Metal-Assisted Aldol Condensation of Chiral α-Halogenated Imide Enolates: A Stereocontrolled Chiral Epoxide Synthesis[1]

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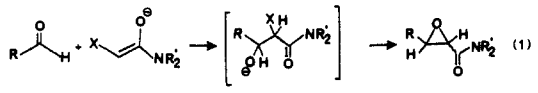
Abstract: Enantiomerically pure benzyl *cis*-α,β-epoxy carboxylates were prepared by a modified Darzens procedure employing an aldol condensation on chiral α-haloimides with various aldehydes. This aldol reaction was mediated by metal and non-metal cations of different oxygen chelating characteristics (Li, Zn, Sn^{II}, Sn^{IV}, and B) in THF or ether generally at −78 °C. Stereoselectivity was found to be dependent on experimental conditions and the metal chosen. Generally, enantio- and diastereoselectivity were highest for boron triflate mediated reactions and lowest for lithium enolates. A unique reversal in the absolute stereochemistry of the principal products was observed in the boron and Sn^{II} mediated reactions as compared to the products obtained by Li, Zn, and Sn^{IV} metal cations.

The epoxide functionality, which affords the chemist an opportunity to manipulate two adjacent functionalized carbons, repeatedly has been demonstrated to be a versatile and useful moiety for organic synthesis.[2] The elegant asymmetric epoxidation procedure reported by Sharpless and Katsuki[3] has provided a facile approach to the chiral epoxides which allows for total stereocontrol of both asymmetric centers. Our interest in chiral epoxidation evolved from efforts to prepare optically active α,β-epoxy acid derivatives.[4a] We envisioned employing the Sharpless procedure to prepare all four stereoisomers. However, in our hands this method proved not to be as efficient with *cis*-allylic alcohols as with the corresponding trans, even though the stereocontrol remained exceptionally high.[4b] Since such loss of conversion efficiency has been observed previously by Sharpless[5] for the Ti^{IV} catalyzed chiral epoxidations of certain secondary olefins, it was our intention to investigate alternative methods of chiral epoxy carboxylate synthesis. A promising solution to this problem appeared to be the addition of chiral α-metalated methyl aryl sulfoxides to aldehydes as reported initially by Durst[6a] and later by Solladie.[6b] However, we obtained low levels of chiral induction and poor chemical yields for enolizable aldehydes.[4b] We then turned our attention to the development of an independent method for the generation of chiral epoxy carboxylates.

Our approach to the solution of this problem is based on the Darzens glycidic ester condensation which has been one of the more reliable methods for the construction of the α,β-epoxy esters.[7] Attempts have been made to develop a chiral modification of the procedure by utilizing α-halo acetates of chiral alcohols. However, disappointingly low levels of chiral induction were reported.[7b,c]



(1)

We reasoned that since the first part of the Darzens epoxidation entails an aldol-type condensation of α-halo esters with aldehydes or ketones, a stereoselective modification could be carried out employing methods developed in several laboratories[8-11] for chiral aldol condensations. In particular, we aimed at using the chiral aldol condensation procedure developed by Evans[10] employing the enolates of *N*-acyl oxazolidinones. Such a modification would involve the use of the enolates of chiral α-haloacyl oxazolidinones (or α-halogenoamides) in aldol-type condensations with aldehydes and then converting the resulting halohydrins to epoxides (eq 1). Since enolates of α-halogenoamides have not been previously explored under aldol condensation conditions, we decided to evaluate the influence of enolate countercations in determining the stereochemical course of this reaction. For this study we chose the readily accessible Li[8b,c13], Sn^{II},[14] Sn^{IV},[15] Zn,[16] B,[10,12] and Zr[17]

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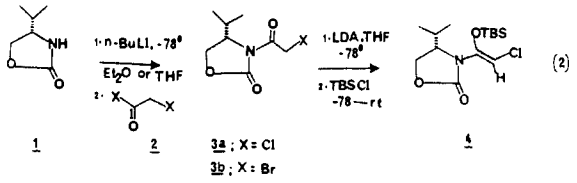
cations. Although cation effect on product stereochemistry from aldol reactions has been extensively studied,[8,9] only the influence of Li, Zr, and B as catalysts in the *N*-acyl amide and imide enolate aldol reactions have been reported.[10,17]

Results

The starting chiral *N*-(α-haloacetyl)oxazolidinones **3** were readily prepared from their respective α-haloacetyl halides **2** and (4*S*)-4-(isopropyl)-2-oxazolidinone (**1**).[10a] The lithium enolate of **3a** was generated under kinetic conditions (LDA, −78°C, THF or ether) and trapped as the *tert*-butyldimethylsilyl enol ether **4**, predominately a single isomer (>40:1 ratio) (eq 2). Our assignment of the *Z* configuration and rotational conformer as represented by **4** is based on arguments presented for the propionamide enolate analogue[10a,b,f] and on our observed >10% NOE of the isopropyl methyls at δ 0.85 on irradiation of the silyl methyls at δ 0.22. Similar irradiation of the olefinic proton at δ 5.56 produced no effect on the isopropyl or silylmethyl groups. The Zn and Sn^{IV} enolates were obtained from lithium enolates by adding ethereal solutions of $ZnCl_2$ or $Sn(n\text{-}Bu)_3Cl$, respectively, at −78 °C and warming the resulting solutions to −20 °C. The Sn^{II} enolates were prepared either by the procedure of Mukaiyama[11a] or from the lithium enolate by adding a THF solution of stannous triflate at −78 °C. Boryl enolates were prepared by the method of Evans.[10d,23] In all cases the aldehyde was added to the solution containing the enolate at −78 °C, except for Zn enolates where the addition was done at −20 or 0 °C. The various aldehydes employed along with subsequent results are shown in Table I.



