Activation of 7-Endo over 6-Exo Epoxide Openings. Synthesis of Oxepane and Tetrahydropyran Systems

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Abstract: Activation of 7-endo over 6-exo hydroxy epoxide opening by placement of an electron-rich double bond furthest away from the hydroxyl group leads to a reliable entry into trans- and cis-substituted oxepane systems. The scope and limitations of the method are discussed and extensions to bicyclic systems are presented.

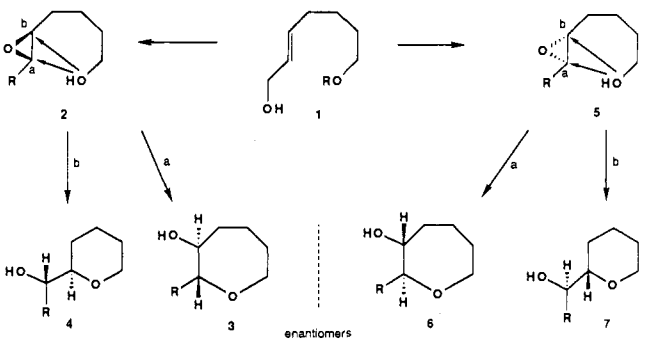
Oxepanes are important structural units both as parts of naturally occurring substances[1] and as synthetic materials. Although several examples leading to special types of oxepanes have been reported,[2] general methods for their synthesis are lacking. As an extension of the work directed toward the selective construction of tetrahydropyran systems described in the preceding article,[3] we initiated a systematic study to explore the possibility of constructing oxepanes by 7-endo cyclizations of hydroxy epoxides. In the present paper we describe our observations in this area which suggest stereocontrolled entries into a number of substituted oxepanes and tetrahydropyrans.

Results and Discussion

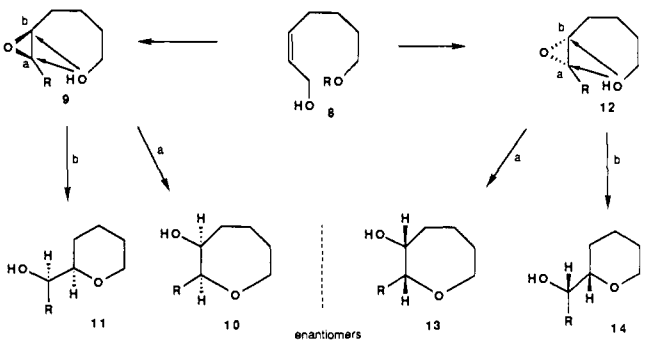
Our purpose for entering this area was to develop stereocontrolled and flexible methods for synthesizing various isomers of substituted oxepane and tetrahydropyran systems such as those found as substructural units in the brevetoxins[4] and other marine-derived natural products.[1] Schemes I and II outline the strategy devised for solving the above problem. According to this strategy, and as shown in Scheme I, the trans allylic alcohol **1** could serve as a precursor to optically active trans epoxides **2** and **5** via the Sharpless asymmetric epoxidation reaction followed by standard functional group chemistry to build the desired substitution (R) and liberate the hydroxyl group. Following the principles delineated in the preceeding paper,[3] it was expected that a π-orbital adjacent to carbon a would activate this position toward ring closure by conjugation, whereas kinetic considerations would favor position b. Thus, it was anticipated that stereoselective and ring-selective cyclizations under acidic or basic conditions would gain access to oxepanes **3** and **6** (7-endo ring closure) and/or tetrahydropyrans **4** and **7** (6-exo ring closure). Scheme II outlines the approach to the other isomeric structures **10** and **11**, and **13** and **14** starting with the cis allylic alcohol **8** and proceeding via cis epoxides **9** and **12**. These studies showed that the extent of stereoselectivity and ring selectivity in these systems depends not only on the nature of R but also on the stereochemistry of the epoxide grouping and the presence or absence of additional rings.

The requisite hydroxy epoxides for this study were prepared as outlined in Scheme III in racemic (**37-40**, mCPBA method)[5]

Scheme I. Plausible 7-Endo (a) and 6-Exo (b) Cyclizations of *trans*-Hydroxy Epoxides To Form Oxepanes and Tetrahydropyrans



Scheme II. Plausible 7-Endo (a) and 6-Exo (b) Cyclizations of *cis*-Hydroxy Epoxides To Form Oxepanes and Tetrahydropyrans



or optically active (**25-29**, Sharpless asymmetric epoxidation method)[6] forms. Thus, the acetylenic silyl ether **15b** (prepared from 1-hexyn-6-ol **15a** by silylation, 95%) was converted to the hydroxy compound **16** by hydroxymethylation [^{n}BuLi-$(CH_2O)_n$, 75% yield]. To gain entry into the trans epoxides **25-29**, the hydroxy acetylene **16** was reduced with REDAL to afford the trans allylic alcohol **17** (76%), which was then subjected to the catalytic Sharpless asymmetric epoxidation reaction[6b] leading to hydroxy epoxide **18** in 85% yield and 97% ee (determined by ^{1}H NMR on the Mosher[7] esters). The aldehyde **19**, generated from **18** by oxidation using SO_3·pyr complex (90% yield), served well as a precursor to olefins **20-23**, which were obtained following standard methods (see Scheme III). The saturated system **24** was also obtained by mild hydrogenation of **20** using diimide. The hydroxy epoxides **25-29** were then generated from **20-24** respectively by the action of fluoride ion (^{n}Bu$_4$NF, THF, 85-95%). For the

(1) For examples, see: (a) Faulkner, D. J. *Nat. Prod. Rep.* **1986**, *3*, 1; **1984**, *1*, 251, 551.

(2) For some examples see: (a) Coppi, L.; Ricci, A.; Taddei, M. *J. Org. Chem.* **1988**, *53*, 911. (b) Whitby, R.; Yeates, C.; Kocienski, P.; Costello, G. *J. Chem. Soc. Chem. Commun.* **1987**, 429. (c) Brady, W. T.; Giang, Y. F.; Weng, L.; Dad, M. M. *J. Org. Chem.* **1987**, *52*, 2216. (d) Overman, L. E.; Blumenkopf, T. A.; Castaneda, A.; Thompson, A. S. *J. Am. Chem. Soc.* **1986**, *108*, 3516. (e) Overman, L. E.; Castaneda, A.; Blumenkofp, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303. (f) Bartlett, P. A.; Ting, P. C. *J. Org. Chem.* **1986**, *51*, 2230. (g) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1985**, *50*, 3017. (h) Barry, C. N.; Evans, S. A., Jr. *J. Org. Chem.* **1981**, *46*, 3361. (i) Nicolaou, K. C.; Claremon, D. A.; Barnett, W. E. *J. Am. Chem. Soc.* **1980**, *102*, 6611. (j) Rastetter, W. H. *J. Am. Chem. Soc.* **1976**, *98*, 6350.

(3) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* preceeding paper in this issue.

(4) Brevetoxin A: Shimizu, Y.; Chou, H. N.; Bando, H.; Van Duyne, G. D.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514. Brevetoxin B: Lin, Y. Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J. C.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773.

(5) This method was used for convenience to demonstrate the feasibility of the strategy. The Sharpless asymmetric epoxidation reaction[6] could also be applied to deliver optically active compounds.

