other contexts as well. Note that once the chiral auxiliaries are removed the ester (X = OEt) derived from exo *si* adduct **7d** corresponds to the minor diastereomer of reaction **3d** + (−)-**5** and visa versa. This relationship permitted us to set the diastereofacial selectivity of these cycloadditions at >25:1 by simply evaluting the level of cross-contamination of these two esters via ^{1}H NMR spectroscopy.

These results suggest that an efficient and enantioselective entry to the quinocarcin family of DNA-reactive alkaloids based on auxiliary controlled 1,3-dipolar cycloaddition is viable. Further work along these lines including confirmation of the proposed model for asymmetric induction is currently underway and will be reported on in due course.

Acknowledgment. This investigation was supported by Public Health Service Grant GM 38805 administered by the National Institute of General Medical Sciences.

Synthesis of Oxepins via the Cope Rearrangement of *cis*-2,3-Divinyl Epoxides

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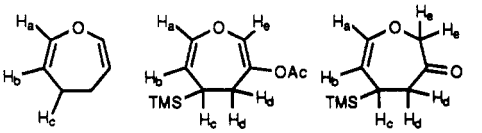
Summary: The Cope rearrangement of *cis*-2,3-divinyl epoxides, which may be readily prepared from enynols, provides a flexible and efficient route to the oxepin ring system.

The presence of the oxepin nucleus in a number of natural products of biological interest[1] has spurred the development of synthetic strategies for preparing this ring system.[2] One potentially attractive approach is the Cope rearrangement of divinyl epoxides, which leads to 4,5-dihydrooxepins through four-carbon ring expansion of the epoxide. The few reported examples of such rearrangements,[3] although supporting the viability of this approach, are mostly limited to a handful of symmetrically substituted substrates. To be truly useful, a general and efficient route to unsymmetrically substituted *cis*-2,3-divinyl epoxides, in particular those that are functionalized to allow for the further elaboration of the oxepin ring following the Cope rearrangement, is needed. We report herein a five-step synthesis of the 4,5-dihydrooxepins **3a–e** from readily available enynols **1a–e**[4] in which the key step is the [3,3] sigmatropic rearrangement of the *cis*-2,3-divinyl epoxides **2a–e**.

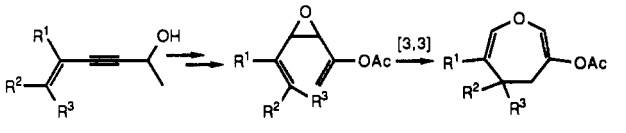
Table I. Assignment of ^{1}H NMR Data[a]



6 **3a** **7**

	6[b]	3a	7[c]
H_a	6.13 (d, 7.4)	6.17 (dd, 7.6, <1)	6.44 (dd, 6.6, 2.7)
H_b	4.82 (m)	4.85 (t, 7.6)	4.78 (ddd, 6.5, 3.5, 1)
H_c	2.30 (m)	1.79 (dtd, 7.6, 4.7, 0.7)	1.71 (dtd, 12.2, 3.6, 2.7)
H_d		2.84 (ddd, 16.4, 4.7, 1.8)	3.21 (t, 12.1)
		2.35 (dd, 16.4, 4.7)	2.52 (ddd, 12.2, 3.6, 1)
H_e		6.39 (d, 1.8)	4.36 (d, 17.6)
			4.32 (d, 17.6)

[a] ^{1}H NMR spectra were obtained at 200 MHz in $CDCl_3$. Chemical shifts are in ppm downfield from TMS calculated by using a shift of 7.26 ppm for $CHCl_3$ as an internal reference. All resonances are for one proton. Following the chemical shifts are the multiplicity and coupling constant(s) in hertz. [b] Reference 15. [c] Reference 16.