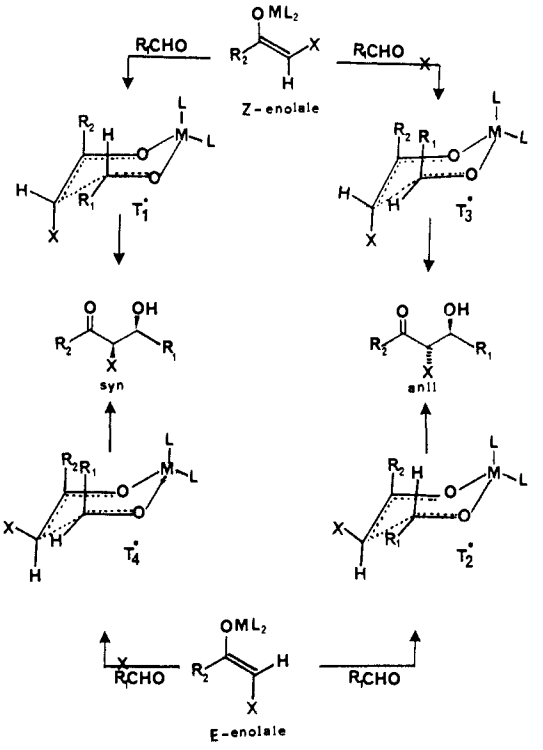
Several conclusions may be derived from the data presented in Table I regarding the intrinsic relationship between the variables that control final product stereochemistry, namely the enolate countercation and the aldehydic bulk. The diastereoselectivity of the aldol reaction with chiral α-haloimide enolates gave predominately syn products which is in agreement with previous findings.[10] However, while this selectivity was generally moderate for lithium catalyzed condensations where X = Cl (e.g., entries 1, 14, and 27),[22] the process was improved by using Zn, Sn^{II}, and Sn^{IV} enolates. In particular, the aldol reactions from boryl enolates exhibited exceptionally high stereoselection (e.g., entries 12, 25, and 39). In fact, none of the anti-isomers could be detected in this case by 90-MHz ^1H NMR or GC.[18]

The diastereoselectivity exhibited for Zn enolate was consistently improved over the range of aldehydes studied at a decreased molar ratio of zinc chloride (e.g., compare entries 3 vs. 4, 5 vs. 6, 16 vs. 17, 18 vs. 19, 29 vs. 30, and 32 vs. 33) (Table I)). Widdowson observed a similar effect using zinc chloride in an aldol reaction between γ-butyrolactone and benzaldehyde.[21] Apparently, in these cases, the zinc cation is capable of intermolecularly binding two enolate molecules and thereby producing more steric demand in the transition state.

Diastereoselectivity in stannous triflate [$Sn(OTf)_2$] mediated reactions was found to be dependent on the method of enolate generation. The α-chloro enolates generated by the method of Mukaiyama[11a] [$Sn(OTf)_2$, tertiary amine, CH_2Cl_2 at 0 °C] resulted in only modest levels of diastereo- and enantioselectivities (entries 7, 20, and 34). The reaction with the α-bromo enolate yielded a dehydration product from the initially formed bromohydrin as the major component of a mixture. By comparison, the diastereoselectivity of this reaction was greatly improved by generating the lithium enolate before adding a THF solution of stannous triflate at −78 °C (entries 8, 21, and 35). Generally, for all the cases reported in Table I an increase in diastereoselectivity was observed in replacing the α-chloro enolate with its α-bromo analogue.

While the excellent diastereoselectivity obtained with the di-*n*-butylboryl enolate was an outstanding result, an even more exciting observation was made concerning the absolute stereochemistry of the syn products (Table I, **5**:**6** ratios). Comparing the stereochemistry of the newly formed chiral centers in the products **5** (product of Sn^{II} and B enolates) with **6** (product of

Scheme I



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(16) Anhydrous $ZnCl_2$ in solution was prepared according to House et al.: House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

(17) Evans, D. A.; McGee, L. R. *Tetrahedron Lett.* **1980**, *21*, 3975.

(18) Diastereomeric ratios were determined by 90-MHz ^1H NMR on a Varian EM-90 in deuteriochloroform with Me_4Si as internal standard and/or with capillary GC (DB-1, 15 m × 0.252 mm).

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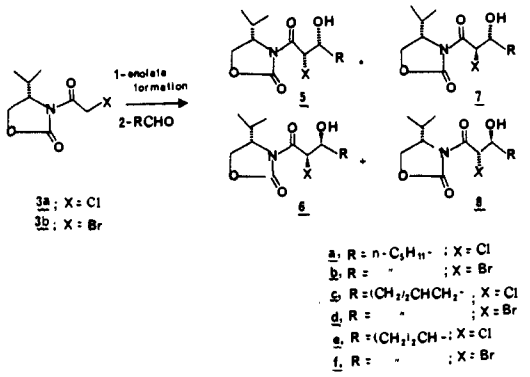
(22) While we did not rigorously study the effect of temperature on this reaction, we did react the chlorohydrin 5a with LDA at −78 °C in THF and allow the solution to stand at −78 °C for 0.5 h before quenching. 90-MHz ^1H NMR analysis did not detect a change in the stereochemical integrity of this material. On the other hand, repeating the reaction under similar conditions and allowing the solution to warm to ambient temperature over 1.5 h produced a mixture of all four possible stereoisomers. Thus, the lower temperature appears to be an absolute precondition to obtained high stereodifferentiation from lithium enolates and avoiding epimerization and/or retro-aldol reactions.

(23) We encountered considerable difficulty in generating the boryl enolate at the genesis of our study. This difficulty was overcome by distilling the pyrophoric tri-*n*-butylborane before use in forming the di-*n*-butylboryl triflate.[12b] We are very grateful to Prof. A. I. Meyers for sharing with us this insight.

Table I. Aldol Condensations of Metal Enolates of **3** with Representative Aldehydes



				product distribution[a]			
				diastereoselection syn/anti	enantioselection		yield,[e]
entry	R	X	metal[b]	(5 + 6:7 + 8)	5:6	7:8	%
1	n-C_5H_{11}-	Cl	Li	2:1	1:2	1:1	52
2		Br	Li	6:1	1:3	4:1	49
3		Cl	Zn (1 equiv)	3:1	1:6	7:1	60
4		Cl	Zn ($^1/_2$ equiv)	5:1	1:4	5:1	60
5		Br	Zn (1 equiv)	4:1	1:7	5:1	63
6	n-C_5H_{11}-	Br	Zn ($^1/_2$ equiv)	8:1	1:7	5:1	65
7		Cl	Sn^{II}[c]	3:1	2.5:1	1:2	84
8		Cl	Sn^{II}	6:1	6:1	2:3	73
9		Br	Sn^{II}	4:1	8:1	1:1	67
10		Cl	Sn^{IV}	3:1	1:4	2:1	75
11		Br	Sn^{IV}	3:1	1:5	12:1	71
12		Cl	B	>50:1	>50:1	*d*	62
13		Br	B	>50:1	>50:1	*d*	55
14	$(CH_3)_2CHCH_2$-	Cl	Li	2:1	1:2	3:2	48
15		Br	Li	6:1	1:2	3:1	52
16		Cl	Zn (1 equiv)	3:1	1:3	7:1	60
17		Cl	Zn ($^1/_2$ equiv)	6:1	1:3	3:1	63
18		Br	Zn (1 equiv)	5:1	1:6	5:1	76
19		Br	Zn ($^1/_2$ equiv)	11:1	1:5	3:1	72
20		Cl	Sn^{II}[c]	4:1	3:1	2:3	68
21		Cl	Sn^{II}	8:1	7:1	3:2	73
22		Br	Sn^{II}	6:1	11:1	1:1	68
23		Cl	Sn^{IV}	2:1	1:4	6:1	70
24		Br	Sn^{IV}	4:1	1:4	20:1	72
25		Cl	B	>50:1	>50:1	*d*	55
26		Br	B	>50:1	>50:1	*d*	48
27	$(CH_3)_2CH$-	Cl	Li	3:1	1:3	3:2	46
28		Br	Li	5:1	1:5	2:1	70
29		Cl	Zn (1 equiv)	17:1	1:8	8:1	68
30		Cl	Zn ($^1/_2$ equiv)	19:1	1:7	9:1	74
31		Br	Zn (1 equiv)(THF)	7:1	1:9	3:1	74
32		Br	Zn (1 equiv)(Et_2O)	24:1	1:10	3:1	84
33		Br	Zn ($^1/_2$ equiv)(Et_2O)	40:1	1:8	4:1	79
34		Cl	Sn^{II}[c]	3:1	2:1	2:3	64
35		Cl	Sn^{II}	13:1	4:1	1:1	77
36		Br	Sn^{II}	16:1	6:1	1:1	65
37		Cl	Sn^{IV}	4:1	1:7	5:1	66
38		Br	Sn^{IV}	6:1	1:10	13:1	76
39		Cl	B	>50:1	>50:1	*d*	52
40		Br	B	>50:1	>50:1	*d*	51