(6) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5976; (b) Gao Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(7) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

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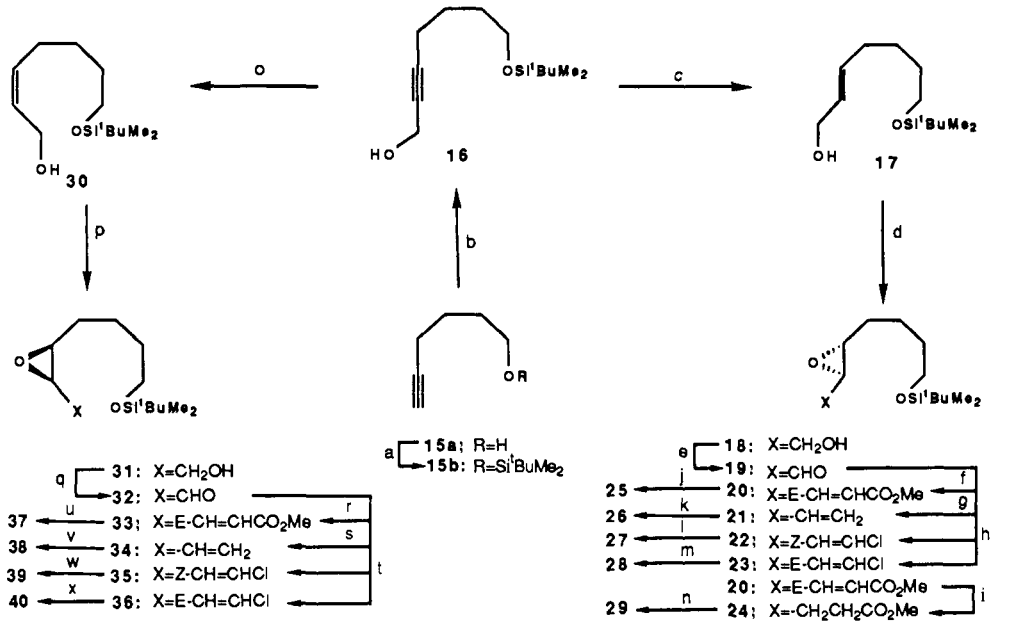
Scheme III[a]

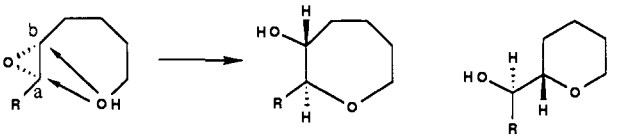


[a] Reagents and conditions: (a) 2.5 equiv of imidazole, DMF, 1.2 equiv of $^tBuMe_2SiCl$, 25 °C, 12 h, 95%; (b) 1.1 equiv of ^nBuLi, 1.14 equiv of $(CH_2O)_n$, THF, −78 to 40 °C, 8 h, 75%; (c) 3.3 equiv of REDAL, Et_2O, 0–25 °C, 3 h, 76%; (d) 0.1 equiv of $Ti(O^iPr)_4$, 0.15 equiv of (−)-DET, 1.5 equiv of ^tBuOOH, 4A MS, CH_2Cl_2, −20 °C, 4 h, 85%, 97% ee; (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, 25 °C, 0.5 h, 80%; (g) 1.9 equiv of $NaN(SiMe_3)_2$, 1.9 equiv of $Ph_3P^+CH_3Br^-$, THF, 0 °C, 0.5 h, 85%; (h) 2.0 equiv of $ClCH_2P^+Ph_3Cl^-$, 2.0 equiv of $NaN(SiMe_3)_2$, THF, 0 °C, 0.5 h, 80%; (i) 3.0 equiv of KO_2CN=NCO_2K, 4.8 equiv of AcOH, pyr, 40 °C, 12 h, 80%; (j) 1.5 equiv of $^nBu_4N^+F^-$, THF, 25 °C, 2 h, 90%; (k) same as j, 92%; (l) same as j, 88%; (m) same as j, 90%; (n) same as j, 90%; (o) 10 wt % of 5%Pd–$CaCO_3$, 0.7 equiv of quinoline, H_2, 6 h, 98%; (p) 1.3 of equiv of mCPBA, CH_2Cl_2, 0 °C, 12 h, 81%; (q) 4.0 equiv of SO_3·pyr, 5.0 equiv of Et_3N, DMSO–CH_2Cl_2 (1:1), 0.5 h, 90%; (r) 1.6 equiv of Ph_3P=CHCOOMe, benzene, 2 h, 81%; (s) 2.2 equiv of $CH_3P^+Ph_3Br^-$, 2.0 equiv of $NaN(SiMe_3)_2$, THF, 0 °C, 1 h, 78%; (t) 2.2 equiv of $ClCH_2P^+Ph_3Cl^-$, 2.0 equiv of $NaN(SiMe_3)_2$, THF, 0 °C, 2 h, 71%; (u) same as j, 86%; (v) same as j, 92%; (w) same as j, 94%; (x) same as j, 94%.

synthesis of the cis epoxide series **37–40**, the Z olefin **30** was generated from acetylene **16** by Lindlar hydrogenation (quinoline, 98%). mCPBA epoxidation of **30** then delivered racemic epoxide **31** (81% yield), which was transformed to compounds **32–40** by methods analogous to those employed for the corresponding trans epoxides (see Scheme III for details).

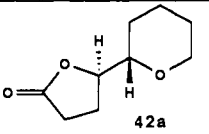
The trans hydroxy epoxides **25–29** were subjected to acid-catalyzed cyclization according to the protocol developed for their lower homologues.[3] The results are summarized in Table I. As expected on kinetic grounds, the saturated substrate **29** upon exposure to catalytic amounts of camphorsulfonic acid (CSA), led exclusively to the tetrahydropyran system **42**, isolated as its γ-lactone **42a**, in 70% yield. In contrast, the α,β-unsaturated hydroxy epoxide **25** gave, under the same conditions, a mixture of oxepane and tetrahydropyran systems **43** and **44** in a ratio of 22:78 (by ^1H NMR and isolation). The structures of **43** and **44** were confirmed by analysis of the ^1H NMR spectra of their acetates, **43a** and **44a** (Table III), prepared under standard conditions. Decoupling experiments and coupling constants (J_{ab} = 7.4 Hz for **43a** and 4.9 Hz for **44a**, Table III) were particularly useful in establishing the assigned structures of these and of subsequent compounds, The more electron-rich double bond in **26** exerted even stronger directing effect in the cyclization of this substrate, producing, under similar conditions, a ca. 82:18 mixture of **45**:**46** (75% total yield). In an attempt to enhance even further this selectivity, the chloro olefins **27** and **28** were utilized in this reaction. Interestingly, the Z-chloro olefin **27** exhibited lower selectivity toward the oxepane system (**47**:**48** ca. 60:40) whereas, the corresponding E isomer **28** furnished **49** and **50** in ca. 92:8 ratio. While the increased selectivity toward the oxepane in the case of **28** was in line with the higher electron density of its alkene π-system, the anomalous behavior of **27** may be attributed to its inability to attain planarity, due to steric interactions; nonplanarity is translated in a lower capacity to stabilize the developing positive charge on the adjacent carbon and thus in loss of selectivity. The structures of products **45–50** were secured by spectroscopic means. Particularly useful again were the coupling constants J_{ab} of their

Table I. Acid-Catalyzed Cyclizations of *trans*-Hydroxy Epoxides Leading to Oxepanes and Tetrahydropyrans



Entry	Hydroxyepoxide	Conditions	Products (Ratio)	Yield(%)
1	**29**: R=$CH_2CH_2CO_2Me$	0.1 equiv CSA CH_2Cl_2, -40 to 25 °C	**41**:**42** (0:100)[a]	70
2	**25**: R=E-CH=$CHCO_2Me$	"	**43**:**44** (22:78)	75
3	**26**: R=$CH=CH_2$	"	**45**:**46** (82:18)	75
4	**27**: R=Z-CH=CHCl	"	**47**:**48** (60:40)	70
5	**28**: R=E-CH=CHCl	"	**49**:**50** (92:8)	75

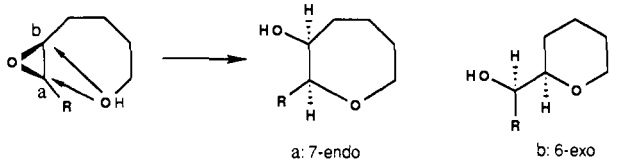
[a] isolated as the γ-lactone (**42a**)



corresponding acetates (Table III) obtained by decoupling experiments.

