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"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 SmI_2 cause cyclization of **7** to **8** which can be taken on to the cytochalasan **13**.

We report a convergent new route to carbocyclic cytochalasins[1] 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[2], this approach allows facile access to the [11] cytochalasan **13**. The same carbon skeleton is present in such natural products as cytochalasin D and zygosporin E.[1] The overall strategy described below uses the Diels-Alder reaction of doubly activated N-benzoylpyrrolinone dienophiles developed in this laboratory[3], together with the observation of Stork et al. that unsymmetrical trienes react selectively at the most substituted diene subunit.[4]

A synthesis of the required triene is described in the Scheme. The dienyl phosphate **2** (from the known alcohol **1**[3b] + BuLi and $(EtO)_2POCl$) was coupled with $LiPPh_2$ followed by methylation (CH_3I) to give the sensitive dienylphosphonium salt **3** which was used at once. Wittig reaction of the corresponding salt-free ylide ($KN[SiMe_3]_2$/THF) with the aldehyde ester **4**[5] occurred with high E-selectivity (one isomer detected), characteristic of this phosphorus substitution pattern.[6] 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**[3c] (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.[3,7] Slow addition of **7** to Rieke zinc[8] 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 SmI_2/THF[9] 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 Et_3N/CH_3SO_2Cl followed by DBU/CH_3CN afforded the E-enone **9** together with a small amount of the Z isomer **10** (**9:10** = 6:1). Lactam deprotection with DBU/C_6H_5SH/CH_3CN occurred with simultaneous addition of mercaptan to the highly reactive enone, and gave **11** in 89% yield. Replacement of the allylic $SiMe_3$ group by SePh was next achieved by reaction of **11** with the $PhSeSe^+(CH_3)Ph\ BF_4^-$ selenenylating reagent,[2] resulting in the selenide **12**. When this substance was treated with 2 eq. of MCPBA/CH_2Cl_2 at - 78 ° followed by warming to 60° in toluene +$CaCO_3$, the desired [11]-cytochalasan **13** was obtained in 91% yield.[7] 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. MCPBA followed by heating at 85° (toluene, $CaCO_3$), a new [11]-cytochalasan **15** was obtained together with the E isomer **13** (1.5:1 **15**:**13**).[7] 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.[10] Extension of the Reformatsky cyclization to more complex cytochalasins will be described in future publications.

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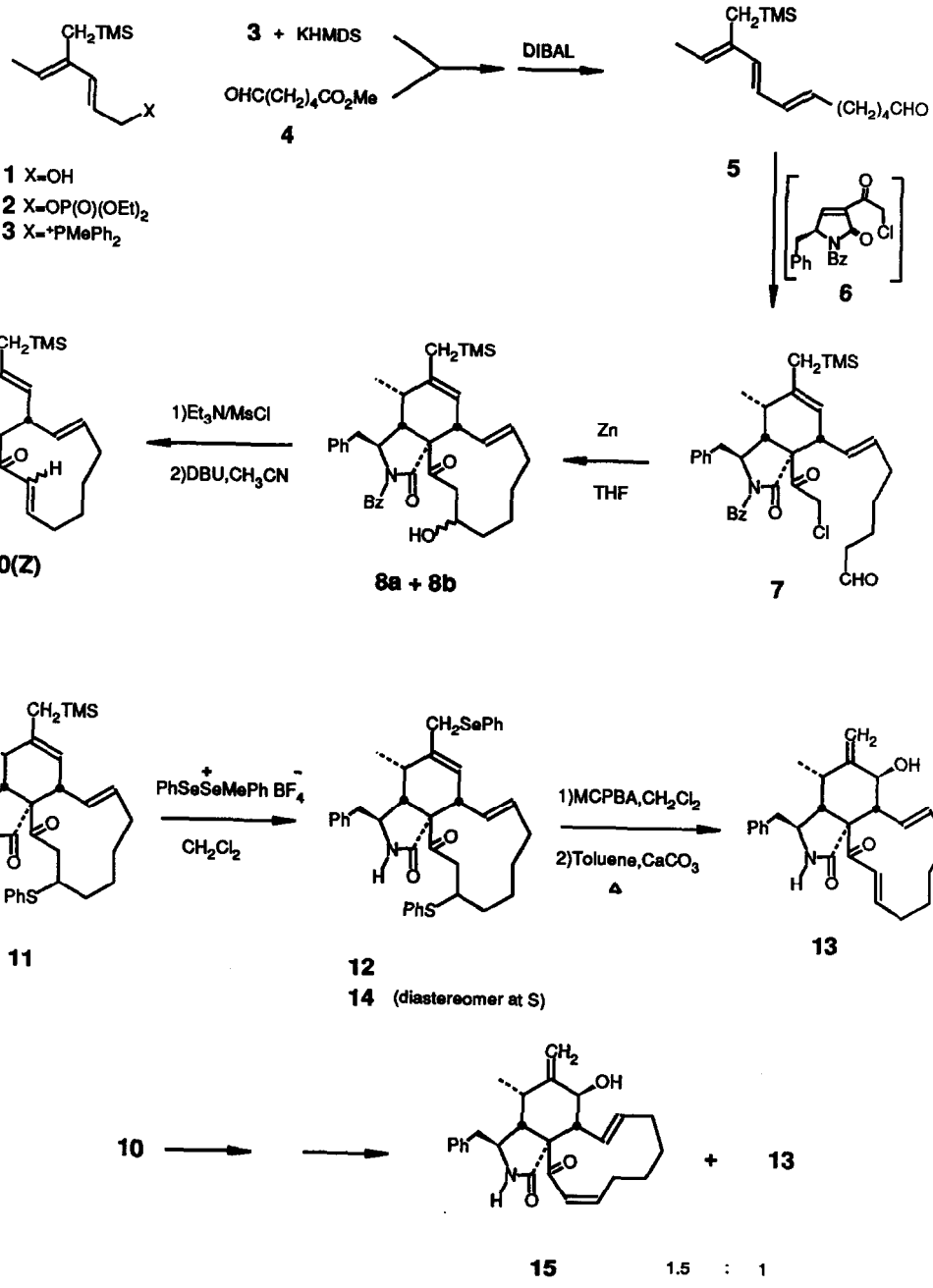
CH2TMS
X
3 + KHMDS
OHC(CH2)4CO2Me
4
DIBAL
(CH2)4CHO
1 X=OH
2 X=OP(O)(OEt)2
3 X=+PMePh2
5
Ph
N
Bz
O
Cl
6
1)Et3N/MsCl
2)DBU,CH3CN
Zn
THF
HO
8a + 8b
7
CHO
9(E) + 10(Z)
6 : 1 from 8a
1 : 6 from 8b
DBU/PhSH
CH3CN
11
PhSeSeMePh BF4
CH2Cl2
CH2SePh
12
14 (diastereomer at S)
1)MCPBA,CH2Cl2
2)Toluene,CaCO3
CH2
OH
13
10
15
1.5 : 1

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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 ($CDCl_3$); 200 MHz **7**: δ 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**: δ 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, δ 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_2Cl_2/hexane); 500 MHz NMR , δ 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_2Cl_2 /hexane); 200 MHz , δ 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.

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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.

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