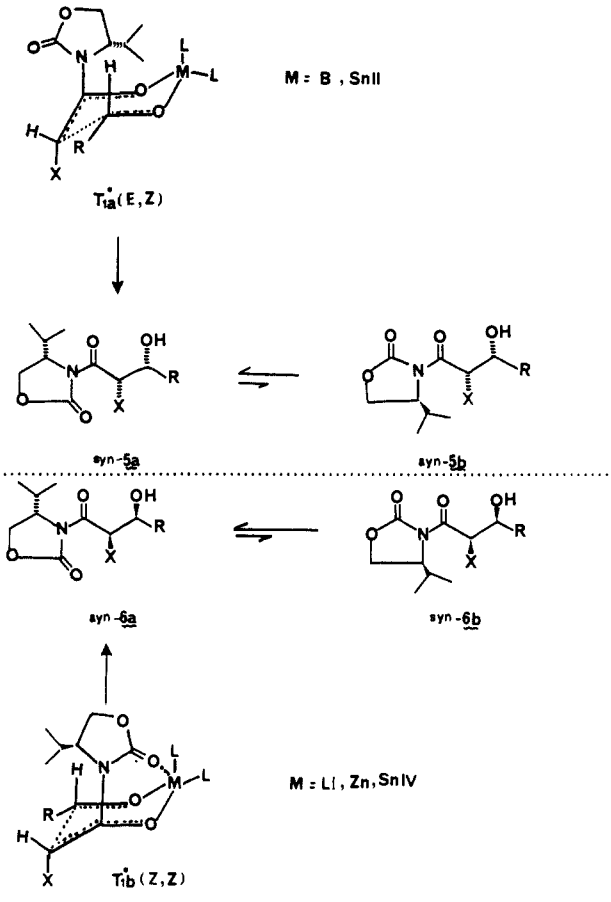
[a] Ratios determined by 90-MHz ^1H NMR and/or capillary GC (0.25 × 15 m, DB-1). [b] The countercation Zn refers to ZnCl; Sn^{II} refers to $Sn(OSO_2CF_3)$. Sn^{IV} refers to $Sn(n\text{-}Bu)_3$ and B refers to $B(n\text{-}Bu)_2$. [c] Conditions reported by Mukaiyama[11a] were used. [d] The syn isomer **5** was the only detected product by ^1H NMR. [e] All reported yields were based on isolated and purified product.

Li, Sn^{IV}, and Zn enolates), we observed a reversal in the stereochemical sense of the process. In all cases studied the absolute configurations were verified by X-ray crystallography and ^1H NMR (vide infra).

Discussion

The stereoselective outcome of boron mediated chiral aldol condensations has previously been interpreted employing the Zimmerman and Traxler[10,19] pericyclic chair-like transition-state model (Scheme I). In this model reference is made to the work of Dubois, who initially demonstrated the interdependence of product stereochemistry and enolate geometry by showing that the reaction of (*Z*)- and (*E*)-lithium enolates with aldehydes gives *syn*- and *anti*-aldol products, respectively. Since it has been generally accepted that kinetically generated lithium enolates (LDA, −78 °C, THF) of *N*-acyl amides and imides exist in the *Z* configuration,[10a,b,f] they react with aldehydes via T_1* and T_3* (Scheme I) to yield products of syn or anti configuration, respectively. The 1,3-diaxial interactions between the ligand (L) and R_1 and R_2 predict T_1* to be favored and the syn isomer to be the major product. The magnitude of these diaxial interactions which control the diastereoselectivity (syn vs. anti) will thus depend on two variables, the chelating cation (including its ligands) and the bulk of the aldehyde. The former is generally of greater

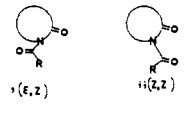
Scheme II



importance and is much more a stereocontrolling factor when R_1 is small.[8d,10b,g]

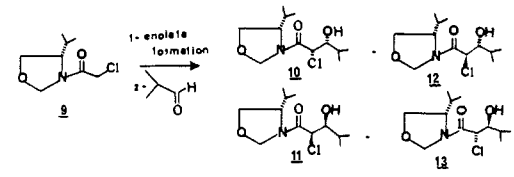
The origin of the unexpected difference in enantioselection with Sn^{II} and B as compared to Li, Zn, and Sn^{IV} enolates is not completely understood. We postulate that a major stereocontrolling factor is the difference in orientation about the exocyclic imide carbonyl as represented by transition states T_{1a}* and T_{1b}* (Scheme II). In this model, enantioselectivity is controlled through the direction of attack of the enolate on the aldehyde, which depends to a large extent on the orientation of the enolate face with respect to the oxazolidinone ring. Because of steric constraints, the aldehyde approaches the enolate on the face that is remote to the isopropyl group on the ring. These differences in the orientation of the enolate then would account for the different enantioselectivity.[24] The enolate orientation as represented in T_{1a}*(*E*,*Z*), where the ring carbonyl is anti to the enolate carbonyl, should yield isomer *syn*-**5**. This isomer was the major product formed in B and Sn^{II} mediated reactions (Table I). The alternative transition state T_{1b}*(*Z*,*Z*) should yield syn-isomer **6**. Such was the case with Li, Zn, and Sn^{IV} mediated reactions. Apparently Li, Zn, and Sn^{IV} overcome the thermodynamic dipolar forces[25] that favor the *E*,*Z* orientation through chelation involving the

(24) Raban has demonstrated through the use of a variety of experimental methods that imides similar to our oxazolidinyl system are more stable in the ground state as the *E*,*Z* configuration (i) than in the dipole–dipole interaction destabilized *Z*,*Z* configuration (ii): Noe, E. A.; Raban, M. *J. Am. Chem. Soc.* **1975**, *97*, 5811.



