

"Synthesis of the 11-Membered Cytochalasin Ring System  
by Modified Reformatsky Cyclization"

E. Vedejs and S. Ahmad

S.M. McElvain Laboratory of Organic Chemistry

Chemistry Department, University of Wisconsin

Madison, WI 53706

Abstract. Zn or  $\text{SmI}_2$  cause cyclization of **7** to **8** which can be taken on to the cytochalasin **13**.

We report a convergent new route to carbocyclic cytochalasins<sup>1</sup> based on a Reformatsky cyclization to close an 11-membered ring. Combined with the method for introduction of the isoindolone substitution pattern described in the accompanying paper<sup>2</sup>, this approach allows facile access to the [11] cytochalasin **13**. The same carbon skeleton is present in such natural products as cytochalasin D and zygosporin E.<sup>1</sup> The overall strategy described below uses the Diels-Alder reaction of doubly activated N-benzoylpyrrolinone dienophiles developed in this laboratory<sup>3</sup>, together with the observation of Stork et al. that unsymmetrical trienes react selectively at the most substituted diene subunit.<sup>4</sup>

A synthesis of the required triene is described in the Scheme. The dienyl phosphate **2** (from the known alcohol **1**<sup>3b</sup> + BuLi and  $(\text{EtO})_2\text{POCl}$ ) was coupled with  $\text{LiPPh}_2$  followed by methylation ( $\text{CH}_3\text{I}$ ) to give the sensitive dienylphosphonium salt **3** which was used at once. Wittig reaction of the corresponding salt-free ylide ( $\text{KN}[\text{SiMe}_3]_2/\text{THF}$ ) with the aldehyde ester **4**<sup>5</sup> occurred with high E-selectivity (one isomer detected), characteristic of this phosphorus substitution pattern.<sup>6</sup> The desired triene aldehyde **5** was then obtained by controlled reduction with DIBAL in toluene, 65% overall from **1**.

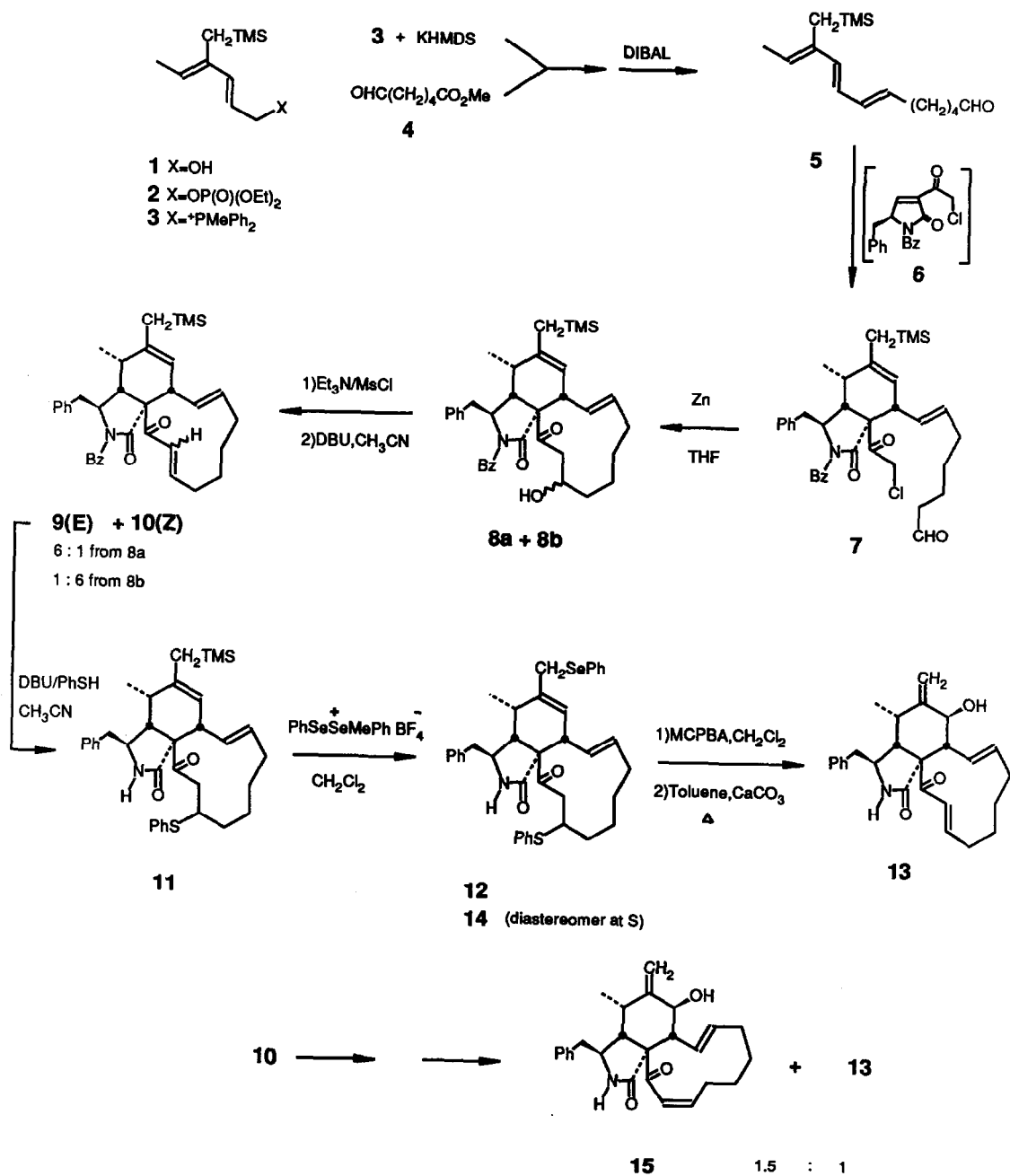
Diels-Alder reaction of triene **5** with the dienophile **6**<sup>3c</sup> (generated via selenoxide elimination) occurred smoothly at 25° to give a single major product (79% isolated) which is assigned the structure **7**. Extensive precedent and detailed NMR comparison with related adducts proved regio- and stereochemistry.<sup>3,7</sup> Slow addition of **7** to Rieke zinc<sup>8</sup> in THF then