In order to expand the scope of this methodology, the series of cis hydroxy epoxides **37–40** (Table II) was examined. In general the cis epoxides exhibited lower selectivities toward the oxepane products than their corresponding trans counterparts. Thus, the α,β-unsaturated ester **37** gave exclusively the tetrahydropyran system **52** in 76% yield. When compound **38**, however, was treated with catalytic amounts of CSA, a mixture of oxepane and tetrahydropyran systems was obtained (ca. 1:1 ratio, 73% total yield). Furthermore, it was determined that the oxepane system was a mixture of cis and trans isomers **53** and **45**. The structural as-

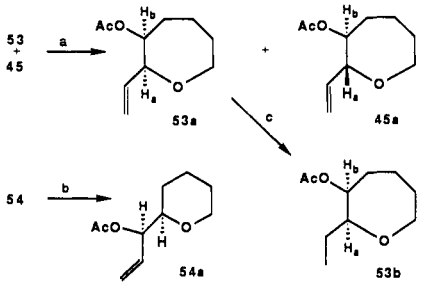
Table II. Acid-Catalyzed Cyclizations of *cis*-Hydroxy Epoxides Leading to Oxepanes and Tetrahydropyrans



Entry	Hydroxyepoxide	Conditions	Products (Ratio)	Yield(%)
1	**37**: R=E-CH=CHCO$_2$Me	0.1 equiv CSA CH_2Cl_2, -40 to 25 °C	**51**:**52** (0:100)	76
2	**38**: R=CH=CH$_2$	"	**53**:**54** (50:50)[a]	73
3	**39**: R=Z-CH=CHCl	"	**55**:**56** (33:67)	78
4	**40**: R=E-CH=CHCl	"	**57**:**58** (68:32)	69

[a]Oxepane was a mixture of *cis* and *trans* isomers (*ca* 1:1)

Scheme IV[a]



[a]Reagents and conditions: (a) 1.3 equiv of Ac_2O, 1.5 equiv of DMAP, CH_2Cl_2, 25 °C, 98%; (b) same as a, 90%; (c) 5 mol % Pd–C, H_2, hexane, 2 h, 95%.

signments of these compounds were decided as shown in Scheme IV. Thus, the ca. 2:1:1 mixture received by cyclization of **38** was chromatographically separated into a less polar fraction (**54**) which upon acetylation gave acetate **54a** and the more polar fraction containing oxepanes **53** and **45** which upon acetylation led to the separable acetates **53a** and **45a**. ^{1}H NMR decoupling experiments on **54** and its acetate **54a** confirmed their tetrahydropyran skeleton, whereas the relative stereochemistry indicated in these structures was tentatively assigned on mechanistic grounds. Similar ^{1}H NMR studies on **53a** failed to reveal the stereorelationship of H_a and H_b due to signal overlap and, hence, the saturated acetate **53b** (Scheme IV) was prepared. Decoupling experiments on **53b** clearly defined the indicated stereochemistry (J_{ab} = 2.1 Hz, Table III) and, therefore, the structural assignments of **53a** and **53** were confirmed. Acetate **45a** was spectroscopically and chromatographically identical with the one derived from the trans epoxide (Table I, entry 3).

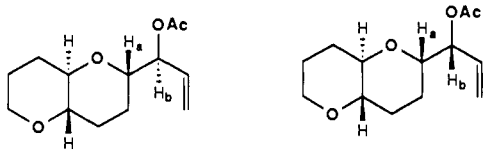
The formation of the trans oxepane **45** from the cyclization of **38** may be explained mechanistically as indicated in Scheme V. Thus, protonation of the epoxide oxygen in **38** followed by C–O rupture is expected to generate the carbonium species **59** (or its equivalent) which can undergo single-bond rotation to its isomer **60** or ring closure to oxepane **53**. Carbonium ion **60** may then undergo ring closure to the trans oxepane **45** via pathway b or to the trans epoxide **26** via pathway a (Scheme V). The trans epoxide **26** could, indeed, be isolated by quenching the acid-induced cyclization of **38** prior to completion. Both the epoxide **26** and carbonium ion **60**, or either of the two may then serve as precursors to trans oxepane **45**.

The cyclization of the *Z*-chloro olefin **39** (Table II) under the standard cyclization conditions led to a ca 33:67 mixture (by ^{1}H NMR and isolation) of compounds **55** and **56** (78% total yield). As expected, from the results with the corresponding trans epoxides (Table I), the cyclization of the *E*-chloro olefin **40** led to a higher ratio (ca. 68:32) of the oxepane (**57**) to tetrahydropyran (**58**) products (69% combined yield). The explanation for the observed

Table III. Coupling Constants (J_{ab}) of Oxepane and Tetrahydropyran Acetate Derivatives

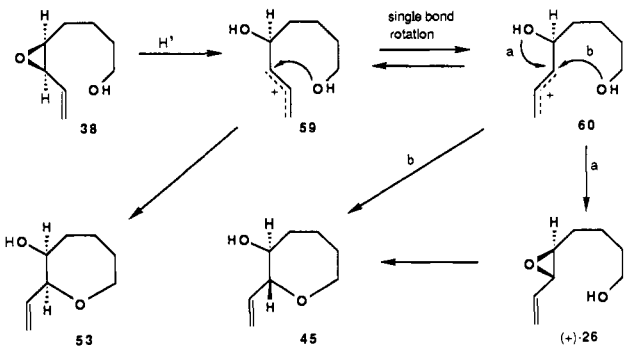
Compound	J_{ab}(Hz)	Compound	J_{ab}(Hz)
43a: R=E-CH=CHCOOMe	7.4	**53a**: R=-CH=CH$_2$	-
45a: R=-CH=CH$_2$	7.2	**53b**: R=-CH$_2$CH$_3$	2.1
47a: R=Z-CH=CHCl	7.0	**55a**: R=Z-CH=CHCl	2.3
49a: R=E-CH=CHCl	7.2	**57a**: R=E-CH=CHCl	2.3

Compound	J_{ab}(Hz)	Compound	J_{ab}(Hz)
44a: R=E-CH=CHCOOMe	4.9	**52a**: R=E-CH=CHCOOMe	4.2
46a: R=-CH=CH$_2$	2.9	**54a**: R=-CH=CH$_2$	4.3
48a: R=Z-CH=CHCl	2.9	**56a**: R=Z-CH=CHCl	4.2
50a: R=E-CH=CHCl	4.8	**58a**: R=E-CH=CHCl	4.8



Compound	J_{ab}(Hz)	Compound	J_{ab}(Hz)
64a	8.0	**65a**	5.5

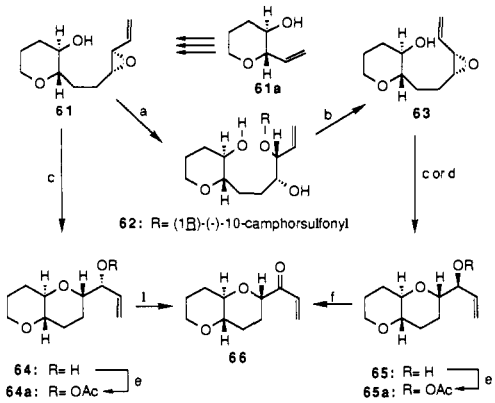
Scheme V, Plausible Mechanism for the Acid-Induced Generation of **45** and **53** from **38**



difference between the *Z* and the *E* olefins **39** and **40** may again lie in their different abilities to assume planar arrangements with the epoxide unit in the transition state. The structures of compounds **55–58** were secured by analysis of the ^{1}H NMR spectra of their respective acetates (**55a–58a**, Table III). Particularly revealing was the coupling constant J_{ab} which was found to be 2.3 Hz in both **55a** and **57a**, confirming the cis substitution in these systems. The tetrahydropyran systems in this series of compounds were assumed to possess the indicated stereochemistry on mechanistic grounds (inversion at the point of attack during cyclization) as mentioned above. The coupling constants J_{ab} for all relevant acetates are tabulated in Table III.

