Reaction of 3 with DIBAL. (4aS,7aR,11aR,12aR)-2,3,4a,5,7a,9,10,11,11a,12a-Decahydro-4a-methyl-1H-dipyrano[3,2-b:2',3'-g]oxocin (31). To a stirred solution of the sulfone **28** (20.0 mg, 0.09 mmol) in dry dichloromethane (1.0 mL) at −78 °C was added DIBAL (0.40 mL, 0.40 mmol, 1 M in hexanes) dropwise. After 15 min, the excess DIBAL was quenched carefully with methanol (1.0 mL), followed by dilution with ether (1.5 mL) and subsequent washing with 1 N HCl (2 × 5 mL) and brine (5 mL). Sequential drying ($MgSO_4$), concentration, and flash chromatography (silica, 5% → 10% ether in petroleum ether) afforded the *cis*-oxocene **31** (10.2 mg, 48%) and its trans isomer **29** (9.8 mg, 46%). **31**: oil; R_f = 0.26 (silica, 10% ether in petroleum ether); $[\alpha]^{21}_D$ +118.2° (*c* 0.28, $CHCl_3$); IR (neat) ν_{max} 3040, 2950, 2870, 1450, 1390, 1260, 1210, 1140, 1110, 1090, 1070, 1020, 995, 970, 945, 895, 870, 825, 800, 710 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 6.50 (dd, *J* = 11.4, 5.0 Hz, H-6), 5.88 (m, 1 H, H-7), 4.46 (m, 1 H, H-5), 4.03 (m, 1 H, H-10), 3.92 (ddd, *J* = 10.0, 3.7, 3.4 Hz, 1 H, H-4), 3.52-3.30 (m, 4 H, H-1 and H-13), 2.44 (dd, *J* = 13.6, 8.6 Hz, 1 H, H-8), 2.30 (dd, *J* = 13.6 and 7.6 Hz, 1 H, H-8), 1.63-1.14 (m, 8 H, CH_2), 1.20 (s, 3 H, CH_3); ^{13}C NMR (50.3 MHz, C_6D_6) δ 132.4 and 128.4 (C-7 and C-8), 76.2, 74.8, 70.2, 63.1, and 60.5 (C-1, C-4, C-5, C-10, and C-13), 40.2 (C-8), 27.6, 27.1, 26.7, and 25.3 (C-2, C-3, C-11, and C-12), 16.7 (CH_3); HRMS calcd for $C_{14}H_{22}O_3$ $(M)^+$ 238.1569, found 238.1554.

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Supplementary Material Available: Data for compounds **33-51** (R_f values, $[\alpha]_D$, IR, ^1H NMR, and MS data) and X-ray crystallographic data for compounds **28** and **51** (11 pages). Ordering information is given on any current masthead page.

Activation of 6-Endo over 5-Exo Hydroxy Epoxide Openings. Stereoselective and Ring Selective Synthesis of Tetrahydrofuran and Tetrahydropyran Systems

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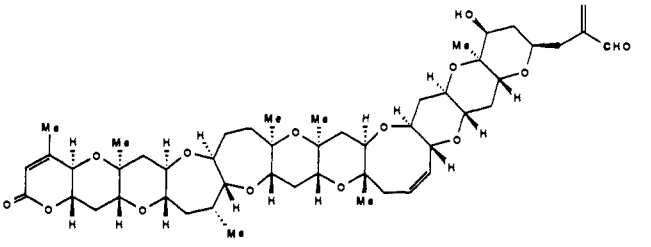
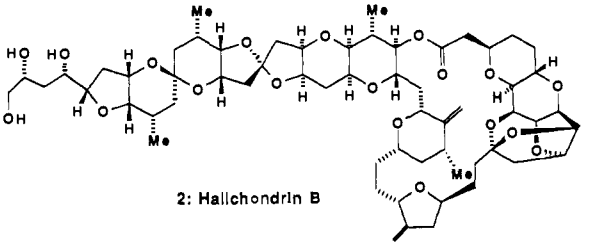
Abstract: A well-defined and predictable route to tetrahydrofurans and tetrahydropyrans is described. The method relies on stereo- and regioselective opening of hydroxy epoxides by acid catalysis. The presence of a saturated chain at the remote (from the hydroxy group) secondary epoxide position leads, as expected, to tetrahydrofuran systems, whereas the placement of an electron-rich double bond at that position leads to the formation of the tetrahydropyran systems. The resulting racemic or optically active systems contain useful functional groups for further elaboration. Reiteration of the sequence provides access to bi- and polycyclic oxaring systems in a predictable way.

Due to their common occurence in nature,[1] O-heterocycles are frequent and important targets for synthesis either as final products or as useful synthetic intermediates. Of particular importance are the ubiquitous tetrahydrofurans and tetrahydropyrans, toward the synthesis of which much work has been done.[2,3] Among recent examples in this field are the elegant contributions of Danishefsky,[4] Still,[5] Schreiber,[6] Hoye,[7] Bartlett,[8] Kozikowski,[9] Simmons,[10] Paquette,[11] Overman,[12] Robinson,[13] Paterson,[14] and Kishi.[15,16] In



1: Brevetoxin B



2: Halichondrin B

connection with a program directed toward the total synthesis of marine natural products such as brevetoxins B (**1**)[17] and halichondrin (**2**),[18] we were in need of stereospecific methods for the

(1) For some recent reviews, see (a) natural products: Faulkner, D. J. *Nat. Prod. Rep.* **1986**, *3*, 1; **1984**, *1*, 251, 551. (b) *Polyether Antibiotics: Naturally Occurring Acid Ionophores*; Westley, J. W., Ed.; Marcel Dekker: New York, 1982. (c) Moore, R. E. *Marine Natural Products: Chemical and Biological Perspectives*, Scheuer, P. J., Ed.; Academic Press: New York, 1978, Vol II.