(25) The decrease in free energy of activation obtained by the chelation of Li, Zn, and Sn^{IV} with the enolate and two carbonyls is apparently sufficient to overcome the unfavorable dipolar destabilization that would be present in the unchelated form. Raban has demonstrated that the Li chelated form of imides prefer the syn orientation: Raban, M.; Noe, E. A.; Yamamoto, G. *J. Am. Chem. Soc.* **1977**, *99*, 6527.

Table II. Aldol Reaction of Metal Enolates of **9** with Isobutyraldehyde



metal	product distribution[a] **10:11:12:13**	diastereoselection syn/anti **10 + 11/12 + 13**	enantioselection syn **10:11**	enantioselection anti **12:13**
Zr	80:6:3:11	86:14	13:1	1:4
Sn^{IV}	60:36:4:–	96:4	2:1	*b*
Li	51:27:4:18	78:22	2:1	1:4
Sn^{II}	48:32:6:14	80:20	3:2	1:2
Zn	33:34:7:26	67:33	1:1	1:4

[a] The ratios were determined by capillary GC. [b] None of **13** was detected by GC.

enolate and both carbonyls. Without loss of ligand (L), boron and Sn^{II} cannot simultaneously bind the three oxygen atoms derived from the enolate and the two carbonyls. Thus, the reaction proceeds through a template similar in character to T_{1a}* with its *E*,*Z* orientation to yield the syn-**5** enantiomer.[26-30]

The observation of *opposite* enantioselectivity for Sn^{II} and Sn^{IV} enolates represent to our knowledge the first example of a chiral aldol-type condensation which is dependent on the oxidation state of the metal cation. However, differences in diastereoselectivity for divalent and tetravalent tin enolates have been reported.[15b,e] To yield **6** tetravalent tin must, for reasons previously stated, proceed via T^*_{1b} which involves chelation to the metal by the oxazolidinone carbonyl. The relatively high coordination potential of Sn^{IV} compared to Sn^{II} has been documented.[15f,g] For divalent tin this type of intramolecular interaction apparently is not the major stereocontrolling factor, as is evidenced by the predominant formation of **5**, the product from T^*_{1a}. The origin of this marked difference in behavior may lie in the difference in the coordination numbers of Sn^{II} and Sn^{IV}. Since the latter could be expected to be pentacoordinated, its coordination as depicted in T^*_{1b} is not unreasonable. Sn^{II}, on the other hand, can be expected to exist as shown in T^*_{1a} with one less ligand.

To further support the premise that the oxazolidinone ring carbonyl is intrinsically involved in chelation as the *Z*,*Z* conformer for Li, Sn^{IV}, and Zn condensations to form predominately **6**, the same metal mediated aldol reactions were conducted with *N*-(α-chloroacetyl)oxazolidine (**9**), where the ring carbonyl is now

(26) There is literature precedent for such a chelation. In a highly stereoselective (17:1 ratio of diastereoisomers) aldol reaction of a lithio enolate and a β-siloyoxy aldehyde, Masamune proposed[27] a lithio chelated transition state that involved simultaneous chelation of the three oxygens.[29] Correspondingly, the dialkylboryl enolate yielded only a 1.5–1.8:1 ratio of diastereoisomers. Presumably, this was due to the inability of boron to bind to all three oxygens at once. A similar rationale was presented by Heathcock in Chapter 2 of ref 8d.

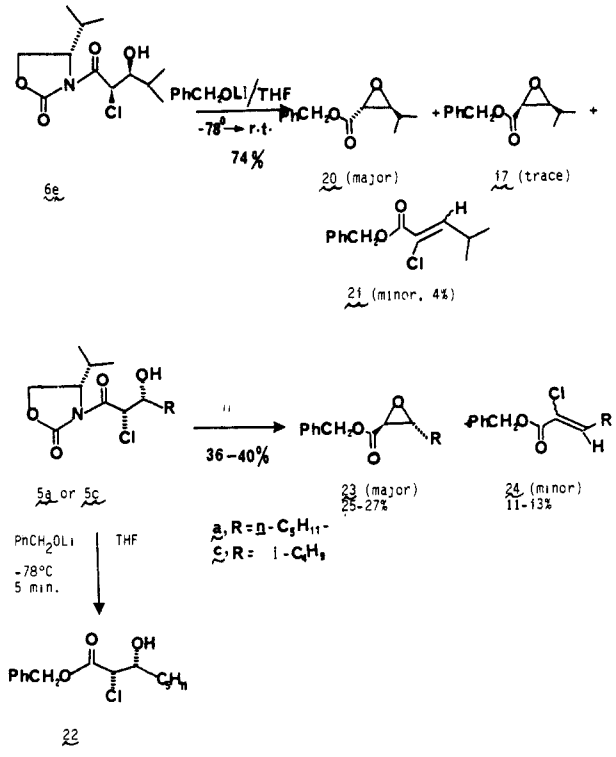
(27) Masamune, S.; Hirama, M.; Mori, S.; Ali, Sk. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568. For similar examples of lithium chelation in aldol type hydroxy alkylations see Multzer[28] and ref 8d.

(28) Multzer, J.; DeLasalle, P.; Chucholowski, A.; Blaschek, U.; Bruntrup, G.; Jibril, I.; Huttner, G. *Tetrahedron* **1984**, *40*, 2211.

(29) The observations that lithium enolates and their subsequent aldol transition states most probably exist as multi-chelated species have been well documented. In fact tetrameric aggregates of lithium enolates derived from 3,3-dimethyl-2-butanone and cyclopenetanone have been characterized by powder X-ray analysis. Conceivably, similar aggregation in solution plays a major role in determining our stereochemical observations: (a) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622. (b) Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Ibid.* **1981**, *64*, 2617. (c) Weidmann, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 31 and ref 13d. (d) Jackman, L. M.; Lange, B. C. *Tetrahedron* **1977**, 33, 2737. (e) Jackman, L. M.; DeBrosse, C. W. *J. Am. Chem. Soc.* **1983**, *105*, 4177.

(30) In another appropriate example, Meyers was successful in effecting a reversal of prochiral faces by isomerization of *E* to *Z* isomers of metalated lithioenamines leading to optical antipodes on alkylation: Meyers, A. I.; Williams, D. R.; White, S.; Erickson, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 3088.