Attempts to prepare bicyclic systems led to some interesting results as outlined in Scheme VI. Thus, the trans hydroxy epoxide **61** was synthesized from compound **61a**[3] by standard methods and subjected to cyclization studies. Reaction of **61** with stoichiometric amounts of (1*R*)-(−)-10-camphorsulfonic acid led,

Scheme VI[a]



[a] Reagents and conditions: (a) 1.0 equiv of (1*R*)-(−)-CSA, CH_2Cl_2, 25 °C, 10 min, 98%; (b) 1.2 equiv of NaOMe, MeOH, 25 °C, 10 min, 95%; (c) 2.0 equiv of KCH_2SOCH_3, 97%; (d) same as a, 45%; (e) 1.2 equiv of Ac_2O, 1.5 equiv of DMAP, CH_2Cl_2, 25 °C, 96%; (f) 10.0 equiv of MnO_2, CH_2Cl_2, 25 °C, 2 h, 75%.

quantitatively, to an isolable intermediate, tentatively assigned structure **62**[8] on the basis of its ^{1}H NMR spectrum. Less amounts of acid led to incomplete reaction but no cyclization product was detected. Upon exposure to NaOMe, however, intermediate **62** gave rise to cis epoxide **63** in 95% yield. Treatment of cis epoxide **63** with stoichiometric amounts of (1*R*)-(−)-CSA led to the bicyclic compound **65** in 45% yield with no detectable intermediate corresponding to **62**. A higher yield of **65** (97%) was realized when **63** was exposed to dimsylpotassium in DMSO. Similarly, the isomeric compound **64** was obtained from the trans epoxide **61** by treatment with dimsylpotassium (96% yield). The structures of **64** and **65** were based on both chemical and spectroscopic data. Thus, acetylation led to acetates **64a** and **65a** which exhibited the expected couplings in their ^{1}H NMR spectra (Table III, decoupling experiments). Furthermore, MnO_2 oxidation of **64** and **65** led to the same enone **66** (75% yield).

Conclusion

Activation of 7-endo over 6-exo hydroxy epoxide openings can be achieved by placing an electron-rich double bond adjacent to the C–O bond furthest away from the hydroxyl group. This design leads to selective entries into trans- and cis-substituted oxepanes with the *E*-chloro vinyl group as the most effective director group. This systematic study revealed, however, limitations of the method in terms of selectivity and substrate structure. Thus, cis hydroxy epoxides lead to lower selectivities, whereas attempts to prepare bicyclic systems containing oxepanes led to clean formation of tetrahydropyran skeletons. The described chemistry, however, opens up efficient entries to selective oxepane and tetrahydropyran targets and is therefore expected to find useful applications in synthesis.

Experimental Section

General Procedures. See ref 3.

(2′*S,4*R**)-4-(Tetrahydropyran-2′-yl)-dihydro-2(3*H*)-furanone (42a) via Compound 42.** To a stirred solution of epoxy alcohol **29** (35.7 mg, 0.16 mmol) in dry dichloromethane (1.6 mL) at 0 °C was added in one portion (1*S*)-(+)-10-camphorsulfonic acid (CSA, 3.8 mg, 0.02 mmol). After stirring for 1 h, the reaction was quenched with triethylamine (50 μL, 0.032 mmol), the solvent was evaporated, and the residue subjected to flash chromatography (silica, 40% ether in petroleum ether) to give directly the γ-lactone **42a** (22.3 mg, 82%). **42a**: oil; R_f = 0.20 (silica, 40% ether in petroleum ether); $[\alpha]^{21}_D$ +7.4° (*c* 1.8, $CHCl_3$); IR (neat) ν_{max} 2950 (s), 2855 (s), 1780 (s, γ-lactone), 1470 (m), 1448 (m), 1350 (m), 1270 (m), 1180 (s), 1095 (s), 1070 (s), 1050 (s), 1000 (s), 910 (s), 875 (w), 810 (w) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.3 (m, 1 H, C*H*OC(O)), 3.93 (m, 1 H, C*H*O), 3.4 (m, 2 H, C*H*O), 2.45 (m, 2 H, CH_2COO), 2.2 (m, 2 H, CH_2), 1.85 (m, 1 H, CH_2), 1.6–1.2 (m, 5 H, CH_2); HRMS calcd for $C_9H_{15}O_3$ (M + H)$^+$ 171.102, found 171.101.

(2*E*,2′*S,3′*R**)-Methyl 3-(3′-Acetoxy-2′-oxepanyl)-2-propenoate (43a) and (2*E*,2′*S**,3*R**)-Methyl 3-Acetoxy-4-(tetrahydropyran-2′-yl)-2-butenoate (44a) via 43 and 44.** To a stirred solution of epoxy alcohol **25** (420 mg, 2.1 mmol) in dry dichloromethane (21 mL) at 0 °C was added in one portion (1*S*)-(+)-10-camphorsulphonic acid (48 mg, 0.20 mmol). The cooling bath was removed and the reaction mixture was stirred for an additional 12 h. The reaction was quenched with triethylamine (0.6 mL, 4.2 mmol) followed by addition of acetic anhydride (0.23 mL, 3.2 mmol) and 4-(dimethylamino)pyridine (76 mg, 0.63 mmol). After 30 min, the reaction mixture was diluted with ether (50 mL) and washed with H_2O (20 mL) and brine (20 mL). Drying ($MgSO_4$), concentration, and flash chromatography (silica, 20% ether in petroleum ether) gave, in order of elution, acetates **43a** (76 mg, 15%) and **44a** (304 mg, 60%). **43a**: oil; R_f = 0.45 (silica, 40% ether in petroleum ether); $[\alpha]^{21}_D$ +23.8° (*c* 1.14, $CHCl_3$); IR (neat) ν_{max} 2950 (s), 2870 (s), 1750 (s, OAc), 1730 (s, COOMe), 1665 (m), C=COOMe), 1442 (s), 1375 (s), 1310 (s), 1240 (s), 1172 (s), 1140 (s), 1095 (s), 1030 (s), 990 (s), 920 (m), 800 (w), 740 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.90 (dd, *J* = 15.6, 4.3 Hz, 1 H, *H*C=CHCOOMe), 6.10 (dd, *J* = 15.6, 1.8 Hz, 1 H, HC=C*H*COOMe), 4.90 (ddd, *J* = 7.4, 7.4, 3.6 Hz, 1 H, C*H*OAc), 4.15 (m, 1 H, C*H*O), 3.9 (m, 1 H, C*H*O), 3.77 (s, 3 H, $COOCH_3$), 3.65 (m, 1 H, C*H*O), 2.10 (s, 3 H, Ac), 1.5–1.9 (m, 6 H, CH_2); HRMS calcd for $C_{12}H_{19}O_5$ (M + H)$^+$ 243.123, found 243.125. **44a**: oil; R_f = 0.40 (silica, 40% ether in petroleum ether); $[\alpha]^{21}_D$ + 19.8° (*c* 5.05, $CHCl_3$); IR (neat) ν_{max} 2945 (s), 2855 (s), 1760 (s, OAc), 1740 (s, COOMe), 1670 (s, C=CHCOOMe), 1440 (s), 1375 (s), 1315 (s), 1240 (s), 1178 (s), 1095 (s), 990 (s), 950 (w), 920 (m), 890 (w), 850 (w), 735 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.95 (dd, *J* = 15.8, 5.5 Hz, 1 H, *H*C=CHCOOMe), 5.98 (dd, *J* = 15.8, 1.6 Hz, 1 H, HC=C*H*COOMe), 5.35 (ddd, *J* = 5.4, 4.6, 1.6 Hz, 1 H, C*H*OAc), 4.0 (br d, *J* = 11.2, Hz, 1 H, C*H*O), 3.74 (s, 3 H, COO*Me*), 3.5–3.4 (m, 2 H, C*H*O), 2.13 (s, 3 H, Ac), 1.8–1.4 (m, 6 H, CH_2); HRMS calcd for $C_{12}H_{19}O_5$ (M + H)$^+$ 243.123, found 243.126.