1a-e **2a-e** **3a-e**

a: R^1 = H, R^2 = TMS, R^3 = H. **b**: R^1 = Me, R^2 = R^3 = H. **c**: R^1 = R^2 = $-(CH_2)_4-$, R^3 = H. **d**: R^1 = H, R^2 = C_5H_{11}, R^3 = H. **e**: R^1 = R^2 = H, R^3 = C_5H_{11}.

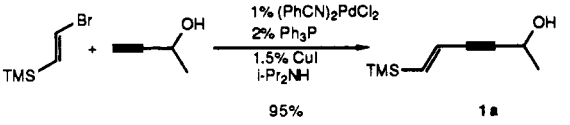
The sequence that was used to transform the enynols into oxepins is illustrated for enynol **1a** in Scheme I. Since

(1) For examples among marine natural products, see: Faulkner, D. J. *Nat. Prod. Rep.* **1984**, *1*, 251–84, 551–90; **1986**, *3*, 1–33; **1988**, *5*, 613–63.

(2) Via the cyclization of epoxy alcohols: (a) Chen, R.; Rowand, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 6609–11. (b) Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E. *J. Am. Chem. Soc.* **1980**, *102*, 6611–2. (c) Kocienski, P.; Love, C.; Whitby, R. *Tetrahedron Lett.* **1988**, *29*, 2867–70. (d) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335–40. Via the cyclization of dithiono esters: (e) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Reddy, K. B.; Marron, B. E.; McGarry, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 6800–2. (f) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1362–4. Via the reduction of mixed ketal derivatives: (g) Nicolaou, K. C.; Duggan, M. E.; Hwang, K.-C. *J. Am. Chem. Soc.* **1986**, *108*, 2468–9. (h) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Veale, C. A.; Furst, G. T. *J. Am. Chem. Soc.* **1987**, *109*, 2504–6. (i) Nicolaou, K. C.; Hwang, C.-K.; Nugiel, D. A. *J. Am. Chem. Soc.* **1989**, *111*, 4136–7. (j) Kotsuki, H.; Ushio, Y.; Kadota, I.; Ochi, M. *J. Org. Chem.* **1989**, *54*, 5153–61. Via the cyclization of an oxonium ion with a carbon nucleophile: (k) Cockerill, G. S.; Kocienski, P.; Threadgold, R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2093–100. (l) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911–3. (m) Molander, G. A.; Andrews, S. W. *J. Org. Chem.* **1989**, *54*, 3114–20. (n) Castañeda, A.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5695–707.

(3) (a) Braun, R. A. *J. Org. Chem.* **1963**, *28*, 1383–4. (b) Stogryn, E. L.; Gianni, M. H.; Passannante, A. J. *J. Org. Chem.* **1964**, *29*, 1275–6. (c) Vogel, E.; Günther, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 385–401. (d) Pommelet, J. C.; Manisse, N.; Chuche, J. *Tetrahedron* **1972**, *28*, 3929–41. (e) Balci, M.; Sütbeyaz, Y. *Tetrahedron Lett.* **1983**, *24*, 4135–8. (f) Sütbeyaz, Y.; Secen, H.; Balci, M. *J. Org. Chem.* **1988**, *53*, 2312–7.

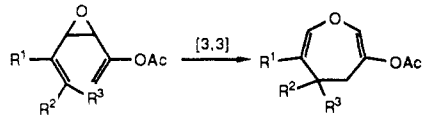
(4) For this study, 5-methyl-5-hexen-3-yn-2-ol (**1b**) was purchased from Farchan Laboratories. Enynol **1c** was prepared by the addition of the lithium acetylide of 1-ethynylcyclohexene (Aldrich Chemical Co.) to acetaldehyde. The remaining enynols, as illustrated for **1a**, were obtained in excellent yield via the Sonogashira reaction.[5]



95% **1a**

(5) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–70.