(2) For recent reviews, see: (a) Boiuin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (b) Rao, A. S.; Paknikar, S. K. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323.

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(5) Still, W. C.; Romero, A. G. *J. Am. Chem. Soc.* **1986**, *108*, 2105.

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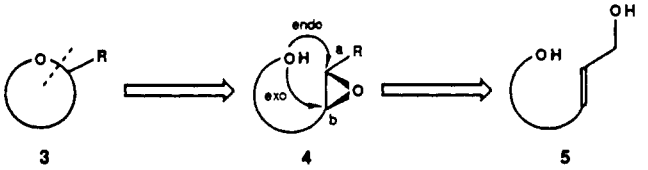
(16) See also Wuts, P. G. M.; D'Costa, R.; Butler, W. *J. Org. Chem.* **1984**, *49*, 2582 and references cited therein.

0002-7863/89/1511-5330$01.50/0

Scheme I



3 4 5

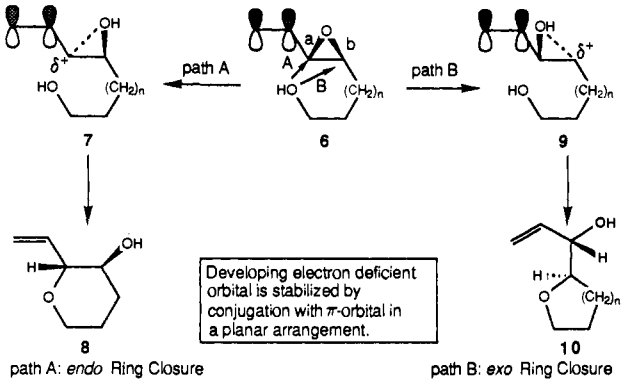
construction of oxaring systems of common and medium ring sizes (5–9-membered). In this series of papers we report our systematic approaches toward these systems. Beginning with this paper we describe a stereocontrolled and flexible synthesis of substituted 5- and 6-membered O-heterocycles.[19]

Results and Discussion

Strategy. Searching for a solution to the construction of the tetrahydropyran systems such as those found in the brevetoxins and halichondrins, we focused on the intramolecular hydroxy epoxide opening and the Sharpless asymmetric epoxidation[20] reactions as the key operations to deliver optically active materials as depicted in Scheme I. Specifically our stategy reduced the problem of cyclic ether **3** formation to (i) allylic alcohol formation, (ii) epoxidation, and (iii) intramolecular epoxide opening. While, at the outset of this work, solutions to operations (i) and (ii) existed, a well-defined and reliable method for the regio- and stereoselective opening of epoxides by internal nucleophilic oxygen was absent. As seen in Scheme I, structure **4**, this problem is one of driving the reaction in the endo or the exo mode of attack,[21] at carbons a or b, respectively, in a selective fashion. The concept on which we relied to achieve this selectivity is shown in Scheme II, which depicts a scenario of an acid-catalyzed cyclization of hydroxy epoxide **6**. According to this concept a π-orbital is placed adjacent to the epoxide unit and acts as an activator of the C–O bond adjacent to it, which then proceeds to rupture selectively. In this scenario, an endo ring closure would proceed to produce the heterocycle **8**, via transition state **7**, in which the developing electron-deficient orbital on carbon a would be stabilized by electron donation from the adjacent π-orbital in a parallel arrangement. The alternative pathway of exo ring closure, leading to the smaller ring **10**, and proceeding via transition state **9** in which the incipient positive charge would accumulate on carbon b, was expected to be less favorable. In a base-induced ring closure, **7** (Scheme II) is also expected to lead selectively to the endo product **8** rather than the exo product **10** as can be deduced by analogous arguments. On the other hand, in the absence of the π-orbital, both acid- or base-induced ring closures were expected to lead to the smaller ring, exo product **10** on the basis of better antiparallel alignment of the incipient and rupturing bonds. Previously recorded observations[22] were in line with these expectations.

Taking advantage of the Sharpless asymmetric epoxidation, the designed technology (Scheme I, 5-/6-membered rings) could lead selectively to any one of the eight possible isomers **11–18** shown in Scheme III. Thus, by varying the geometry of the double bond in the allylic substrate **5**, the stereochemistry of the epoxide **4**, and the nature of the substituent R, one could, in principle, be able to produce any desired target from the series **11–18** at will and in optically active form. As the investigations showed, the above strategy proved extremely powerful, particularly in the exploitation of the ring openings of trans epoxides producing

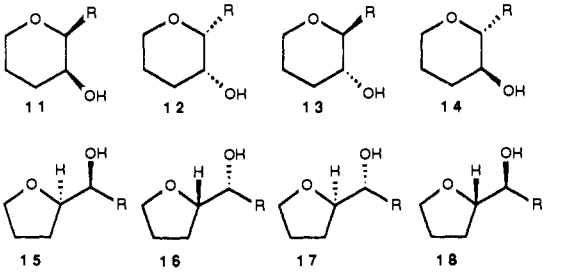
Scheme II



7 6 9 8 10

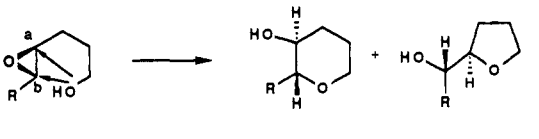
path A: *endo* Ring Closure path B: *exo* Ring Closure