(2*S,3*R**)-3-Acetoxy-2-ethenyloxepane (45a) and (1*R**,2′*S**)-1-(Tetrahydropyran-2′-yl)-2-propenyl Acetate (46a) via Alcohols 45 and 46.** The acetates **45a** and **46a** were prepared from hydroxy epoxide **26** via compounds **45** and **46** as described above for **43a** and **44a**. **45a**: oil; R_f = 0.40 (silica, 40% ether in petroleum ether); $[\alpha]^{21}_D$ −21.1° (*c* 1.1, $CHCl_3$); IR (neat) ν_{max} 2945 (s), 2875 (s), 1740 (s, OAc), 1448 (m), 1375 (s), 1240 (s), 1170 (m), 1150 (m), 1110 (m), 1030 (s), 990 (s), 930 (s), 738 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.73 (ddd *J* = 17.2, 10.5, 5.7 Hz, 1 H, C*H*=CH_2), 5.2 (ddd, *J* = 17.2, 1.6, 1.6 Hz, 1 H, CH=CH_2), 5.05 (ddd, *J* = 10.5, 1.5, 1.5 Hz, 1 H, CH=CH_2), 4.80 (ddd, *J* = 7.2, 7.2, 3.6 Hz, 1 H, C*H*OAc), 3.85 (m, 2 H, C*H*O), 3.53 (m, 1 H, C*H*O), 1.95 (s, 3 H, *Ac*), 1.9–1.5 (m, 6 H, CH_2); HRMS calcd for $C_{10}H_{17}O_3$ (M + H)$^+$ 185.118, found 185.119. **46a**: oil; R_f = 0.50 (silica, 40% ether in petroleum ether); $[\alpha]^{21}_D$ +9.3° (*c* 2.65, $CHCl_3$); IR (neat) ν_{max} 2945 (s), 2860 (s), 1750 (s, OAc), 1650 (w), 1445 (m), 1375 (s), 1240 (s), 1180 (m), 1095 (s), 1053 (s), 1025 (s), 990 (s), 940 (s), 920 (s), 889 (m), 840 (m), 810 (w), 735 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.83 (m, 1 H, *H*C=CH_2), 5.23 (m, 2 H, HC=CH_2), 5.11 (dd, *J* = 6.9, 4.0 Hz, C*H*OAc), 3.96 (m, 1 H, C*H*O) 3.35 (m, 2 H, C*H*O), 2.03 (s, 3 H, *Ac*), 1.79 (m, 1 H, CH_2), 1.53–1.4 (m, 5 H, CH_2); HRMS calcd for $C_{10}H_{17}O_3$ (M + H)$^+$ 185.118, found 185.119.

(*Z*,2′*S,3′*R**)-1-Chloro-2-(3′-acetoxy-2′-oxepanyl)ethylene (47a) and (2*Z*,1*R**,2′*S**)-1-(Tetrahydropyran-2′-yl)-3-chloro-2-propenyl Acetate (48a) via Alcohols 47 and 48.** The acetates **47a** and **48a** were prepared from hydroxy epoxide **27** via compounds **47** and **48** as described above for **43a** and **44a**. **47a**: oil; R_f = 0.60 (silica, 40% ether in petroleum ether); $[\alpha]^{21}_D$ + 78.3° (*c* 5.23, $CHCl_3$); IR (neat) ν_{max} 2940 (s), 2870 (m), 1740 (s, OAc), 1640 (m, C=CHCl), 1450 (m), 1375 (s), 1120 (s), 1040 (s), 1030 (s), 990 (m), 880 (w), 815 (w), 760 (m), 740 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.05 (d, *J* = 7.3 Hz, 1 H, C=C*H*Cl), 5.68 (dd, *J* = 8.2, 7.3 Hz, 1 H, C*H*=CHCl), 4.80 (ddd, *J* = 7.3, 7.3, 4.0 Hz, 1 H, C*H*OAc), 4.32 (dd, *J* = 8.2, 7.3 Hz, 1 H, OC*H*CH=CHCl), 3.89 (m, 1 H, C*H*O), 3.57 (m, 1 H, C*H*O), 1.91 (s, 3 H, *Ac*), 1.9–1.5 (m, 6 H, CH_2); HRMS calcd for $C_{10}H_{16}ClO_3$ (M + H)$^+$ 219.079, found 219.081. **48a**: oil; R_f = 0.50 (silica, 40% ether in petroleum ether); $[\alpha]^{21}_D$ +3.9° (*c* 2.1, $CHCl_3$); IR (neat) ν_{max} 2945 (s), 2860 (s), 1750 (s, Ac), 1640 (m), 1445 (m), 1375 (s), 1298 (w), 1240 (s), 1182 (w), 1095 (s), 1075 (m), 1050 (s), 1030 (s), 987 (m), 910 (m), 810 (w), 740 (m) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.30 (d, *J* = 7.3 Hz, 1 H, C=C*H*Cl), 5.92 (dd, *J* = 7.8, 7.3 Hz, 1 H, C*H*=CHCl), 5.70 (dd, *J* = 7.8, 2.9, 1 H, C*H*OAc), 4.02 (m, 1 H, C*H*O), 3.6 (m, 1 H, C*H*O), 3.43 (m, 1 H, C*H*O), 2.1 (s, 3 H, *Ac*), 1.9–1.8 (m, 1 H, CH_2), 1.6–1.2 (m, 5 H, CH_2); HRMS calcd for $C_{10}H_{16}ClO_3$ (M + H)$^+$ 219.079, found 219.082.

(*E*,2′-*S,3′*R**)-1-Chloro-2-(3′-acetoxy-2′-oxepanyl)ethylene (49a) and (2*E*,1*R**,2′*S**)-1-(Tetrahydropyran-2′-yl)-3-chloro-2-propenyl Ace-**

(8) The formation of this intermediate (**62**) in this case, from all the ones examined, is rather surprising and further studies to explain this stereoselective reaction are ongoing.

tate (50a) via Alcohols 49 and 50. The acetates **49a** and **50a** were prepared from hydroxy epoxide **28** via compounds **49** and **50** as described above for **43a** and **44a**. **49a**: oil; R_f = 0.71 (silica, 40% ether in petroleum ether); $[\alpha]^{21}_D$ −19.3° (*c* 6.05, $CHCl_3$); IR (neat) ν_{max} 2945 (s), 2880 (m), 1745 (s, Ac), 1645 (m, C=CCl), 1450 (m), 1375 (s), 1240 (s), 1130 (s), 1030 (s), 990 (m), 938 (m), 815 (m), 740 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.20 (dd, *J* = 13.4, 1.4 Hz, 1 H, C=C*H*Cl), 5.87 (dd *J* = 13.4, 5.8 Hz, 1 H, *H*C=CHCl), 4.76 (ddd, *J* = 7.2, 7.2, 3.5 Hz, 1 H, C*H*OAc), 3.90 (m, 2 H, C*H*O), 3.53 (m, 1 H, C*H*O), 2.00 (s, 3 H, *Ac*), 1.9–1.5 (m, 6 H, CH_2); HRMS calcd for $C_{10}H_{16}O_3Cl$ $(M + H)^+$ 219.079, found 219.081. **50a**: oil; R_f = 0.65 (silica, 40% ether in petroleum ether); $[\alpha]^{21}_D$ −44.9° (*c* 0.33, $CHCl_3$); IR (neat) ν_{max} 2930 (s), 2840 (s), 1740 (s), 1370 (m), 1240 (s), 1095 (m), 1054 (m), 1030 (m), 985 (m), 940 (m), 830 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.3 (d, *J* = 14.0 Hz, 1 H, C=C*H*Cl), 6.0 (dd, *J* = 14.0, 8.3 Hz, 1 H, C*H*=CHCl), 5.13 (dd, *J* = 8.3, 4.2 Hz, 1 H, C*H*OAc), 4.0 (m, 1 H, C*H*O), 3.4 (m, 2 H, C*H*O), 2.0 (s, 3 H, *Ac*), 1.9–1.2 (m, 6 H, CH_2); HRMS calcd for $C_{10}H_{16}ClO_3$ $(M + H)^+$ 219.079, found 219.081.

