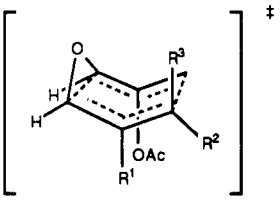
isomeric *cis*-2,3-divinyl epoxides **2d** and **2e**, the cis double bond isomer **2e** rearranged slower and in lower yield than the trans double bond isomer **2d**. This result is consistent with the boatlike transition state **8** for the rearrangement in which there appears to be greater steric congestion for a cis double bond (R^2 = H, R^3 = alkyl) than for a trans double bond (R^2 = alkyl, R^3 = H).[17]



8

The importance of *cis*-epoxide stereochemistry in these Cope rearrangements has also been demonstrated. *trans*-2,3-Divinyl epoxide **10** was prepared as shown in Scheme II by the same route used to prepare the *cis*-epoxides **2a–e**, except that the propargylic alcohol was reduced ($LiAlH_4$, Et_2O, 25 °C) to give mostly the *trans*-allylic alcohol **9**. *trans*-Epoxide **10** was stable to conditions (145 °C, 16 h) that would lead to the complete rearrangement of the corresponding *cis*-epoxide **2d**. Prolonged heating (180 °C, 16 h) of epoxide **10** under conditions that were found to leave oxepin **3d** unchanged led to two unidentified products.

In summary, we have developed an efficient five-step synthesis of 4,5-dihydrooxepins that features the Cope rearrangement of *cis*-2,3-divinyl epoxides. Our method for preparing the *cis*-2,3-divinyl epoxides has sufficient flexibility to allow for a variety of vinyl appendages to be incorporated into the 1,5-diene. Furthermore, the 4,5-dihydrooxepins produced are well functionalized to allow for the further elaboration of the ring system. These studies are in progress and will be reported in due course.

Acknowledgment. We thank the Robert A. Welch Foundation, the National Institutes of Health (GM40033-01), and the donors of the Petroleum Research Foundation, administered by the American Chemical Society, for their generous support of this research. Exact mass spectral data were obtained at the Michigan State University Mass Spectroscopy Facility, which is supported, in part, by a grant (DRR-00480) from the Biotechnology Research Branch, Division of Research Resources, National Institutes of Health.

Supplementary Material Available: Complete spectroscopic data (IR, ^1H and ^{13}C NMR, and MS) for all compounds and complete experimental details for the preparation of **1a**, **4a**, **5a**, **2a**, **3a**, **7**, and **9** (15 pages). Ordering information is given on any current masthead page.

(17) Because they are racemic and rearrange to a product with only one chiral center, epoxides **2d** and **2e** both give a racemic mixture of **3d** and **3e**. Based on this transition state model, potential chiral centers at C.4 and C.5 of the oxepin nucleus could be controlled by controlling the stereochemistry of either the epoxide or alkene functional groups of a homochiral 2,3-divinyl epoxide.

Total Synthesis of (+)-Latrunculin A

Amos B. Smith, III,* Ichio Noda, Stacy W. Remiszewski, Nigel J. Liverton, and Regina Zibuck

Department of Chemistry, the Laboratory for Research on the Structure of Matter, and the Monell Chemical Senses Center, University of Pennsylvania, Philadelphia, Pennsylvania 19104

Received April 20, 1990

Summary: The total synthesis of (+)-latrunculin A (1) has been achieved by a highly convergent and stereocontrolled route (longest linear sequence, 17 steps).

As a defense mechanism, the Red Sea sponge *Latrunculia magnifica* (Keller) emits a reddish fluid which causes fish to flee. This observation led Kashman et al. to isolate and characterize two architecturally novel toxins, termed latrunculin A (1) and B (2) (Scheme I),[1,2] which dramatically influence both mammalian and nonmammalian cells. Of particular importance, submicromolar quantities of 1 and 2 induce marked, reversible changes in cell morphology, disrupt the organization of microfilaments, and suppress microfilament-mediated processes during fertilization and early development.[1c,3] At the molecular level, latrunculin A binds reversibly to the cytoskeletal protein actin and inhibits actin polymerization.[3a] Thus, the latrunculins hold considerable promise as specific probes of actin-microfilament structure and function.[3]