Table II. Cope Rearrangement of *cis*-2,3-Divinyl Epoxides 2a–e

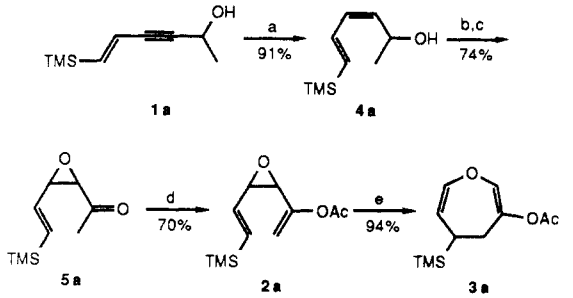


2a-e 3a-e

entry	R^1	R^2	R^3	temp, °C	time, h	yield,[a] %
a	H	TMS	H	135	12	94
b	Me	H	H	100	14	80
c		$-(CH_2)_4-$	H	150	2	80
d	H	C_5H_{11}	H	140	13	86
e	H	H	C_5H_{11}	150	26	61

[a] Isolated yield after silica gel chromatography.

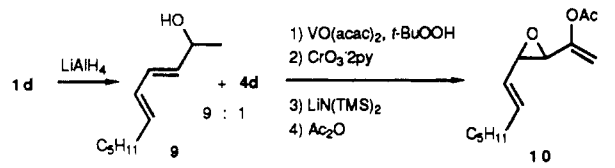
Scheme I[a]



[a] (a) 2.2 equiv of $ZnBr_2$, 4 equiv of K, THF, reflux 4 h; 1a, MeOH, reflux 15 min; H_2O, reflux 10 min; (b) $VO(acac)_2$, *t*-BuOOH, CH_2Cl_2, 0 °C, 3 h; (c) 6 equiv of CrO_3·2py, CH_2Cl_2, 25 °C, 25 min; (d) 3 equiv of $LiN(TMS)_2$, THF, −70 °C, 1 h; 3.5 equiv of Ac_2O, −70 °C, 15 min; (e) CCl_4, 12 h, 135 °C.

it was anticipated and later demonstrated that *trans*-2,3-divinyl epoxides would make inferior substrates for the Cope rearrangement, it was deemed necessary to reduce selectively the alkyne to the *cis*-alkene. It was discovered early in the model studies, however, that the more common methods for this reduction failed.[6] One alternative for the cis reduction of conjugated enynes to 1,3-dienes is zinc dust in a protic solvent system.[6b] These conditions led to high selectivity for cis reduction, but the yields were low. The yields could be improved by the addition of potassium cyanide, but this led to unacceptable mixtures of cis and trans dienols.[7] However, the use of highly activated Rieke zinc ($THF/MeOH/H_2O$)[8] led to the reduction of enynol **1a** in high yield (~100% crude, 91% after silica gel chromatography) and high selectivity (cis:trans > 15:1)[9] to provide dienol **4a**.[10] The allylic double bond was selectively epoxidized using either 2% $VO(acac)_2$/*t*-BuOOH[11] or peroxytrichloroacetimidic acid (Cl_3CCN/30% H_2O_2).[12] The diastereomeric mixture of epoxy alcohols was then oxidized to the epoxy ketone **5a** using Collins reagent.[14]

Scheme II



The synthesis of the 1,5-diene was completed by the conversion of the methyl ketone to an alkene derivative. For the initial study, an enol derivative was of greatest interest, since the Cope rearrangement generates a new enol derivative that would allow for the further functionalization of the oxepin ring. The lithium enolate of epoxy ketone **5a** was prepared by kinetic deprotonation ($LiN(TMS)_2$, THF, −70 °C), but the enolate itself did not undergo the Cope rearrangement. The enolate was stable below −30 °C and decomposed upon warming to room temperature. However, the enol acetate derived from the enolate (Ac_2O, −70 °C) cleanly rearranged upon heating (135 °C, CCl_4, 12 h) to 4,5-dihydrooxepin **3a** in 94% isolated yield. Particularly characteristic of the 4,5-dihydrooxepin nucleus is the ^1H NMR data of the enol ethers. The chemical shifts and coupling constants for **3a** are given in Table I along with the corresponding data for 4,5-dihydrooxepin (**6**)[3a,d,15] and oxepinone **7**.[16]