gave the cytochalasin ring system in 75% yield. Two diastereomers **8a** and **8b** were isolated from this cyclization in a ratio of ca. 1:1. Similar product ratios were observed using Rieke zinc in benzene or in DMSO, but the yields were lower. On the other hand, treatment of **7** with  $\text{SmI}_2/\text{THF}$ <sup>9</sup> resulted in cyclization to a single major isomer **8b** (46% isolated). The stereochemistry of **8a/b** is not known with certainty, but the two isomers differ only with respect to hydroxyl stereochemistry according to observations outlined below.

Treatment of **8a** with  $\text{Et}_3\text{N}/\text{CH}_3\text{SO}_2\text{Cl}$  followed by  $\text{DBU}/\text{CH}_3\text{CN}$  afforded the E-enone **9** together with a small amount of the Z isomer **10** (9:10 = 6:1). Lactam deprotection with  $\text{DBU}/\text{C}_6\text{H}_5\text{SH}/\text{CH}_3\text{CN}$  occurred with simultaneous addition of mercaptan to the highly reactive enone, and gave **11** in 89% yield. Replacement of the allylic  $\text{SiMe}_3$  group by  $\text{SePh}$  was next achieved by reaction of **11** with the  $\text{PhSeSe}^+(\text{CH}_3)\text{Ph BF}_4^-$  selenenylating reagent,<sup>2</sup> resulting in the selenide **12**. When this substance was treated with 2 eq. of  $\text{MCPBA}/\text{CH}_2\text{Cl}_2$  at  $-78^\circ$  followed by warming to  $60^\circ$  in toluene  $+\text{CaCO}_3$ , the desired [11]-cytochalasin **13** was obtained in 91% yield.<sup>7</sup> At lower temperatures, an intermediate sulfoxide could also be detected, but both the selenoxide rearrangement and sulfoxide elimination were highly specific and eventually gave a single isomer **13**.

The other cyclization diastereomer **8b** could be taken through the same sequence, but with somewhat different results. Thus, mesylation and DBU treatment as before gave the Z-enone **10** as the major product (ratio of 10:9 = 6:1). Subsequent steps according to the same procedures used starting from **9** gave a selenide **14** (sulfur stereochemistry unknown, but different from that of **12**). When **14** was treated with 2 eq.  $\text{MCPBA}$  followed by heating at  $85^\circ$  (toluene,  $\text{CaCO}_3$ ), a new [11]-cytochalasin **15** was obtained together with the E isomer **13** (1.5:1 15:13).<sup>7</sup> This sequence proves that **8a** and **8b** differ only in hydroxyl stereochemistry. Since the yield of **13+15** from **8b** is 54%, the overall efficiency of the route from Diels-Alder adduct **7** to the trans enone **13** is 40%. Thus, substantial quantities of 11-membered cytochalasin carbocycles can readily be prepared.<sup>10</sup> Extension of the Reformatsky cyclization to more complex cytochalasins will be described in future publications.