Scheme III



11 12 13 14 15 16 17 18

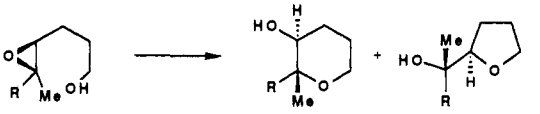
Table I. Acid-Catalyzed Cyclization of Trans Hydroxy Epoxides



19 20 21

a: 6-*endo* b: 5-*exo*

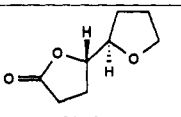
Entry	Substrate	Conditions	Products(Ratio)	yield(%)
1	**19a**:R=$CH_2CH_2CO_2Me$	0.1 equiv CSA CH_2Cl_2, -40 to 25 °C	**20a:21a**(0:100)[a]	94
2	**19b**:R=E-CH=$CHCO_2Me$	"	**20b:21b**(60:40)	96
3	**19c**:R=$CH=CH_2$	"	**20c:21c**(100:0)	95
4	**19d**:R=$CH=CBr_2$	"	**20d:21d**(100:0)	90



22 23 24

5	**22a**:R=E-CH=$CHCO_2Me$	"	**23a:24a**(66:34)	92
6	**22b**:R=$CH=CH_2$	"	**23b:24b**(100:0)	96

[a]Isolated as the γ-lactone (**21a-lactone**)



21a-lactone

monocyclic and bicyclic systems with high stereoselectivity and ring selectivity.

Cyclization Reactions

Table I exhibits the results of the acid-catalyzed cyclizations of a number of trans hydroxy epoxides. Acid catalysis was determined to be superior to base-catalyzed cyclizations; camphorsulfonic acid (CSA) was proven to be a convenient and highly efficient catalyst for these reactions. Thus, the hydroxy epoxide **19a**, upon treatment with catalytic amounts of CSA (0.1 equiv) in CH_2Cl_2 at −40 to 25 °C gave exclusively and in high yield (94%) the tetrahydrofuran system **21a** by 5-exo ring closure as expected. Substrates **19b–d** were expected to show increasing ability to favor the 6- over the 5-membered ring on electronic grounds as discussed above. Indeed, **19b** exhibited partially the expected effect leading

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(19) For a preliminary communication, see: Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K.; Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359.
(20) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, 102, 5976. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
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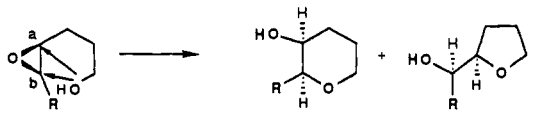
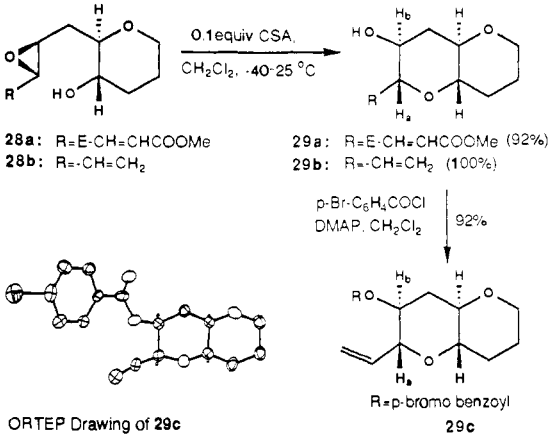
Table II. Acid-Catalyzed Cyclization of Cis Hydroxy Epoxides.



25 26 27
a: 6-*endo* b: 5-*exo*

Entry	Substrate	Conditions	Products (Ratio)	Yield (%)
1	**25a**: R=E-CH=CHCO$_2$Me	0.1 equiv CSA, CH_2Cl_2, -40 to 25 °C	**26a**:**27a** (0:100)	86
2	**25b**: R=CH=CH$_2$	"	**26b**:**27b** (44:56)	95
3	**25c**: R=E-CH=CHCl	"	**26c**:**27c** (76:24)	94
4	**25d**: R=Z-CH=CHCl	"	**26d**:**27d** (33:67)	92
5	**25e**: R= C≡CBr	"	**26e**:**27e** (0:100)	87

