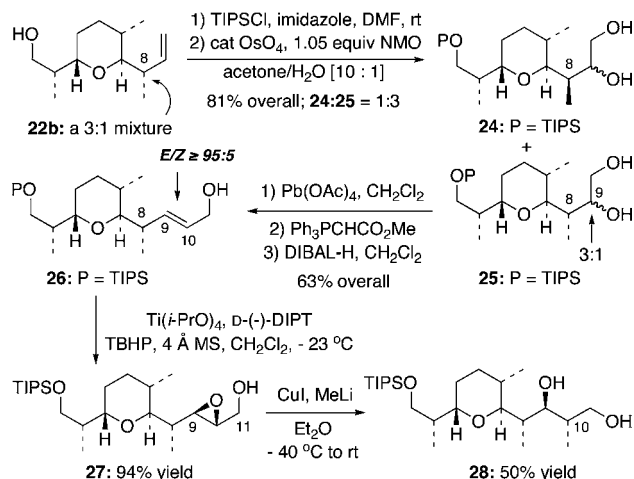
(24) In our C7-crotylations, when ruling out transition states from either the anti-periplanar or the synclinal approach with excessive **2** to severe gauche interactions, and when assuming an anomerically favored axial addition of *E*- or *Z*-crotylsilane, what is left behind would be a synclinal approach for the *E*-crotylation in which *E*<sup>SI</sup> is more favored in leading to **22a**, whereas both anti-periplanar and synclinal pathways could be at play for the *Z*-crotylation with *Z*<sup>AI</sup> playing a more dominant role to favor the formation of **22b**.



our C7-crotylation can be illustrated<sup>24</sup> employing Danishefsky's C3-crotylation model.<sup>3</sup>

To complete our formal synthesis, the crotylated pyran **22b** was carried on as a 3:1 isomeric mixture in a sequence of TIPS-protection and dihydroxylation, leading to diols **24** and **25**, which were readily separated (Scheme 7). Oxidative

### Scheme 7. Intercepting Miyashita's Advanced Intermediates



cleavage of **25** with Pb(OAc)<sub>4</sub> followed by a modified-Wittig olefination and DIBAL-H reduction provided allyl alcohol **26**. Sharpless asymmetric epoxidation of **26** gave epoxide **27**, and the subsequent directed epoxide ring-opening with Me-cuprate afforded alcohol **28**. Both **27** and **28** spectroscopically matched Miyashita's advanced intermediates.<sup>15</sup> Our synthetic sequence leading up to this point is comparable to Miyashita's approach.

We have described here a formal total synthesis of (+)-zincophorin through matching Miyashita's advanced intermediates. Our synthesis features a highly stereoselective hetero [4 + 2] cycloaddition of an allenamide and an unusual urea-directed Stork–Crabtree hydrogenation. This work provides the first application of chiral allenamides in natural product synthesis.

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**Supporting Information Available:** Experimental and <sup>1</sup>H NMR spectra and characterizations for all new compounds, as well as X-ray structural data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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