(2*E*,2′*R*,3*R*)- and (2*E*,2′*S*,3*S*)-Methyl 3-acetoxy-4-(tetrahydropyran-2′-yl)-2-butenoate (52): prepared from **37** as described for **44**; oil; R_f = 0.68 (silica, 80% ether in petroleum ether); IR (neat) ν_{max} 2940, 2843, 1725, 1658, 1435, 1165, 1088 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.81 (dd, *J* = 15.6, 4.8 Hz, 1 H, olefin), 6.05 (dd, *J* = 15.6, 1.7 Hz, 1 H, olefin), 4.00 (ddd, *J* = 4.8, 4.2, 3.3 Hz, 1 H, C*H*OH), 3.92 (m, 1 H, CH_2O), 3.62 (s, 3 H, OCH_3), 3.32 (dt, *J* = 11.4, 3.8 Hz, 1 H, CH_2O), 3.13 (m, 1 H, C*H*O), 3.00 (d, *J* = 3.3 Hz, 1 H, O*H*), 1.75 (m, 1 H, CH_2), 1.38 (m, 5 H, CH_2); HRMS calcd for $C_{10}H_{20}O_4N$ $(M + NH_4)^+$ 218.1392, found 218.1409.

***cis*-3-Acetoxy-2-ethenyloxepane (53a)**: prepared from **38** via **53** by acetylation and flash chromatography as described for **45a**; oil; R_f = 0.33 (silica, 20% ether in petroleum ether); ^1H NMR (250 MHz, $CDCl_3$) δ 5.79 (ddd, *J* = 17.2, 10.6, 4.8 Hz, 1 H, olefin), 5.32 (m, 1 H, olefin), 5.15 (m, 2 H, olefin, C*H*OAc), 4.11 (m, 2 H, C*H*O, CH_2O), 3.56 (m, 1 H, CH_2O), 2.07 (s, 3 H, *Ac*), 1.96–1.54 (m, 6 H, CH_2). **45a**: R_f = 0.38 (silica, 20% ether in petroleum ether); identical with **45a** obtained from **26** as described above.

***cis*-3-Acetoxy-2-ethyloxepane (53b).** To a stirred solution of acetate **53a** (37.0 mg, 0.2 mmol) in hexane (4 mL) under a hydrogen atmmosphere was added 10% Pd–C (5 mg) and the reaction mixture was stirred for 2 h. The catalyst was filtered through a Celite pad. Evaporation of the solvent followed by flash chromatography (silica, 20% ether in petroleum ether) gave the acetate **53b** (37 mg, 100%). **53b**: oil; R_f = 0.35 (silica, 20% ether in petroleum ether); IR (neat) ν_{max} 2940, 1736, 1370, 1240, 1110 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.05 (dt, *J* = 4.9, 2.1 Hz, 1 H, C*H*OAc), 4.05 (m, 1 H, CH_2O), 3.50 (m, 1 H, CH_2O), 3.33 (ddd, *J* = 8.8, 4.6, 2.1 Hz, 1 H, C*H*O), 2.09 (s, 3 H, *Ac*), 1.96–1.31 (m, 8 H, CH_2), 0.93 (t, *J* = 7.4 Hz, 3 H, CH_3); HRMS calcd for $C_{10}H_{19}O_3$ $(M + H)^+$ 187.1334, found 187.1356.

(1*R*,2*R*)- and (1*S*,2*S*)-1-(Tetrahydropyran-2′-yl)-2-propenyl acetate (54a): prepared from **54** as described for **46a**; oil; R_f = 0.15 (silica, 10% ether in petroleum ether); IR (neat) ν_{max} 2940, 2850, 1746, 1240, 1100 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 17.2, 10.3, 6.8 Hz, 1 H, olefinic), 5.25 (m, 3 H, olefinic, C*H*OAc), 3.99 (ddd, *J* = 6.1, 4.3, 2.3 Hz, 1 H, C*H*O), 3.37 (m, 2 H, CH_2O), 2.08 (s, 3 H, *Ac*), 1.46 (m, 6 H, CH_2); HRMS calcd for $C_{10}H_{17}O_3$ $(M + H)^+$ 185.1178, found 185.1171.

(*Z*)-1-Chloro-2-(*cis*-3′-acetoxy-2′-oxepanyl)ethylene (55a): prepared from **39** as described above for **47a**; R_f = 0.35 (silica, 20% ether in petroleum ether); IR (neat) ν_{max} 2930, 2856, 1735, 1630, 1472, 1235, 1112 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.10 (dd, *J* = 7.4, 1.1 Hz, 1 H, olefin), 5.88 (t, *J* = 7.4 Hz, 1 H, olefin), 5.15 (ddd, *J* = 7.7, 5.1, 2.3 Hz, 1 H, C*H*OAc), 4.55 (ddd, *J* = 7.4, 2.3, 1.2 Hz, 1 H, C*H*O), 4.05 (m, 1 H, CH_2O), 3.66 (m, 1 H, CH_2O), 2.07 (s, 3 H, *Ac*), 2.02–1.50 (m, 6 H, CH_2); HRMS calcd for $C_{10}H_{16}O_3Cl$ $(M + H)^+$ 219.0788, found 219.0796.

(2*Z*,1*R*,2*R*)- and (2*Z*,1*S*,2*S*)-1-(Tetrahydropyran-2′-yl)-3-chloro-2-propenyl acetate (56a): prepared from **39** as described above for **48a**; R_f = 0.41 (silica, 20% ether in petroleum ether); IR (neat) ν_{max} 2930, 2850, 1742, 1630, 1376, 1235, 1098 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.20 (dd, *J* = 7.3, 1.0 Hz, 1 H, olefin), 5.86 (dd, *J* = 8.5, 7.3 Hz, 1 H, olefin), 5.72 (dd, *J* = 8.5, 4.2 Hz, 1 H, C*H*OAc), 4.0 (m, 1 H, C*H*O), 3.39 (m, 2 H, CH_2O), 2.10 (s, 3 H, *Ac*), 1.85 (m, 1 H, CH_2), 1.53 (m, 5 H, CH_2); HRMS calcd for $C_{10}H_{16}O_3Cl$ $(M + H)^+$ 219.079, found 219.081.

(*E*)-1-Chloro-2-(*cis*-3′-acetoxy-2′-oxepanyl)ethylene (57a) and (2*E*,1*R*,2*R*)- and (2*E*,1*S*,2*S*)-1-(Tetrahydropyran-2′-yl)-3-chloro-2-propenyl Acetate (58a) via Alcohols 57 and 58. The acetates **57a** and **58a** were prepared from hydroxy epoxide **40** via compounds **57** and **58** (mixture) as described above for **49a** and **50a**. The inseparable mixture of acetates **57a** and **58a** was analyzed by ^1H NMR spectroscopy. The following data were assigned for **57a** and **58a**. **57a**: ^1H NMR (250 MHz, $CDCl_3$) δ 6.27 (dd, *J* = 13.3, 1.6 Hz, 1 H, olefin), 5.88 (dd, *J* = 13.3, 5.2 Hz, 1 H, olefin), 5.09 (dt, *J* = 5.5, 2.3 Hz, 1 H, C*H*OAc), 4.14 (ddd, *J* = 5.2, 2.3, 1.6 Hz, 1 H, C*H*O), 3.55 (m, 1 H, CH_2O), 4.03 (m, 1 H, CH_2O), 2.07 (s, 3 H, *Ac*), 1.94–1.46 (m, 6 H, CH_2). **58a**: ^1H NMR (250 MHz, $CDCl_3$) δ 6.34 (dd, *J* = 13.3, 0.6 Hz, 1 H, olefin), 5.98 (dd, *J* = 13.3, 8.0 Hz, 1 H, olefin), 5.26 (ddd, *J* = 8.0, 4.8, 0.6 Hz, 1 H, C*H*OAc), 4.08 (m, 1 H, C*H*O), 3.41 (m, 2 H, CH_2O), 2.09 (s, 3 H, *Ac*), 1.94–1.46 (m, 6 H, CH_2).