Scheme III



absent. These reactions yielded mostly *syn*-chlorohydrin aldol products (Table II) of the same enantiomeric sense as **5** in Scheme II. This stereoisomer was also predominately obtained[10h] by bis(cyclopentadienyl)zirconium dichloride (Cp_2ZrCl_2) mediated aldol reaction of the propionamide analogue of **9** which is reported to react as the *Z* enolate. Thus, in the absence of the chelating potential of the oxazolidone ring carbonyl, addition to the aldehyde occurs thru the more favored *E,Z*-like transition state similar to T^*_{1a} since this would appear to minimize steric interactions on amide deprotonation.[10a,b,f]

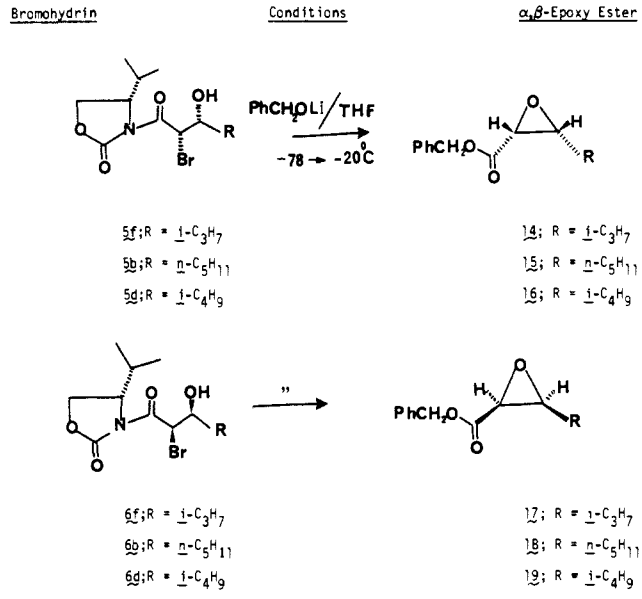
Epoxide Formation: Results and Discussion

With stereoselective methods for preparing chiral bromo- and chlorohydrins **5–8** in hand we turned our attention to their stereospecific conversion to chiral epoxides. Our initial efforts employing chlorohydrins under a variety of base catalyzed conditions failed because of concurrent epimerization before cyclization as evidenced by the formation of trans epoxide from *syn*-**6e**. Mukaiyama[31] has reported his success in employing KF and CsF to effect conversion of α-bromo-β-hydroxy ketones to α,β-epoxy ketones. However, these conditions were unsuccessful on our system.

Application of the mild lithium benzyloxide[32] hydrolysis conditions to chlorohydrins (**5a**, **5e**, and **6e**, Scheme III) was only effective upon allowing the reaction mixture to warm to ambient temperature. The major products in both reactions were trans epoxides **20** and **23** which apparently result from base catalyzed epimerization at C_7 before chloride displacement. Minor quantities of elimination products **21** and **24** were also isolated. The reason for the lower yield of **23** from **5** (in comparison to **20** from **6e**) could possibly be due to retro-aldol reaction and/or disproportionation. In one case we successfully prepared the chlorohydrin benzyl ester **22** from **5a** by quenching the hydrolysis reaction after 5 min at −78 °C.

Conversely, *syn*-bromohydrins **5** and **6** were stereospecifically and cleanly converted to the *cis*-benzyl α,β-epoxy esters **14–19** with lithium benzyloxide[32] (THF, −78° → −20 °C) with no evidence of epimerization to trans epoxides (Scheme IV) in 70–74% isolated yields. Such a facile and clean conversion may be a manifestation of the relative ease of bromide displacement as compared to chloride. This successful cyclization thus satisfies our original goal of a stereospecific chiral epoxide synthesis.

Scheme IV. Base-Catalyzed Conversion of Oxazolidinone Bromohydrins **5** and **6** to Benzyl α,β-Epoxy Esters **14–19**[a]



[a] The epoxides were prepared from diastereomerically pure bromohydrins. The enantiomeric purity of epoxides **14** and **17** was checked employing 270-MHz ^1H NMR and the chiral shift reagent $Eu(tfc)_3$.

Summary

We have demonstrated the synthesis of both antipodes of α,β-epoxy esters from diastereomeric bromohydrins (enantiomeric at C_7 and C_8) which in turn were synthesized from the same chiral α-haloimide. By exploiting the different chelating ability of selected cations we have been able to direct aldehydic attack to either diastereotopic face of the imide enolate to yield addition products that result via diastereomeric transition states. Conversion of these diastereomeric bromohydrins to their (−) and (+) cis-α,β-epoxy benzyl esters was accomplished in good yield and with minimal loss of optical activity. Conversely, using our conditions, conversion of the chlorohydrins to the cis epoxides could not be effected without concurrent epimerization at C_7 resulting in cyclization to trans epoxides. This conversion, however, was not as efficient as the former. These result represent, to our knowledge, the first example of employing the same chiral precursor to obtain both enantiomers in high enantioselectivity in a metal mediated aldol reaction.[42]

Sample X-ray: Structure Description of 6e. In the orthorhombic space group $P2_12_12_1$ with eight formula units in the cell there are

(31) Mukaiyama, T.; Hagar, T.; Iwasawa, N. *Chem. Lett.* **1982**, 1601.
(32) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(33) Johnson, C. K. *ORTEPII*; Oak Ridge National Laboratory Report ORNL-5138, 1976.
(34) Benedetti, E.; Morelli, G.; Nemethy, G.; Scheraga, H. A. *Int. J. Peptide Protein Res.* **1983**, *22*, 1.
(35) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. M. *MULTAN 80, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data*; Universities of York: England and Louvain, Belgium, 1980.
(36) $R = \sum||F_o| - |F_c||/\sum|F_o|$; $R_w = [\sum w(|F_o| - |F_c|)^2 \sum w(F_o)^2]^{1/2}$.
(37) Cornfield, P. W. R.; Doedens, R. J.; Ibers, J. A. *Inorg. Chem.* **1967**, *6*, 197.
(38) Hamilton, W. C. *Acta Crystallogr.* **1965**, *18*, 502.
(39) Ibers, J. A.; Hamilton, W. C. Eds. *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974. (a) Volume IV, Table 2.2A, p 72. (b) Volume IV, Table 2.3.1, p 149.
(40) Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Phys. Chem.* **1965**, *42*, 3176.
(41) Enraf-Nonius Structure Determination Package 1982, Enraf-Nonius, Delft: Holland.
(42) During the preparation of this manuscript Liebeskind reported his observations describing a similar dependence of stereoselectivity on the metal counterion in the aldol reaction employing the enolate of η^5-CpFe(CO)-$(PPh_3)COCH_3$. Liebeskind, L. S.; Welker, M. E. *Tetrahedron Lett.* **1984**, *25*, 4341.