In 1986, we disclosed the first total synthesis of (+)-latrunculin B (2).[4] Central to that endeavor was the development of a unified strategy for the preparation of latrunculins A and B as well as other congeners. Herein we describe the successful implementation of this plan, culminating in the total synthesis of (+)-latrunculin A.[5]

(1) (a) Neeman, I.; Fishelson, L.; Kashman, Y. *Marine Biol.* **1975**, *30*, 293. (b) Kashman, Y.; Groweiss, A.; Shueli, U. *Tetrahedron Lett.* **1980**, *21*, 3929. (c) Spector, I.; Shochet, N. R.; Kashman, Y.; Groweiss, A. *Science* **1983**, *219*, 493. (d) Groweiss, A.; Shueli, U.; Kashman, Y. *J. Org. Chem.* **1983**, *48*, 3512. (e) Kashman, Y.; Groweiss, A.; Lidor, R.; Blasberger, D.; Carmely, S. *Tetrahedron* **1985**, *41*, 1905. (f) Kashman, Y.; Lidor, R.; Brasberger, D.; Carmely, S. *Tetrahedron Lett.* **1986**, *27*, 1367. (g) Blasberger, D.; Green, D.; Carmely, S.; Spector, I.; Kashman, Y. *Tetrahedron Lett.* **1987**, *28*, 459. (h) Blasberger, D.; Carmely, S.; Cojocaru, M.; Spector, I.; Shochet, N. R.; Kashman, Y. *Justus Liebigs Ann. Chem.* **1989**, 1171.

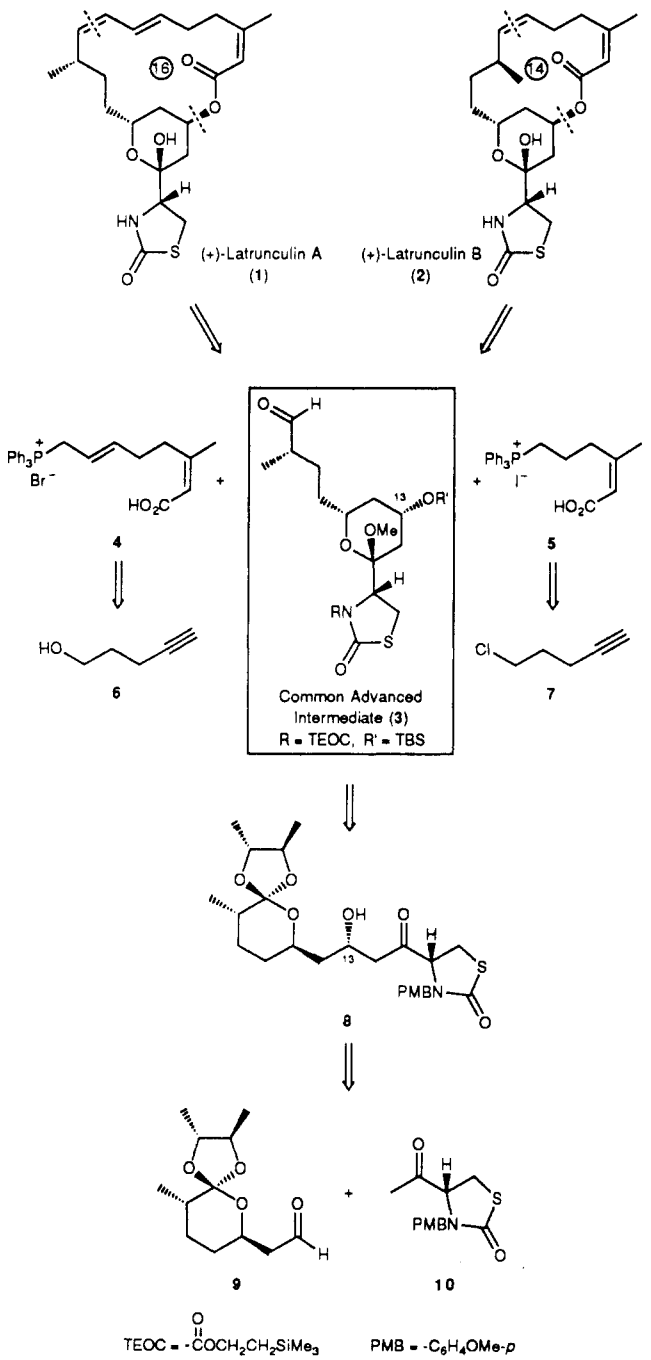
(2) Latrunculin A has more recently been found in the Pacific nudibranch *Chromodoris elisabethina* and in the Fijian sponge *S. mycofijiensis*; see, respectively: Okuda, R. K.; Scheuer, P. J. *Experientia* **1985**, *41*, 1355 and Kakou, Y.; Crews, P.; Bakus, G. J. *J. Nat. Prod.* **1987**, *50*, 482. Four congeners designated Latrunculins C, D, M, and 6,7-epoxylatrunculin A have also been isolated.[1e,h]