Scheme IV

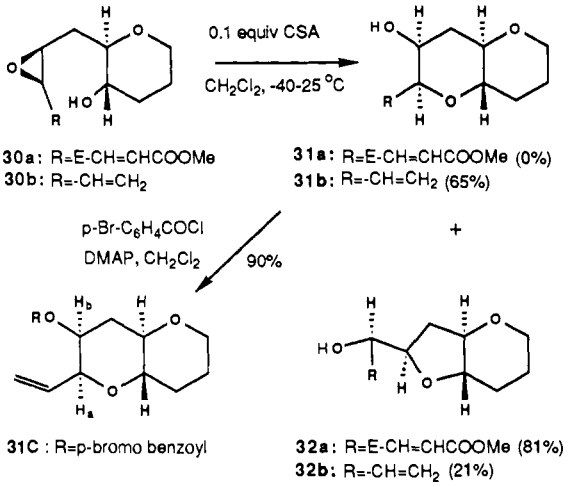


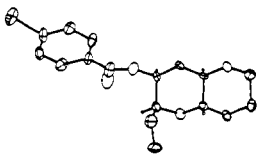
to a ca. 60:40 mixture of tetrahydropyran and tetrahydrofuran systems **20b–21b** in excellent yield (96%), whereas **19c** and **19d** produced exclusively and in high yield the corresponding tetrahydropyran systems **20c** (95%) and **20d** (90%). Further substitution at carbon b (structure **22**, Table I) can be tolerated and in certain cases enhances the selectivity as expected. Thus, the methyl-substituted epoxide **22a** led to a ca. 66:34 mixture at compounds **23a** and **24a**, whereas epoxide **22b** gave exclusively the tetrahydropyran system **23b**. All cyclized products described in this work were acetylated and isolated as their acetates by flash or preparative layer (PL) chromatography. ^{1}H NMR spectroscopic analysis of the acetate derivatives (decoupling experiments and coupling constants) assisted in the structural and stereochemical assignments of the products.

Table II presents the results of acid-catalyzed cyclizations of a series of cis epoxides. Under the same conditions utilized for the trans hydroxy epoxide (0.1 equiv of CSA, CH_2Cl_2, -40 to 25 °C), the cis isomer **25a** led exclusively to the 5-membered ring **27a** (86% yield). Apparently, the cis epoxide stereochemistry disfavors the 6-endo ring closure despite the presence of the π-orbital in substrate **25a**. This tendency is manifested in the remaining examples included in Table II, with the highest diversion into the 6-membered ring system attained in entry 3 with the *E*-chloro olefin **25c**. Difficulties of these systems to assume planar arrangements necessary for maximum stabilization in the transition state and steric interactions may be responsible for the low selectivities toward the tetrahydropyran systems. Interestingly, the acetylenic substrate **25e** (entry 5, Table II) led exclusively to the 5-membered ring system **27e** (87% yield).

In order to explore the scope of the hydroxy epoxide openings in the construction of bicyclic systems, we synthesized the substrates shown in Schemes IV–VI and investigated their acid-catalyzed cyclizations. The results were quite interesting and led to some rather selective avenues to a number of O-heterocycles. Thus the trans epoxides **28a** and **28b** (Scheme IV) with a preexisting trans junction were both exclusively converted to the

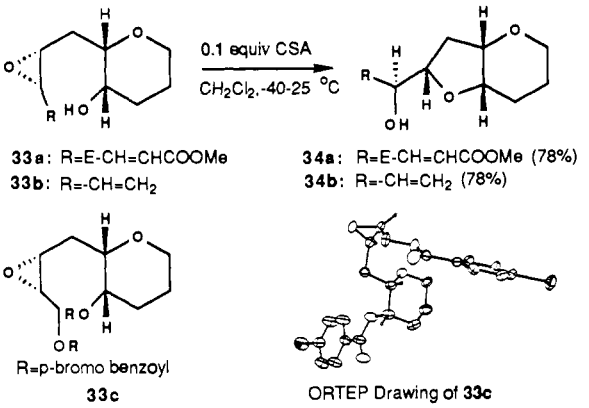
Scheme V





ORTEP Drawing of **31c**

Scheme VI



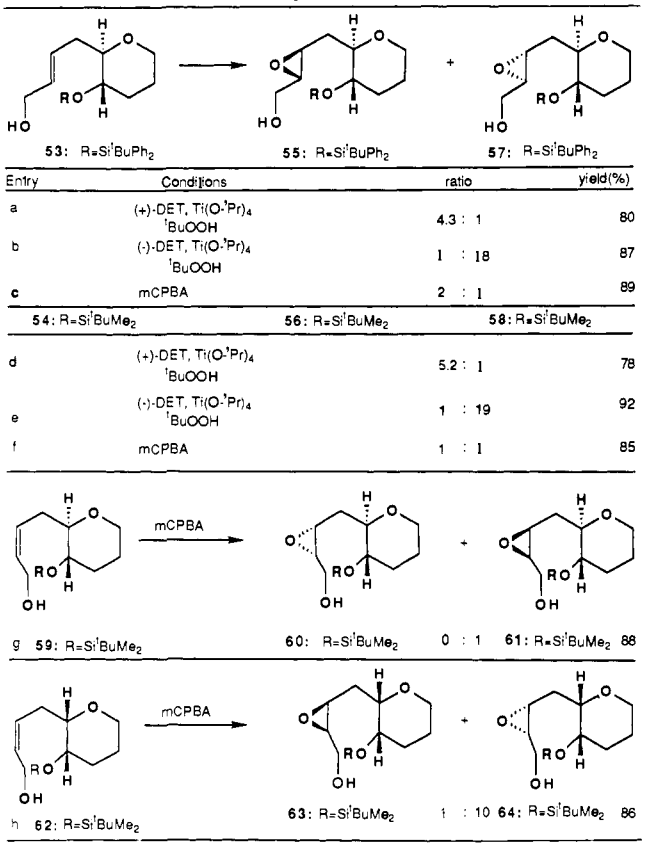
ORTEP Drawing of **33c**

bicyclic systems **29a** (92%) and **29b** (100%), respectively, under the standard acid-catalyzed conditions (CSA, CH_2Cl_2, $-40 \rightarrow 25$ °C). Just as the ring closures described above, these cyclizations were accompanied by inversion of stereochemistry at the carbon undergoing nucleophilic attack as expected and as supported by the coupling constant $J_{a,b} = 8.5$ Hz, found in the acetate of **29a** and the *p*-bromobenzoate **29c** derived from **29b**. An X-ray crystallographic analysis of **29c** confirmed these stereochemical assignments (see ORTEP drawing, Scheme IV).