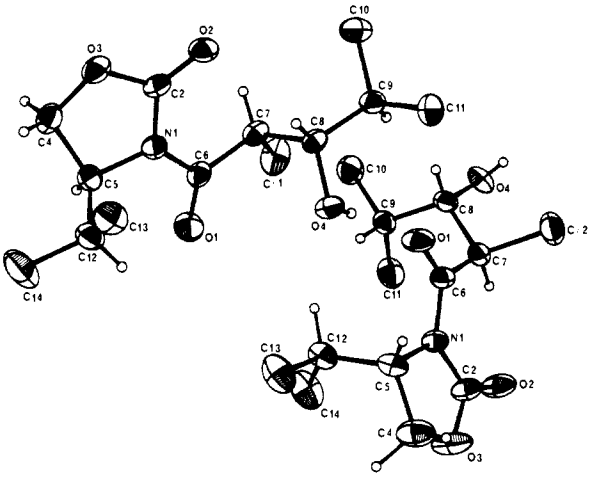


Figure 1. X-ray crystallographic structure of (4S)-3-[2′(R)-chloro-3′-(S)-hydroxy-4′-methylpentanoyl]-4-(1-methylethyl)-2-oxazolidinones **6e**.

Table III. Comparison of Torsion Angles (deg)

N1-C6-C7-Cl	-149.5	N1′-C6′-C7′-Cl2	-105.4
O1-C6-C7-Cl	27.6	O1′-C6′-C7′-Cl2	76.0
O1-C6-C7-C8	-94.1	O1′-C6′-C7′-C8′	-42.9
C6-C7-C8-O4	50.1	C6′-C7′-C8′-O4′	176.6
Cl1-C7-C8-O4	-69.4	Cl2-C7′-C8′-O4′	60.9
C6-C7-C8-C9	177.8	C6′-C7′-C8′-C9′	-62.8
N1-C5-C12-C13	60.8	N1′-C5′-C12′-C13′	61.2
N1-C5-C12-C14	-175.5	N1′-C5′-C12′-C14′	-173.5

two crystallographically independent molecules comprising the asymmetric unit. An Ortep[33] diagram of the two independent molecules is displayed as Figure 1. The crystallographic experiment has established the absolute configuration of this syn isomer as follows: the configuration at C5 is *S*, at C7 it is *R*, and at C8 it is *S*. The two independent molecules have the same stereochemistry at each asymmetric center; however, they represent different conformational isomers of this material.

Intramolecular bond distances and angles, all of which are quite normal for the types of bonds present in this molecule, are available as supplementary material. The oxazolidine ring is nonplanar in both molecules. The atom sets N1, C2, O2, O3 and N1′, C2′, O2′, O3′ each define a virtual plane, but atoms C4 and C4′ both sit below and atoms C5 and C5′ both sit above the plane of their respective sets.

Of greater interest is a comparison between the torsion angles of the two molecules. The syn isomers are characterized by values of −69.4° and 60.9° for torsion angles defined by atoms Cl1-C7-C8-O4 and Cl2-C7′-C8′-O4′, respectively. The conformational difference between the two molecules is most dramatically illustrated by the disposition of the isopropyl group attached at C8; relative to the carbonyl carbon, C6, in the unprimed molecule it is trans as reflected in the C6-C7-C8-C9 torsion angle of 177.8°, whereas in the primed molecule the disposition of the isopropyl group relative to C6 is gauche with the C6′-C7′-C8′-C9′ torsion angle = −62.8°. Alternatively, of course, the disposition of the hydroxyl group attached to C8 could have been used to illustrate the point. There are additional differences in the molecular conformations as indicated in Table III.

Interestingly, the disposition of the isopropyl group attached to the oxazolidine ring in both molecules is very nearly the same, as reflected in the torsion angles about the C5-C12 bond. The resulting gauche(+)/trans conformation of the "valinyl" side chain is one of the two least frequently observed in peptide structures containing this residue.[34]

The crystal structure is stabilized by intermolecular hydrogen bonding. The observed conformational isomerism is undoubtedly facilitated by the formation of these interactions. The two crystallographically independent molecules are joined by a hydrogen bond with hydroxyl oxygen O4 acting as a donor to carbonyl oxygen O1′ of the adjacent molecule. The associated distances and angle are O4---O1′ = 2.892 (3) Å, H104---O1′ = 2.18 (4) Å, and O4 H104---O1′ = 174 (4) Å. Asymmetric units are linked together by a second hydrogen bond in which hydroxyl oxygen O4′ is a donor to carbonyl oxygen O2′ of a symmetry-related molecule. The associated metrical parameters are O4′---O2′ = 2.939 (3) Å, H104′---O2′ = O2′ = 2.33 (5) Å, and O4′ H104′---O2′ = 161 (5) Å. X-ray data for **6e** are included as supplementary data.

Experimental Section

General Procedures. Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Fourier transform Infrared (FT-IR) spectra were recorded on a Nicolet 6000 Fourier transform infrared spectrometer. Gas chromatography (GC) was done with a Carlo-Erba capillary gas chromatograph model FV4160-02 with LT430 multiramp temperature programmer and DB-1, 15 m × 0.252 mm capillary column. Flash column chromatography[43] was done on "Baker silica for flash columns" (~40 μm average particle diameter). Zinc chloride ($ZnCl_2$) solutions in ether were prepared by the procedure of House et al.[16] Stannous triflate [$Sn(OTf)_2$] was prepared according to Batchelor et al.[14b] Di-*n*-butylboron triflate (*n*-Bu_2B OTf) was prepared from freshly distilled tri-*n*-butylboron and trifluoromethane sulfonic acid by the procedure of Mukaiyama.[12b]

(+)-(4*S*)-3-Chloroacetyl-4-(1-methylethyl)-2-oxazolidinone (3a). To a solution of (+)-(4*S*)-4-(1-methylethyl)-2-oxazolidinone (**1**)[10a] (1.29 g, 10 mmol) in dry ether (50 mL) cooled to −78 °C under nitrogen was added a hexane solution of *n*-butyllithium (10 mmol). The mixture stirred for 30 min during which time the reaction was allowed to warm to −20 °C and was subsequently cooled to −78 °C. Chloroacetyl chloride (1.12 g, 10 mmol) in dry ether (15 mL) was added with stirring while allowing the reaction to slowly warm to room temperature. The reaction was quenched with pH 7 phosphate buffer, and the product was extracted with ether. The extract was washed with distilled water and brine and then dried ($MgSO_4$). Evaporation of the solvent in vacuo gave the crude product which was purified by flash column chromatography on silica gel with 30% ether in hexane to give the pure product as a colorless oil (1.82 g, 88.5%). This material solidified on standing and was recrystallized from ether/hexane: mp 48–49 °C; $[\alpha]^{25}_D$ +97.9 (*c*, 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.71 (s, 2 H), 4.58–3.97 (m, 3 H), 2.68–2.1 (m, 1 H), 0.95 and 0.84 (2d, 6 H); ^{13}C NMR (CCl_3) δ 165.8 (s), 153.7 (s), 64.2 (t), 58.7 (d), 43.6 (t), 28.1 (d), 17.7 (q), 14.5 (q); mass spectrum [*m*/*z* (% abundance)] 206 (M + H, 100), 170 (40), 162 (7), 130 (26); FT-IR (KBr) 3018, 1964, 2938, 2878, 1774, 1720, 1494, 1487, 1404, 1391, 1372, 1366, 1331, 1302, 1239, 1215, 1143, 1118, 1104, 1054, 1018, 996, 967, 924, 833, 791, 776, 758, 738, 694, 569, 528 cm^{-1}. Anal. Calcd for $C_8H_{12}ClNO_3$: C, 46.73; H, 5.88; N, 6.67. Found: C, 46.42; H, 5.82; N, 6.67.