Acknowledgement. This work was supported by the National Institutes of Health (CA17918).



## References.

1. "Cytochalasins, Biochemical and Cell Biological Aspects"; Tanenbaum, S.W., Ed.; North-Holland Publishing Co.: Amsterdam, 1978.
2. Vedejs, E.; Rodgers, J.D.; Wittenberger, S. *J. Tetrahedron Lett.* **1988**, *29*, preceeding.
3. a) Vedejs, E.; Gadwood, R.C. *J. Org. Chem.* **1978**, *43*, 376; b) Vedejs, E.; Campbell, J.; Gadwood, R.G.; Spear, K.L.; Rodgers, J.D.; Watanabe, Y. *J. Org. Chem.* **1982**, *47*, 1534; c) Vedejs, E.; Reid, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 4617.
4. Stork, G.; Nakamura, Y.; Greenlee, W.G. *J. Am. Chem. Soc.* **1978**, *100*, 7775.
5. Aldehyde **4** was prepared from caprolactone via methyl 6-hydroxyhexanoate (MeOH/NaOMe) followed by Swern oxidation.
6. Vedejs, E.; Huang Wen Fang *J. Org. Chem.* **1984**, *49*, 210.
7. Partial NMR (CDCl<sub>3</sub>); 200 MHz **7**:  $\delta$  9.70 (1H, s); 5.69 (1H, dd, J= 15.3, 9.6 Hz); 5.37-5.18 (2H, m); 4.33-4.24 (1H, m); 4.23 (1H, d, J= 17.4 Hz); 3.27 (1H, dd, J= 13.5, 6.3 Hz); 2.93 (1H, d, J= 17.4 Hz); 1.10 (3H, d, J= 7.1 Hz); 0.02 (9H, s). **8a**:  $\delta$  6.01 (1H, dd, J= 15.3, 6.7 Hz); 5.3-5.11 (2H, m); 4.35-4.25 (1H, m); 4.06-3.93 (1H, m); 3.66 (1H, dd, J= 18.3, 7.5 Hz); 3.03 (1H, dd, J= 16.0, 5.3 Hz); 2.93 (2H, d, J= 5.0 Hz); 1.01 (3H, d, J= 7.5 Hz); -0.04 (9H, s). **8b**: 500 MHz,  $\delta$  6.03 (1H, dd, J= 17.0, 10.5 Hz); 5.38-5.29 (1H, m); 5.25-5.20 (1H, m); 4.32-4.27 (1H, m); 3.01 (1H, dd, J= 12.9, 2.4 Hz); 2.84 (1H, dd, J= 12.9, 8.5 Hz); 1.01 (3H, d, J= 7.5 Hz); 0.01 (9H, s). **13**: mp 177-178 °C (cryst from CH<sub>2</sub>Cl<sub>2</sub>/hexane); 500 MHz NMR,  $\delta$  7.04 (1H, d, J= 16.0 Hz); 6.64 (1H, td, J= 7.2, 16.0 Hz); 5.82 (1H, dd, J= 9.7, 15.5 Hz); 5.47 (1H, br s); 5.29-5.22 (2H, m); 5.09 (1H, br s); 4.02 (1H, d, J= 10.2 Hz); 2.73 (1H, dd, J= 4.6, 15.3 Hz); 2.43 (1H, dd, J= 8.9, 15.3 Hz); 2.37 (1H, t, J= 10.0 Hz); 0.98 (3H, s). **15**: mp 203-204 °C (cryst from CH<sub>2</sub>Cl<sub>2</sub> /hexane); 200 MHz,  $\delta$  6.40-6.15 (2H, m); 6.24 (1H, dd, J= 2.4, 11.4 Hz); 6.06 (1H, dd, J= 9.8, 15.7 Hz); 5.53 (1H, br s); 5.22 (1H, br s); 5.04 (1H, br s); 0.94 (3H, d, J= 7.0 Hz). All compounds leading to **13** were characterized by high resolution mass spectrometry.
8. Arnold, R.T.; Kulenovic, S.T. *Synth. Commun.* **1977**, *7*, 223.
9. Reformatsky macrocyclization has previously been used to make lactones; Zn: Maruoka, K.; Hashimoto, S.; Kitagawa, Y.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 7705; Sm(II): Tabuchi, T.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3889.
10. For comparisons with other methods, see ref. 3c and references therein.

(Received in USA 5 January 1988)