The cis epoxide **30a** with the preexisting trans junction on the 6-membered ring (Scheme V) led, upon acid catalysis, to the 6,5-bicycle **32a** in 81% yield with no detectable amounts of the corresponding 6,6-bicycle **31a**. From molecular models, it appears that the 6-endo pathway leading to the corresponding 6,6-bicyclic system suffers from serious steric interactions in the transition state. Substrate **30b** with a more electron-rich double bond, however, led, under the same conditions, to a mixture of 6,6- and 6,5-bicyclic systems **31b** and **32b** (86% total yield, **31b**:**32b** ca 75:25 ratio). *p*-Bromobenzoate **31c** was prepared from **31b** by standard conditions (Scheme V). A coupling constant for $J_{a,b}$ in **31c** of 5.9 Hz suggested its stereochemistry which was confirmed by an X-ray crystallographic analysis (see ORTEP drawing of **31c**, Scheme V).

The cis epoxides **33a** and **33b** with the preexisting cis junction on the 6-membered ring (Scheme VI) were finally investigated

Table III. Selectivities in the Epoxidations of **53**, **54**, **59**, and **62**

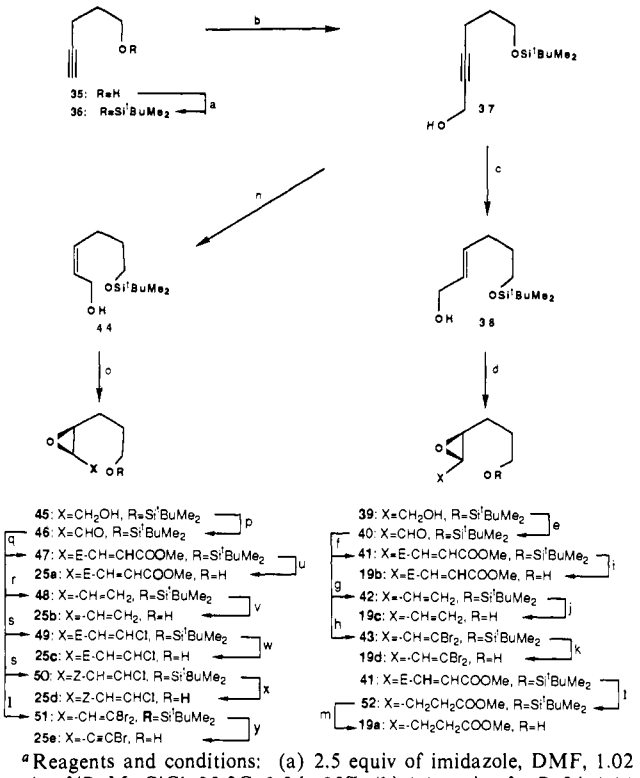


Entry	Conditions	ratio	yield(%)
a	(+)-DET, Ti(O-^{i}Pr)$_4$ ^{t}BuOOH	4.3 : 1	80
b	(-)-DET, Ti(O-^{i}Pr)$_4$ ^{t}BuOOH	1 : 18	87
c	mCPBA	2 : 1	89
	54: R=Si^{t}BuMe$_2$ **56**: R=Si^{t}BuMe$_2$	**58**: R=Si^{t}BuMe$_2$	
d	(+)-DET, Ti(O-^{i}Pr)$_4$ ^{t}BuOOH	5.2 : 1	78
e	(-)-DET, Ti(O-^{i}Pr)$_4$ ^{t}BuOOH	1 : 19	92
f	mCPBA	1 : 1	85
g	**59**: R=Si^{t}BuMe$_2$	**60**: R=Si^{t}BuMe$_2$ 0 : 1 **61**: R=Si^{t}BuMe$_2$	88
h	**62**: R=Si^{t}BuMe$_2$	**63**: R=Si^{t}BuMe$_2$ 1 : 10 **64**: R=Si^{t}BuMe$_2$	86

as precursors to bicyclic systems. Under the acid-catalyzed conditions both hydroxy epoxides led to 6,5-systems (**34a** and **34b**, respectively) in 78% yield. Inspection of the halichondrin B structure reveals the presence of a number of 6,5-bicyclic subunits resembling **34a** and **34b**. Applications of this technology to substructures of this marine natural product have, therefore, considerable potential. The stereochemistry of the epoxide moiety in **33a** and **33b** was secured by X-ray crystallographic analysis of the bis(*p*-bromobenzoate) **33c** (see ORTEP drawing, Scheme VI) obtained from the diol corresponding to **64** (R = H, Table III). The synthesis of this and the other hydroxy epoxides utilized in this work is discussed below.