(3) For leading references, see: (a) Cone, M.; Breuner, S. L.; Spector, I.; Kom, E. D. *FEBS Lett.* **1987**, *13*, 316. (b) Schatten, G.; Schatten, H.; Spector, I.; Cline, C.; Paweletz, N.; Simerly, C.; Petzelt, C. *Exp. Cell Res.* **1986**, *166*, 191. (c) Spector, I.; Shochet, N. R.; Blasberger, D.; Kashman, Y. *Cell Motil. Cytoskeleton* **1989**, *13*, 127.

(4) Zibuck, R.; Liverton, N. J.; Smith, III, A. B. *J. Am. Chem. Soc.* **1986**, *108*, 2451. Also see: Smith, A. B., III; Zibuck, R.; Livertow, N. J. In *New Synthetic Methodology and Functionally Interesting Compounds*; Yoshida, Z., Ed.; Kodansha: Tokyo, 1986; Series in Organic Chemistry 25, pp 183–202.

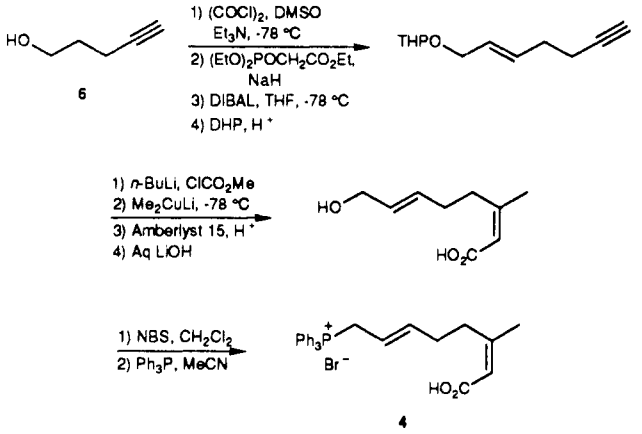
(5) Concurrent with our work, White and Kawasaki (Oregon State University) also completed a total synthesis of (+)-latrunculin A. We thank Professor White for informing us of his unpublished work.

Scheme I



From the retrosynthetic perspective, cleavage of the macrolide linkage in **1** and disconnection of the cis olefin lead to Wittig reagent (**4**)[6] and the common advanced intermediate, aldehyde **3** (Scheme I). Analysis of **3** in turn generates β-hydroxy ketone **8**, the aldol product of aldehyde **9** with ketone **10**. As performed in the latrunculin B synthesis,[4] this aldol reaction afforded **8** in modest yield (ca. 59%) with predominantly the S configuration at C(13) (4:1 mixture of diastereomers). This stereoselectivity dictated macrolactonization with inversion of configuration at C(13); for latrunculin B the Mitsunobu reaction proved ideal.[7] Accordingly, improvement of the aldol process and stereocontrolled formation of the cis–trans diene moiety

Scheme II



emerged as major objectives of the latrunculin A effort.