(4*S*)-3-[2′-Chloro-1′-(*tert*-butyldimethylsilyloxy)ethenyl]-4-(1-methylethyl)-2-oxazolidinone (4a). To a cooled (−78 °C) solution of lithium diisopropylamide (5.5 mmol) in THF (50 mL) under argon was slowly added a solution of **3a** (1.05 g, 5 mmol) in THF (10 mL), and the resulting solution was stirred at −78 °C for 20 min. A solution of *tert*-butyldimethylchlorosilane (1.1 g, 7.3 mmol) in THF (10 mL) was added, and the reaction temperature was allowed to rise to room temperature. The reaction was followed by TLC until the disappearance of **3a** and then quenched with pH 7 phosphate buffer solution. The product was extracted with ether. The organic layer was dried ($MgSO_4$) and then concentrated to give the crude silyl enol ether as a brown oil. The 90-MHz ^1H NMR of this product showed two olefinic protons at δ 5.56 and 5.38 in a ratio of 40:1, respectively. Flash column chromatography with 10% ether in hexane gave the pure major product as a pale yellow oil (1.2 g, 75%) which solidified at about 5 °C. FT-IR (neat) 2961, 2932, 2897, 2886, 2861, 1761, 1655, 1473 1465, 1401, 1393, 1381, 1366, 1327, 1311, 1256, 1239, 1209, 1147, 1127, 1058, 884, 845, 823, 806, 789, 697, 616 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.56 (s, 1 H), 4.33–3.78 (m, 3 H), 2.14–1.85 (m, 1 H), 1.0–0.78 (s and 2d, 15 H), 0.26 (s, 3 H), 0.19 (s, 3 H).

(4*S*)-3-(2′-Chloro-3′-hydroxyoctanoyl)-4-(1-methylethyl)-2-oxazolidinones (5a, 6a, 7a, and 8a). (a) Using Li Enolate of 3a (General Procedure). To a cooled (−78 °C) solution of lithium diisopropylamide (2.7 mmol) in dry ether (15 mL) was added a solution of (4*S*)-3-(chloroacetyl-4-(1-methylethyl)-2-oxazolidinone (**3a**) (0.5 g, 2.5 mmol) in ether (12 mL) under nitrogen. After 15 min, *n*-hexanal (0.25 g, 2.5 mmol) was added and the mixture was stirred at −78 °C for 30 min. Subsequently, the reaction was quenched with 5% aqueous citric acid solution. The product was extracted with ether, washed with distilled water and brine,

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

and dried ($MgSO_4$). The solvent was removed in vacuo to give the crude product mixture. The 90-MHz ^1H NMR of this mixture indicated the presence of all four isomeric chlorohydrins **5a**, **6a**, **7a**, and **8a** in a ratio of 22:46:15:17, respectively (by comparing the integrations of the -CO-C*H*-Cl- protons resonating as doublets at δ 5.68, 5.75, 5.58, and 5.46, respectively). A flash column chromatography of this mixture on silica gel (25 g) with 30% Et_2O in hexane afforded the clean mixture (0.4 g, 52%). A total of 2 g of this mixture was further chromatographed on silica gel (100 g) with 20% Et_2O in hexane as an initial eluent and gave the anti product **7a** as a solid: mp 52–54 °C; FT-IR (KBr) 3438, 2960, 2929, 2875, 2861, 1766, 1714, 1486, 1468, 1404, 1381, 1310, 1223, 1145, 1121, 1058, 1042, 1022, 974, 766, 719, 694, 631, 533, 521 cm^{-1}; ^1H NMR ($CDCl_3$) 5.58 (d, J = 8 Hz, 1 H), 4.6–3.83 (m, 4 H), 2.6 (br s, 1 H), 2.58–2.2 (m, 1 H); mass spectra (EI) [m/z, (% abundance)] 305 (M, 0.06), 252 (16), 234 (20), 207 (12), 206 (4), 205 (37), 156 (10), 130 (44), 126 (18), 86 (79), 85 (53), 71 (23), 69 (36), 68 (100). High resolution mass spectra calculated for $C_{14}H_{24}ClNO_4$ 305.139, found 305.138.

Further elution afforded the syn isomer **6a** as a solid: mp 51–53 °C (Et_2O/hexane); $[\alpha]^{25}_D$ +58.0° (*c*, 1.0; $CHCl_3$); FT-IR (KBr) 3514, 2961, 2953, 2927, 2871, 1790, 1716, 1468, 1389, 1327, 1304, 1209, 1143, 1122, 1109, 1074, 1057, 1022, 969, 771, 682, 571 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.75 (d, J = 3 Hz, 1 H), 4.68–4.02 (m, 4 H), 2.68 (br s, 1 H), 2.5–2.1 (m, 1 H), 1.79–1.1 (m, 8 H), 1.0–0.82 (9 H); ^{13}C NMR ($CDCl_3$) δ 167.7 (s), 153.4 (s), 71.7 (d), 64 (t), 60.8 (d), 58.7 (d), 33.9 (t), 31.3 (t), 28.4 (d), 24.8 (t), 22.2 (t), 17.5 (q), 14.6 (q), 13.7 (q); mass spectra [m/z (% abundance)] 306 (M + H, 36), 290 (34), 289 (17), 288 (100), 252 (25), 234 (6), 206 (27), 130 (45). Anal. Calcd for $C_{14}H_{24}ClNO_4$: C, 54.99; H, 7.91; N, 4.58; Cl, 11.59. Found: C, 54.85; H, 7.82; N, 4.43; Cl, 11.48.