Synthesis of Hydroxy Epoxides. The hydroxy epoxides **19a–d** (Table I) and **25a–e** (Table II) were synthesized either from the mono *tert*-butyldimethylsilyl ether of 1,4-butanediol or 1-pentyn-5-ol as summarized in Scheme VII. Compounds **22a,b** (Table I) were also obtained from the mono silyl ether of 1,4-butanediol as described elsewhere.[23] The epoxides were obtained in either racemic (**19a,b,d**, **25a–e**, mCPBA) or optically active (**19c**, Sharpless asymmetric epoxidation) forms. The methods used in Scheme VII to synthesize the desired hydroxy epoxides were similar to those utilized to prepare the corresponding homologues[24] of these compounds and, therefore, will not be discussed further here. The optically active tetrahydropyran system **20c** (Table I) was utilized to prepare the trans allylic alcohol **53** (Table III, (i) silylation, (ii) hydroboration, (iii) Swern oxidation, (iv) Wittig olefination, and (v) DIBAL reduction) which in turn served as precursor to epoxides **28a,b** (Scheme IV, (i) Sharpless epoxidation, (ii) Swern oxidation, (iii) Wittig olefination, and (iv) desilylation). The same tetrahydropyran **20c** (Table I) served as a precursor to the cis epoxides **30a,b** (Scheme V) via compound **59** (Table III, (i) silylation, (ii) hydroboration, (iii) Swern oxidation, (iv) dibromoolefination, (v) acetylide formation–carboxymethylation, (vi) DIBAL reduction, and (vii) Lindlar hydrogenation) and **61**

Scheme VII[a]



[a] Reagents and conditions: (a) 2.5 equiv of imidazole, DMF, 1.02 equiv of ^{t}BuMe$_2$SiCl, 25 °C, 0.5 h, 95%; (b) 1.1 equiv of n-BuLi, 1.14 equiv $(CH_2O)_n$, THF, 40 °C, 0.5 h, 75%; (c) 3.3 equiv of REDAL, ether, 0–25 °C, 3 h, 76%; (d) 1.2 equiv of mCPBA, CH_2Cl_2, 0 °C, 0.5 h, 83%; (e) 4.0 equiv of SO_3·pyr, 5.0 equiv of Et_3N, DMSO–CH_2Cl_2 (1:1), 0.5 h, 90%; (f) 1.5 equiv of Ph_3P=CHCOOMe, benzene, 0.5 h, 80%; (g) 1.7 equiv of $NaN(SiMe_3)_2$, 1.7 equiv of $Ph_3P^+CH_3Br^-$, 0 °C, THF, 0.5 h, 88%; (h) 2.3 equiv of CBr_4, 4.6 equiv of PPh_3, CH_2Cl_2, −78 °C, 20 min, 78%; (i) 1.5 equiv of $^nBu_4N^+F^-$, THF, 25 °C, 1.5 h, 90%; (j) same as i, 92%; (k) same as i, 88%; (l) 3.0 equiv of KO_2C-N=CO_2K, 2.4 equiv of AcOH, pyr, 25 °C, 12 h, 80%; (m) same as i, 85%; (n) 10 wt % of 10% Pd–$CaCO_3$, 0.07 equiv of quinoline, H_2, 6 h, 98%; (o) 1.3 equiv of mCPBA CH_2Cl_2, 0 °C, 12 h, 81%; (p) 4.0 equiv of SO_3·pyr, 5.0 equiv of Et_3N, DMSO–CH_2Cl_2 (1:1), 0.5 h, 90%; (q) 1.6 equiv of Ph_3P=CHCOOMe, benzene, 2 h, 81%; (r) 2.2 equiv of $CH_3P^+Ph_3Br^-$, 2.0 equiv of $NaN(SiMe_3)_2$, THF, 0 °C, 1 h, 92%; (s) 2.2 equiv of $ClCH_2P^+Ph_3Cl^-$, 2.0 equiv of $NaN(SiMe_3)_2$, THF, 0 °C, 2 h, 76%; (t) 2.0 equiv of CBr_4, 4.0 equiv of PPh_3, −78 °C, 78%; (u) same as i, 86%; (v) same as i, 92%; (w) same as i, 94%; (x) same as i, 94%; (y) 3.0 equiv of $^nBu_4N^+F^-$, THF, 25 °C, 89%.

(Table III, (i) Swern oxidation, (ii) Wittig olefination, and (iii) desilylation). The cis epoxides **33a,b** (Scheme VI) with the cis junction on the tetrahydropyran system were prepared by analogous methods via cis allylic alcohol **62** (Table III).

Table III summarizes some interesting results of epoxidation studies on allylic alcohols **53**, **54**, **59**, and **62**. As can be seen, the two enantiomers of diethyltartrate lead to different degrees of selectivity in the Sharpless asymmetric epoxidation of the trans allylic alcohols **53** and **54** (entries a and b, d and e) due to the influence of the optically active tetrahydropyran system. Whereas, the mCPBA epoxidation of either **53** or **54** was essentially nonselective, this method delivered epoxides **61** and **64** (Table III) in excellent selectivity as proven by ^{1}H NMR studies (ratio) and X-ray crystallographic analysis (stereochemistry). Thus, desilylation of **64** followed by exposure to excess *p*-bromobenzoyl chloride gave the crystalline derivative **33c**, whose ORTEP drawing is shown in Scheme VI. The stereochemistry of **61** was proven by an X-ray crystallographic analysis of the bicyclic derivative **31c** derived from it by the sequence depicted in Scheme V.