After considerable experimentation, the aldol addition of (−)-**10** to (−)-**9** was significantly improved by employing boron enolate technology.[8] Specifically, treatment of (−)-**10** (2.5 equiv) with *n*-Bu_2BOTf (3.2 equiv) and *i*-Pr_2NEt (3.0 equiv) in CH_2Cl_2 at −78 °C, followed by reaction with aldehyde (−)-**9** at −78 °C for 4 h, cleanly afforded (−)-**8** as the major component of an inseparable diastereomer mixture; although the isomer ratio remained only 3–4:1, the yield increased to 87%. Moreover, we were delighted to find that acid-catalyzed reorganization of the aldol mixture [THF–2 N HCl (5:1), room temperature, 24 h] effected equilibration of the C(13) stereocenter as well, delivering a 12.5:1 mixture of triol (+)-**11**[9a] and its C(13) epimer[9a] in 68–75% yield overall from (−)-**9**. This remarkable transformation presumably involves the intermediacy of oxonium ion **12**, thus exploiting and extending methodology developed in our earlier syntheses of talaromycins A and B.[10] Methanolysis of (+)-**11** [CSA (catalytic), CH_3OH–toluene] and protection (TBSCl, imidazole, DMAP, DMF) of the derived mixed ketal (+)-**13**[9a] then furnished bis(*t*-butyldimethylsilyl) ether (+)-**14**[9] (81%, two steps).

Aldehyde **3**, the requisite southern fragment, was best obtained 10 ester **14** via a reduction/oxidation sequence. At this juncture, the nitrogen protecting group also required exchange (PMB → TEOC).[11] Thus, reduction of (+)-**14** ($LiAlH_4$, THF, 0 °C), followed by removal of the PMB group according to the Williams protocol (*t*-BuLi, THF, −78 °C, then O_2),[12] gave alcohol (+)-**16**[9a] in 60% yield for the two steps. Oxidation (PCC/Al_2O_3)[13] and treatment of the resultant aldehyde [(+)-**17**][9a] with Me_3Si-

(6) For reviews on the Wittig olefination process, see: Trippett, S. *Q. Rev. Chem. Soc.* **1963**, *17*, 406. Maercker, A. *Org. React.* **1965**, *14*, 270.

(7) Mitsunobu, O. *Synthesis* **1981**, 1. Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, 2455.

(8) (a) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, Chapter 1. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. In *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; John Wiley & Sons: New York, 1982; Vol. 13, pp 1–116. (c) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(9) (a) The structure assignment for each new compound was in accord with its infrared and 500-MHz ^1H and 125-MHz ^{13}C NMR spectra as well as appropriate parent ion identification by high-resolution mass spectrometry. (b) In addition, an analytical sample of this new compound, obtained by recrystallization or chromatography (LC or TLC), gave satisfactory C and H combustion analysis within 0.4%.

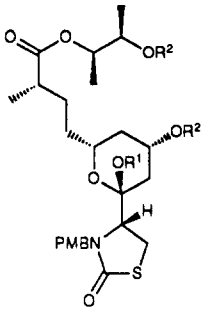
(10) Smith, A. B., III; Thompson, A. S. *J. Org. Chem.* **1984**, *49*, 1469. See also: Mrozik, H.; Eskola, P.; Arison, B. H.; Albers-Schönberg, G.; Fisher, M. H. *J. Org. Chem.* **1982**, *47*, 489. Similar equilibrations to 15 eq congeners observed by Kashman et al.[1h] can be explained in terms of oxonium ion **12**.

(11) We initially prepared *O*-methyl-*N*-(4-methoxybenzyl)latrunculin A but were unable to remove the nitrogen protecting group, in contrast with the latrunculin B synthesis wherein CAN was used successfully. The diene moiety presumably was responsible for this unanticipated difficulty.

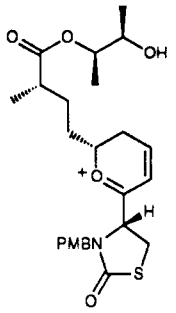
(12) Williams, R. M.; Kwast, E. *Tetrahedron Lett.* **1989**, *30*, 451.

(13) Cheng, Y.-S.; Liu, W.-L.; Chen, S. *Synthesis* **1980**, 223.