(2*S,3*R**,3′*R**,4′*R**)-2-(3′,4′-Epoxy-5′-hexenyl)tetrahydropyran-3-ol (61)**, Compound **61** was prepared by standard methods from **61a**.[3] **61**: oil; R_f = 0.45 (silica, 70% ether in petroleum ether); $[\alpha]^{23}_D$ −184.0° (*c* 0.3, CH_2Cl_2); IR (neat) ν_{max} 3450 (s, OH), 2930, 2855, 1450, 1275, 1100, 920, 742 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.55 (m, 1 H, C*H*=CH_2), 5.42 (d, *J* = 17.2 Hz, 1 H, CH=CH_2), 5.23 (d, *J* = 10.8 Hz, 1 H, CH=CH_2), 3.85 (m, 1 H, CH_2O), 3.27 (m, 2 H, CH_2O, C*H*O), 3.12 (dd, *J* = 5.5, 2.4 Hz, 1 H, C*H*O-epoxide), 2.96 (m, 1 H, C*H*O, or CH_2O), 2.82 (m, 1 H, C*H*O, epoxide), 2.18 (br s, 1 H, O*H*), 2.10–1.30 (m, 8 H, CH_2); HRMS calcd for $C_{11}H_{19}O_3$ $(M + H)^+$ 199.1334, found 199.1315.

Reaction of Hydroxy Epoxide 61 with Camphorsulfonic Acid. Compound 62. 1(*R*)-(−)-Camphorsulfonic acid (23.0 mg, 0.1 mmol) was added in one portion to a solution of compound **61** (19.8 mg, 0.1 mmol) in dry CH_2Cl_2 (3 mL) at 25 °C. The reaction mixture was stirred at room temperature for 30 min before the solvent was removed under reduced pressure at 0 °C to afford essentially pure **62** (42.14 mg, 98%). **62**: oil; R_f = 0.25 (silica, 70% ethyl acetate in benzene); $[\alpha]^{23}_D$ −6.28° (*c* 1.8, CH_2Cl_2); IR (neat) ν_{max} 3420 (s, OH), 2931, 2862, 1750, (s, ketone), 1442, 1364 (s, sulfonate), 1162, 903, 725 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.89 (m, 2 H, C*H*=CH_2), 5.50 (d, *J* = 16.8 Hz, 1 H, CH=CH_2), 5.38 (d, *J* = 10.5 Hz, 1 H, CH=CH_2), 4.95 (dd, *J* = 6.5, 7.3 Hz, 1 H, C*H*OSO$_2$), 4.8 (br s, 2 H, O*H*), 3.85 (m, 1 H, CH_2O), 3.68 (m, 1 H, C*H*O), 3.55, 3.02 (2 × d, *J* = 15.0 Hz, 1 H each, CH_2SO_3-camphorsulfonyl), 3.43 (m, 2 H, CH_2O or C*H*O), 3.06 (m, 1 H, CH_2O or C*H*O), 2.58–1.48 (m, 15 H, CH_2, C*H*), 1.07 (s, 3 H, CH_3), 0.93 (s, 3 H, CH_3).

(2*S,3*R**,3′*R**,4′*S*)-2-(3′,4′-Epoxy-5′-hexenyl)tetrahydropyran-3-ol (63).** Sodium methoxide (6.5 mg, 0.12 mmol) was added in one protion to a solution of compound **62** (43.1 mg, 0.1 mmol) in MeOH (3 mL) at 25 °C. The reaction mixture was stirred at that temperature for 30 min before it was diluted with ether (50 mL) and washed with H_2O (2 × 10 mL) and brine (5 mL). Drying ($MgSO_4$) followed by concentration and flash chromatography (silica, 40% ether in petroleum ether) furnished compound **63** (18.8 mg, 95%). **63**: oil; R_f = 0.30 (silica, 60% ether in petroleum ether); $[\alpha]^{23}_D$ −40.50° (*c* 0.2, CH_2Cl_2); IR (neat) ν_{max} 3430 (s, OH), 2925, 2850, 1448, 1275, 1100, 932, 815 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.75 (m, 1 H, C*H*=CH_2), 5.49 (d, *J* = 16.5 Hz, 1 H, CH=CH_2), 5.35 (d, *J* = 10.4 Hz, 1 H, CH=CH_2), 3.85 (m, 1 H, CH_2O, equatorial), 3.42 (dd, *J* = 7.3, 3.7 Hz, 1 H, epoxide), 3.28 (m, 2 H, CH_2O, C*H*O), 3.15 (m, 1 H, CH_2O), 3.02 (m, 1 H, CH_2O or C*H*O), 2.15–1.30 (m, 8 H, CH_2); HRMS calcd for $C_{11}H_{19}O_3$ $(M + H)^+$ 199.1334, found 199.1353.

Reaction of Trans Hydroxy Epoxide 61 with Dimsylpotassium, Preparation of (1*R,1′*S**,3′*R**,8′*S**)-2-(2′,7′-Dioxabicyclo[4.4.0]decan-3′-yl)-2-propanol (64) and Its Acetate (64a).** Dimsylpotassium (0.2 mL, 1 M solution, 0.2 mmol) (prepared from 160 mg of potassium hydride and 4.0 mL of DMSO) was added dropwise to a solution of compound **61** (19.8 mg, 0.1 mmol) in dry DMSO at 25 °C. The reaction mixture was allowed to stir at that temperature for 1 h before it was diluted with ether (50 mL) and washed with H_2O (10 mL) and brine (5 mL). Drying ($MgSO_4$) followed by solvent removal and flash column chromatography (silica, 40% ether in petroleum ether) gave compound **64** (19.2 mg, 97%). **64**: oil; R_f = 0.50 (silica, 60% ether in petroleum ether); $[\alpha]^{23}_D$ −8.80° (*c* 0.5, CH_2Cl_2); IR (neat) ν_{max} 3450 (s, OH), 2918, 2842, 1438, 1270, 1214, 1100, 962, 920, 745 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.83 (m, 1 H, C*H*=CH_2), 5.31 (d, *J* = 17.2 Hz, 1 H, CH=CH_2), 5.24 (d, *J* = 11.0 Hz, 1 H, CH=CH_2), 4.18 (br s, 1 H, =CHC*H*O), 3.86 (m, 1 H, CH_2O, equatorial), 3.38 (m, 2 H, C*H*O), 3.10 (m, 1 H, C*H*O), 2.92 (m, 1 H, C*H*O), 2.30 (br s, 1 H, O*H*), 2.10–1.40 (m, 8 H, CH_2); HRMS calcd for $C_{11}H_{22}O_3N$ $(M + NH_4)^+$ 216.1599, found 216.1585. Acetylation of **64** with Ac_2O and DMAP under standard conditions (see above) gave acetate **64a** in 96% yield. **64a**: oil; R_f = 0.5 (silica, 30% ether in petroleum ether); $[\alpha]^{23}_D$ −15.0° (*c* 0.2, CH_2Cl_2); IR (neat) ν_{max} 2942, 2865, 1755 (s, Ac), 1385, 1245, 1110, 755 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.85 (m, 1 H, C*H*=CH_2), 5.32–5.25 (m, 2 H, CH=CH_2), 5.18 (dd, *J* = 7.8, 8.2 Hz, 1 H, C*H*OAc), 3.90 (m, 1 H, CH_2O, equatorial), 3.49 (m, 1 H, C*H*O), 3.35 (m, 1 H, C*H*O), 3.00 (m, 2 H, C*H*O), 2.10 (s, 3 H, OCH_3), 1.99–1.50 (m, 8 H, CH_2); HRMS calcd for $C_{13}H_{21}O_4$ $(M + H)^+$ 241.1439, found 241.1437.