Conclusion

These studies establish well-defined and predictable routes to tetrahydrofuran and tetrahydropyran systems of predesigned stereochemistry and substitution. The described sequences are

(23) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Veale, C. A. *J. Am. Chem. Soc.* Accompanying paper in this issue.
(24) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* Accompanying paper in this issue.

flexible to deliver racemic or optically active materials containing useful functional groups for further elaboration. This methodology is extendable to bicyclic systems with 6,6- or 6,5-frameworks similar to those found in the brevetoxins and halichondrins as well as other marine natural products. Furthermore, reiteration may be continued to form polycyclic systems. The principles on which the present technology relies may be extended to higher ring homologues as in the systematic study described in the following paper.[24]

Experimental Section

General Procedures. NMR spectra were recorded on one of the following instruments: IBM WP-200, Bruker WM-250, IBM AF-250 or Bruker AM-500. IR spectra were recorded on a Perkin-Elmer Model 781 infrared spectrophotometer. UV and visible spectra were recorded on a Perkin-Elmer Model 553 ultraviolet–visible spectrophotometer.

High-resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VC ZAB E instrument under FAB conditions.

All reactions were monitored by thin-layer chromatography carried out on 0.25-mm E. Merck silica gel plates (60F-254) with UV light and 7% ethanolic phosphomolybdic acid–heat as developing agent. Preparative layer chromatography was performed on 0.5 or 0.25 mm × 20 cm × 20 cm E. Merck silica gel plates (60F-254). E. Merck silica gel (60, particle size 0.040–0.63 mm) was used for flash column chromatography.

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials unless otherwise stated.

Cyclization of (4*S,5*S**)-4,5-Epoxy-6-hepten-1-ol (19c). Preparation of (2*R**,3*S**)-2-Ethenyltetrahydropyran-3-ol (20c) and (2*R**,3*S**)-2-Ethenyltetrahydropyran-2-yl Acetate (20c-Ac).** To a stirred solution of hydroxy epoxide **19c** (50 mg, 0.39 mmol) in dry dichloromethane (4 mL) at −40 °C was added in one portion (1*S*)-(+)-10-camphorsulfonic acid (CSA, 9.0 mg, 0.04 mmol). After stirring for 1 h (−40 → 25 °C), the reaction was quenched with triethylamine (0.02 mL, 0.12 mmol), the solvent was evaporated, and the residue was subjected to flash chromatography (silica, 40% ether in petroleum ether to give **20c** (47 mg, 95%). This alcohol (**20c**) was converted to the corresponding acetate (**20c-Ac**) under standard conditions (1.5 equiv of Ac_2O, 2.0 equiv of pyr, 0.1 equiv of DMAP, CH_2Cl_2, 0–25 °C, 1 h) in quantitative yield. **20c**: oil; R_f = 0.30 (silica, 60% ether in petroleum ether) IR (neat) ν_{max} 3400 (s, OH), 3090 (m), 2940 (s), 2860 (s), 2735 (m), 1750 (m), 1649 (m), 1469 (s), 1445 (s), 1431 (s), 1415 (s), 1380 (s), 1330 (s), 1270 (s), 1215 (s), 1190 (s), 1080 (s, br), 1030 (s), 1000 (s), 930 (s), 901 (s), 860 (m), 845 (s), 650 (w) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.0–5.83 (m, 1 H, C*H*=CH_2), 5.45–5.31 (m, 2 H, CH=CH_2), 3.93 (m, 1 H, epoxide), 3.53–3.30 (m, 3 H, epoxide), 2.24–2.11 (m, 1 H, CH_2), 1.91 (br s, 1 H, O*H*), 1.75–1.68 (m, 2 H, CH_2), 1.51–1.45 (m, 1 H, CH_2); HRMS calcd for $C_7H_{16}NO_2$ $(M + NH_4)^+$ 146.118, found 146.119.

20c-Ac: oil; R_f = 0.42 (silica, 30% ether in petroleum ether); IR (neat) ν_{max} 2955 (s), 2860 (s), 1740 (s, acetate), 1650 (w), 1445 (w), 1430 (w), 1378 (s), 1240 (s), 1090 (s), 1048 (s), 995 (m), 950 (m), 935 (m), 880 (m), 860 (m), 850 (m), 675 (w) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.87–5.73 (m, 1 H, *H*C=CH_2), 5.35–5.18 (m, 2 H, HC=CH_2), 4.60 (ddd, J = 9.2, 9.2, 4.6 Hz, 1 H, C*H*OAc), 4.0–3.93 (m, 1 H, C*H*O), 3.7 (dd, J = 9.2, 6.6 Hz, 1 H, C*H*O), 3.42 (ddd, J = 10.0, 9.2, 3.8 Hz, 1 H, C*H*O), 2.18 (m, 1 H, CH_2), 2.0 (s, 3 H, *Ac*), 1.74 (m, 2 H, CH_2), 1.53 (m, 1 H, CH_2); HRMS calcd for $C_9H_{16}NO_3$ $(M + NH_4)^+$ 188.126, found 188.126.