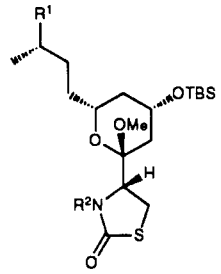
CH_2CH_2OCOCl (*i*-Pr_2NEt, DMAP, CH_2Cl_2)[14] then afforded (−)-**3**.[9a] The overall yield from **16** was 60%.



(+)-**11** $R^1 = R^2 = H$
(+)-**13** $R^1 = Me$, $R^2 = H$
(+)-**14** $R^1 = Me$, $R^2 = TBS$



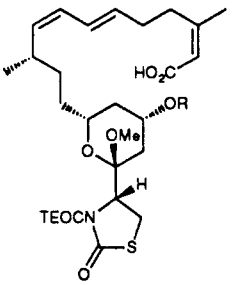
12



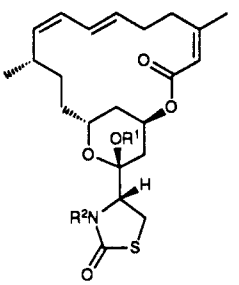
(+)-**15** $R^1 = CH_2OH$, $R^2 = PMB$
(+)-**16** $R^1 = CH_2OH$, $R^2 = H$
(+)-**17** $R^1 = CHO$, $R^2 = H$
(·)-**3** $R^1 = CHO$, $R^2 = TEOC$

The northern perimeter Wittig reagent (**4**)[9a] was prepared in 10 steps (30% overall yield) as outlined in Scheme II.

Wittig coupling[15] proceeded via generation of the dianion of **4** [2.0 equiv, with 3.8 equiv of $NaN(TMS)_2$, THF–HMPA (5:1)], followed by addition of aldehyde (−)-**3**, to furnish the desired cis–trans diene [(+)-**18**][9a] as a 7:1 mixture (80% yield). After removal of the TBS group [pyridine·$(HF)_x$, THF],[16] Mitsunobu macrocyclization of (+)-**19**[9a] (5.0 equiv of DEAD–Ph_3P, benzene)[7] provided lactone (+)-**20**[9a] (25% yield from **18**), which in turn was converted to (+)-latrunculin A (**1**) by removal of the TEOC group (*n*-Bu_4NF, 83%) and ketal hydrolysis [3 N HCl, THF (3:1)] (49% yield, 72% based upon recovered starting material). Synthetic latrunculin A was identical with the natural material by 500-MHz ^1H NMR, IR, TLC (three solvent systems), and chiroptical analysis.[17]



(+)-**18** R = TBS
(+)-**19** R = H



(+)-**20** $R^1 = Me$, $R^2 = TEOC$
(+)-**21** $R^1 = Me$, $R^2 = H$
(+)-**1** $R^1 = R^2 = H$

In summary, our route to latrunculin A is short (longest linear sequence, 17 steps) and highly convergent. Importantly, the aldol and reorganization–equilibration protocols described herein markedly increase the efficiency and stereoselectivity of our latrunculin B synthesis as well.[4] Full details of both synthetic ventures will be reported in due course.

Acknowledgment. Support for this work was provided by the National Institutes of Health (Institute of General Medical Sciences) through Grant GM-33833 and by Merck Sharp and Dohme Research Laboratories.

Supplementary Material Available: Spectroscopic data for **1**, **3**, **4**, **8**–**11**, **13**–**21** (6 pages). Ordering information is given on any current masthead page.

(14) Shute, R. E.; Rich, D. H. *Synthesis* **1987**, 346.
(15) (a) Schaaf, T. K.; Corey, E. J. *J. Org. Chem.* **1972**, *37*, 2922. (b) Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*; Academic: New York, 1977.
(16) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R.; Petasis, N. A. *J. Org. Chem.* **1979**, *44*, 4011.

(17) We thank Professor Hirama (Tohoku University) for a sample of natural latrunculin A, which was originally furnished by Professor Kashman (Tel Aviv University). In addition, we thank Professor Kashman for the high-field ^1H NMR spectrum of latrunculin A.