The enol acetates **2b–e** have also been prepared from the corresponding enynols **1b–e** by the same scheme used to synthesize **2a**. These *cis*-2,3-divinyl epoxides all underwent [3,3] sigmatropic rearrangement upon heating (100–150 °C) to give 4,5-dihydrooxepins **3b–e** in good yield (see Table II). Among these examples, *cis*-2,3-divinyl epoxide **2b**, which lacks an alkyl or silyl substituent at the terminus of the diene, rearranged under the mildest conditions, presumably due to lessened steric strain in the transition state. It was also observed that between the two

(6) For example, catalytic hydrogenation over Lindlar's catalyst of enynols **1b** or **1c** led to mixtures of *cis*- and *trans*-alkene, starting material, and products from over reduction. Such a result for conjugated enynes is precedented. For examples, see: (a) Marvell, E. N.; Tashiro, J. *J. Org. Chem.* **1965**, *30*, 3991–3. (b) Morris, S. G.; Herb, S. F.; Magidman, P.; Luddy, F. E. *J. Am. Oil Chem. Soc.* **1972**, *49*, 92–4.

(7) This result is consistent with the reported Zn/KCN reduction of a similar 4-en-2-ynol. See: Oppolzer, W.; Fehr, J.; Warneke, J. *Helv. Chim. Acta* **1977**, *60*, 48–58.

(8) These conditions have been used to reduce a conjugated enyne that contained a homopropargylic alcohol. See: Winter, M.; Näf, F.; Furrer, A.; Pickenhagen, W.; Giersch, W.; Meister, A.; Willhalm, B.; Thommen, W.; Ohloff, G. *Helv. Chim. Acta* **1979**, *62*, 135–9.

(9) Only in the Rieke zinc reduction of 5-methyl-5-hexen-3-yn-2-ol (**1b**) was there any significant amount (~5%) of the trans isomer. It was necessary to subject enynol **1e** to two consecutive batches of Rieke zinc to obtain complete reduction of the triple bond. Products from further reduction of the 2,4-dienols have not been observed.

(10) Satisfactory spectroscopic data (^1H and ^{13}C NMR, IR, MS) have been obtained for all new compounds. All compounds were judged to be >95% pure from their NMR spectra, and high resolution mass spectra have been obtained for **5a–e**, **2a**, **2c–e**, **3a**, and **3c–d**.

(11) Tanaka, S.; Yamamoto, H.; Nozaki, H.; Sharpless, K. B.; Michaelson, R. C.; Cutting, J. D. *J. Am. Chem. Soc.* **1974**, *96*, 5254–5.

(12) Arias, L. A.; Adkins, S.; Nagel, C. J.; Bach, R. D. *J. Org. Chem.* **1983**, *48*, 888–90. We have found that the use of an ultrasonic bath greatly accelerates this two-phase reaction. These conditions give somewhat lower yields than obtained from the Sharpless reaction, but higher diastereoselectivity (9:1 versus 2:1). Both epoxidation conditions led to the same major diastereomer. The epoxyalcohols were somewhat sensitive to silica gel and were best purified by flash chromatography[13] on Florisil.

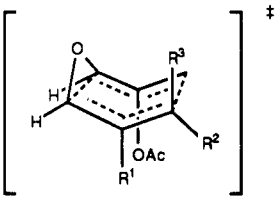
(13) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–5.

(14) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000–2.

(15) We have independently prepared 4,5-dihydrooxepin (**6**) (M.S. thesis of Yusheng Liao, The University of Texas at Arlington, 1989). Manuscript in preparation.

(16) Oxepinone **7** was obtained by saponification of oxepin **3a** (NaOMe/MeOH/0 °C).

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

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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.