Reaction of Cis Hydroxy Epoxide 63 with Dimsylpotassium. Preparation of (1S*,1'S*,3'R*,8'S*)-1-(2',7'-Dioxabicyclo[4.4.0]decan-3'-yl)-2-propanol (65) and Its Acetate (65a). The bicyclic compound **65** was prepared from compound **63** (19.8 mg, 0.1 mmol) by the same procedure used to convert **61** to **64**. Flash chromatography (silica, 40% ether in petroleum ether) gave compound **65** (19.0 mg, 96%). Compound **65** also can be prepared from compound **63** (19.8 mg, 0.1 mmol) by the same procedure used to convert **61** to **62** via acid catalysis. (9.0 mg, 45% after flash column chromatography). **65**: oil; R_f = 0.47 (silica, 60% ether in petroleum ether); $[\alpha]^{23}_D$ +7.0° (*c* 0.1, CH_2Cl_2); IR (neat) ν_{max} 3440 (s, OH), 2940, 2838, 1438, 1262, 1100, 962, 842 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.78 (m, 1 H, C*H*=CH_2), 5.33 (d, *J* = 17.1 Hz, 1 H, CH=CH_2), 5.20 (d, *J* = 10.5 Hz, 1 H, CH=CH_2), 3.84 (m, 2 H, C*H*O, =CHC*H*O), 3.48 (m, 1 H, C*H*O), 3.25 (m, 1 H, C*H*O), 2.99 (m, 2 H, C*H*O), 2.75 (br s, 1 H, O*H*), 2.18-1.38 (m, 8 H, CH_2); HRMS calcd for $C_{11}H_{22}O_3N$ $(M + NH_4)^+$ 216.1599, found 216.1582. Acetylation of **65** with Ac_2O and DMAP under standard conditions led to acetate **65a** in 97% yield. **65a**: oil; R_f = 0.48 (silica, 30% ether in petroleum ether); $[\alpha]^{23}_D$ +21.67° (*c* 0.3, CH_2Cl_2); IR (neat) ν_{max} 2950, 2859, 1750 (s, Ac), 1452, 1378, 1242, 1100, 970, 848 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.82 (m, 1 H, C*H*=CH_2), 5.25 (m, 3 H, CH=CH_2), and C*H*OAc), 3.88 (m, 1 H, CH_2O, equatorial), 3.48 (m, 1 H, C*H*O), 3.38 (m, 1 H, C*H*O), 2.95 (m, 2 H, C*H*O), 2.18 (s, 3 H, OCH_3), 2.08-1.80 (m, 8 H, CH_2); HRMS calcd for $C_{13}H_{21}O_4$ $(M + H)^+$ 241.1440, found 241.1465.

(1'S*,3'R*,8'S*)-1-(2',7'-Dioxabicyclo[4.4.0]decan-3'-yl)-2-propen-1-one (66). Manganese dioxide (87 mg, 1.0 mmol) was added in one protion to a solution of **64** or **65** (19.8 mg, 0.1 mmol) in dry CH_2Cl_2 (3 mL) at 25 °C. The reaction mixture was stirred at room temperature for 2 h before the solid was removed by filtration through a Celite pad. Solvent removal followed by flash column chromatography (silica, 20% ether in petroleum ether) gave pure **66** (14.7 mg, 75%) and recovered starting material, **64** (4.2 mg, 21%) or **65** (4.0 mg, 20%). **66**: oil; R_f = 0.5 (silica, 20% ether in petroleum ether); $[\alpha]^{23}_D$ -11.0° (*c* 0.1, CH_2Cl_2); IR (neat) ν_{max} 2910, 2842, 1705 (s, ketone), 1610, 1460, 1095, 968 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.00 (dd, *J* = 10.6, 17.3 Hz, 1 H, C*H*=CH_2), 6.54 (d, *J* = 17.3 Hz, 1 H, CH=CH_2), 5.45 (d, *J* = 10.6 Hz, 1 H, CH=CH_2), 3.85 (m, 2 H, C*H*O), 3.24 (m, 1 H, C*H*O), 2.98 (m, 1 H, C*H*O), 2.92 (m, 1 H, C*H*O), 2.10-1.50 (m, 8 H, CH_2); HRMS calcd for $C_{11}H_{17}O_3$ $(M + H)^+$ 197.1178, found 197.1181.

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Supplementary Material Available: Data for compounds **15b-40** (R_f values, $[\alpha]_D$, IR, ^1H NMR, and MS data) (10 pages). Ordering information is given on any current masthead page.

Asymmetric Diels-Alder Reaction Catalyzed by a Chiral Titanium Reagent

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Abstract: A highly enantioselective Diels-Alder reaction has been developed by employing a chiral titanium reagent generated in situ from dichlorodiisopropoxytitanium and the chiral diol **1d**, which is easily derived from tartaric acid. With a catalytic amount of the titanium reagent, various acyloxazolidinone derivatives of α,β-unsaturated carboxylic acids react smoothly with dienes in the presence of 4A molecular sieves to give the corresponding optically active cycloadducts. Examination of the solvents revealed that the enantioselectivity and the reactivity of this reaction are widely dependent on the acceptor and donor properties of the solvents. By utilizing mesitylene, $CFCl_3$, or a mixed solvent of toluene and petroleum ether (or hexane), high enantioselectivity is achieved, and various synthetically useful chiral intermediates are obtained by a simple reaction procedure.

The Diels-Alder reaction has long been recognized as one of the most important methods for construction of cyclohexene derivatives. Due to the concerted and secondary orbital controlled reaction pathway, usually high, predictable stereoselectivity can be realized, making this reaction particularly useful in the stereoselective synthesis of various useful synthetic intermediates.

The control of absolute stereochemistry in the Diels-Alder reaction has been studied extensively since the first observation reported by Korolev et al. that optically active cycloadducts could be obtained by the reaction of menthyl fumarate and butadiene.[1] Another milestone was established by Walborsky, and the addition of a Lewis acid such as aluminum chloride, tin(IV) chloride, and titanium(IV) chloride was found to greatly enhance the enantioselectivity of the above reaction.[2] Since these findings, great progress has been made, and nearly complete asymmetric induction can be achieved with ingeniously designed chiral dienes or dienophiles.[3] Although these methods afford facile entry into the preparation of chiral cyclohexene derivatives, the processes for the introduction and removal of chiral auxiliary are necessitated and at least a stoichiometric amount of the chiral auxiliary is indispensable.

It is well-known that Lewis acids promote the Diels-Alder reaction,[4] but use of chiral Lewis acid to induce chirality in the Diels-Alder reaction has met with only limited success at the time when we started to study the asymmetric Diels-Alder reaction, probably due to the difficulty in designing appropriate chiral Lewis

(1) Korolev, A.; Mur, V. *Dokl. Akad. Nauk SSSR* **1948**, *59*, 251.
(2) (a) Walborsky, H. M.; Barash, L.; Davis, T. C. *J. Org. Chem.* **1961**, *26*, 4778. (b) Walborsky, H. M.; Barash, L.; Davis, T. C. *Tetrahedron* **1963**, *19*, 2333.
(3) (a) Paquette, L. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: Orlando, 1984; Vol. 3, p 455. (b) Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Springer-Verlag: Berlin, 1986; Vol. 4, p 262. (c) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876. (d) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1984**, *106*, 4261. (e) Masamune, S.; Reed, L. A.; Davis, J. T.; Choy, W. *J. Org. Chem.* **1983**, *48*, 4441. (f) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.* **1986**, *108*, 3510.
(4) Yates, D.; Eaton, P. E. *J. Am. Chem. Soc.* **1960**, *82*, 4436.

0002-7863/89/1511-5340$01.50/0