(2*S,2′*R**,3*S**,3′*S**)-4-[3′-(*tert*-Butyldiphenylsilyloxy)tetrahydropyran-2′-yl]-2,3-epoxy-2-butanol (55).** A stirred mixture of powdered, activated 4A molecular sieves (35 mg), allylic alcohol **53** (205 mg, 0.5 mmol), and dry dichloromethane (3.0 mL) was cooled to −40 °C and treated sequentially with L-(+)-diethyltartarate (16 mg, 0.075 mmol) and titanium(IV) isopropoxide (14 mg, 0.05 mmol). After 30 min, *tert*-butyl hydroperoxide (0.25 mL of 3.0 M in dichloroethane, 0.75 mmol) was added and the reaction mixture was stored in a −20 °C freezer for 16 h. The sieves were removed by filtration, the filtrate was diluted with ether (10 mL), and while stirring vigorously saturated Na_2SO_4 solution (0.1 mL) was added. After 1 h, the fine suspension was removed by filtration through a Celite pad. The filtrate was concentrated followed by flash chromatography (silica, 50% ether in petroleum ether) to yield an inseparable mixture of epoxides **55** and **57** (170 mg, 80%) in a ratio of 4.3:1. The following data were assigned for **55** and **57**. **55**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.34 (m, 10 H, aromatic), 3.87 (m, 1 H, C*H*O), 3.76 (m, 1 H, CH_2O, equatorial), 3.58 (ddd, J = 11.0, 11.0, 4.4 Hz, 1 H, C*H*O), 3.46 (m, 1 H, C*H*O), 3.25 (m, 2 H, C*H*O, CH_2O), 3.03 (m, 1 H, C*H*O, epoxide), 2.88 (m, 1 H, epoxide), 2.10–1.40 (m, 6 H, CH_2), 1.05 (s, 9 H, ^{t}*Bu*Si). **57**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70–7.35 (m, 10 H, aromatic), 3.84 (m, 1 H, C*H*O), 3.34 (m, 2 H, C*H*O, CH_2O), 3.29 (m, 1 H, C*H*O), 3.09 (m, 1 H, epoxide), 2.85 (m, 1 H, epoxide), 2.15–1.40 (m, 6 H, CH_2), 1.05 (s, 9 H, ^{t}BuSi).

(2*R,2′*R**,3*S**,3′*S**)-4-[3′-(*tert*-Butyldimethylsilyloxy)tetrahydropyran-2′-yl]-2,3-epoxy-1-butanol (61).** To a stirred solution of allylic alcohol **59** (2.86 g, 10.0 mmol) in dichloromethane (100 mL) at 0 °C was added mCPBA (2.24 g, 13 mmol) and the mixture was stirred at ambient temperature for 6 h. The reaction mixture was diluted with ether (100 mL) and washed with saturated aqueous $NaHCO_3$ solution (20 mL), 10% NaOH solution (10 mL) and brine (15 mL), and 10% NaOH solution (10 mL) and brine (15 mL). Drying ($MgSO_4$) followed by concentration and flash chromatography (silica, 50% ether in petroleum ether) gave epoxide **61** (2.66 g, 88%). **61**: oil; R_f = 0.56 (silica, ether); $[\alpha]^{21}_D$ + 42.7° (*c* 0.70, $CHCl_3$); IR (neat) ν_{max} 3450, 2950, 2920, 2846, 1462, 1255, 1098, 836 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.93 (m, 1 H, CH_2O), 3.84 (m, 1 H, C*H*O), 3.58 (m, 1 H, CH_2O), 3.48 (m, 1 H, C*H*O), 3.34 (m, 1 H, epoxide), 3.18 (m, 1 H, epoxide), 3.11 (m, 2 H, C*H*O), 2.83 (dd, J = 8.5, 4.6 Hz, 1 H, O*H*), 2.11 (m, 1 H, CH_2), 2.02 (m, 1 H, CH_2), 1.72 (m, 1 H, CH_2), 1.63 (m, 2 H, CH_2), 1.43 (m, 1 H, CH_2), 0.88 (s, 9 H, ^{t}*Bu*Si), 0.06 (s, 6 H, *Me*$_2$Si); HRMS calcd for $C_{15}H_{31}O_4Si$ $(M + H)^+$ 303.199, found 303.200.

4-[3′-(*tert*-Butyldimethylsilyloxy)tetrahydropyran-2′-yl]-2,3-epoxy-1-butanol (64): obtained from **62** in 86% yield by epoxidation with mCPBA as described above for the preparation of **61**; oil; R_f = 0.46 (silica, ether); IR (neat) ν_{max} 3438, 2948, 2924, 2850, 1465, 1250, 1100, 1025 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.92 (m, 1 H, CH_2O), 3.70 (m, 3 H, CH_2OH, C*H*O), 3.45 (m, 2 H, CH_2O, C*H*O), 3.19 (m, 1 H, epoxide), 3.10 (dt, J = 6.0, 4.5 Hz, 1 H, epoxide), 2.39 (t, J = 6.1 Hz, 1 H, O*H*), 1.96 (m, 2 H, CH_2), 1.71 (m, 1 H, CH_2), 1.63 (m, 2 H, CH_2), 1.34 (m, 1 H, CH_2), 0.78 (s, 9 H, ^{t}BuSi), 0.05 (s, 3 H, *Me*$_2$Si), 0.03 (s, 3 H, *Me*$_2$Si); HRMS calcd for $C_{15}H_{31}O_4Si$ $(M + H)^+$ 303.199, found 303.198.

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Supplementary Material Available: Data for compounds **19a–34b** (R_f values, $[\alpha]_D$, IR, ^{1}H NMR, MS data) and X-ray crystallographic data for compounds **29c**, **31c**, and **33c** (28 pages). Ordering information is given on any current masthead page.