Further elution gave the syn isomer **5a** as an oil: $[\alpha]^{25}_D$ +69.4° (*c*, 1.0; $CHCl_3$): FT-IR (neat) 3526–3489, 2962, 2933, 2874, 2862, 1782, 1711, 1486, 1467, 1389, 1333, 1302, 1206, 1143, 1121, 1105, 1057, 1021, 974, 773, 711, 702, 665, 518 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.68 (d, J = 3.5 Hz, 1 H), 4.68–4.0 (m, 4 H), 2.85 (br s, 1 H), 2.63–2.15 (m, 1 H), 1.74–1.13 (m, 8 H), 1.03–0.82 (9 H); ^{13}C NMR ($CDCl_3$) δ 168.4 (s), 70.8 (d), 63.6 (t), 59.1 (d), 58.4 (d), 33.4 (t), 31.3 (t), 27.8 (d), 24.9 (t), 22.2 (t), 17.5 (q), 14.3 (q), 13.7 (q); mass spectra [m/z (% abundance)] 306 (M + H, 32), 288 (100), 252 (11), 234 (3), 206 (8), 130 (64), 99 (23). Anal. Calcd for $C_{14}H_{24}ClNO_4$: C, 54.99; H, 7.91; N, 4.58; Cl, 11.59. Found: C, 54.90; H, 7.83; N, 4.48; Cl, 11.58.

The last fraction afforded a few milligrams of the anti isomer **8a**: ^1H NMR ($CDCl_3$) δ 5.46 (d, J = 8 Hz, 1 H), 4.67–3.79 (m, 4 H), 3.2 (br s, 1 H), 2.55–2.0 (m, 1 H), 1.8–1.1 (m, 8 H), 1.05–0.77 (9 H).

(b) Using Zn Enolate of 3a. One Equivalent of Zn (General Procedure). To the lithium enolate of **3a** (2.5 mmol) made as described above was added an ether solution of $ZnCl_2$ (2.5 mmol) at −78 °C and the mixture was stirred at 0 °C under nitrogen for 30 min. *n*-Hexanal (0.25 g, 2.5 mmol) was added and stirring was continued for 15 min at 0 °C. The reaction was worked up and the crude product was obtained as previously described in the lithium enolate case. Flash column chromatography afforded a total combined yield of 0.46 g (60%).

(c) Using Sn^{II} Enolate of 3a (General Procedure). (i) To a suspension of stannous triflate (1.25 g, 3 mmol) in dry methylene chloride (15 mL) was added **3a** (0.5 g, 2.5 mmol) followed by *N*-ethylpiperidine (0.34 g, 3 mmol) at 0 °C. The mixture was stirred at this temperature under nitrogen for 2 h during which time most of the suspension had dissolved. *n*-Hexanal (0.25 g, 2.5 mmol) was added and stirring was continued for 30 min. The reaction was quenched with 5% aqueous citric acid solution, and the product was extracted with ether. The extract was washed with distilled water and brine and then dried ($MgSO_4$). Removal of the solvent under vacuum afforded the crude product. Flash column chromatography gave a combined yield of 0.64 g (83.5%).

(ii) To the lithium enolate of **3a** (2.5 mmol) in dry THF (15 mL) cooled to −78 °C under nitrogen was added a solution of stannous triflate (1.25 g, 3 mmol) in THF (10 mL). The mixture was stirred for 30 min, *n*-hexanal (0.25 g, 2.5 mmol) was subsequently added, and stirring was continued at −78 °C for 10 min. The reaction was then allowed to warm to 0 °C. The reaction was worked up as described in the general procedure for the lithium enolate, and the crude product was flash column chromatographed to give a total yield of 0.55 g (73%).

(d) Using the Sn^{IV} Enolate of 3a (General Procedure). The Sn^{IV} enolate was prepared by adding tri-*n*-butyltin chloride (0.81 g, 2.5 mmol) to the lithium enolate (2.5 mmol) in ether at −78 °C. The mixture was allowed to warm to 0 °C and cooled again to −78 °C. *n*-Hexanal (0.25 g, 2.5 mmol) was added and the reaction mixture was slowly warmed to −40 °C and quenched with 5% aqueous citric acid. The total isolated yield was 0.56 g (73%).

(e) Using Boron Enolate of 3a (General Procedure). To dry CH_2Cl_2 (15 mL) at 0 °C was added **3a** (1.05 g, 5 mmol), di-*n*-butylboron triflate (1.508 g, 5.5 mmol), and diisopropylethylamine (1.05 mL, 5.6 mmol). The mixture was stirred at 0 °C for 30 min and at −78 °C for another 30-min period. *n*-Hexanal (0.55 g, 5.5 mmol) was added and stirring was continued at −78 °C for 30 min and then at room temperature for 1.5 h. The resulting solution was cooled to 0 °C and quenched with a mixture of 25 mL of methanol and 12 mL of pH 7 phosphate buffer. The resulting borate was oxidized by 30% H_2O_2 (12 mL) for 1 h at 0 °C. The product was extracted with ether, washed with distilled water and brine, and dried ($MgSO_4$). Removal of the solvent in vacuo gave the crude product in which the only detectable product by 90-MHz ^1H NMR was the syn isomer **5a**. Flash column chromatography gave pure **5a** (0.95 g, 62%).

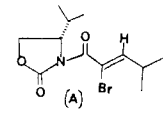
(4*S*)-3-(2′-Bromo-3′-hydroxy-4′-methylpentanoyl)-4-(1-methylethyl)-2-oxazolidinones 5f, 6f, 7f, and 8f. (a) Using Lithium Enolate of 3b. The lithium enolate of **3b** (8 mmol) was reacted with isobutyraldehyde in ether at −78 °C as previously described for **5–8a**. The combined yield was 70%. Flash column chromatography with 15% ether in hexane as an initial eluent gave **7f** as a solid: mp 120–122 °C (Et_2O/hexane); $[\alpha]^{25}_D$ +57.8° (*c*, 1.0; $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.76 (d, J = 9 Hz, 1 H), 4.63–4.16 (m, 3 H), 4.12–3.85 (m, 1 H), 2.74 (d, J = 7 Hz, 1 H), 2.61–2.03 (m, 2 H), 1.08–0.83 (m, 12 H). Anal. Calcd for $C_{12}H_{20}BrNO_4$: C, 44.73; H, 6.26; N, 4.35. Found: C, 44.90; H, 6.55; N, 4.33. The absolute stereochemistry of this compound was confirmed by X-ray crystallography.

Further elution afforded **6f** as a solid: mp 93–95 °C (Et_2O/hexane); $[\alpha]^{25}_D$ +41.8° (*c*, 1.0; $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.99 (d, J = 3 Hz, 1 H), 4.62–4.19 (m, 3 H), 3.6 (dd, J = 3 and 7 Hz, 1 H), 2.80 (br s, 1 H), 2.65–2.18 (m, 1 H), 1.12–0.84 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 169.1 (s), 153.3 (s), 76.0 (d), 64.0 (t), 59.1 (d), 50.1 (d), 32.3 (d), 28.8 (d), 18.7 (q), 18.0 (2q), 14.9 (q). Anal. Calcd for $C_{12}H_{20}BrNO_4$: C, 44.73; H, 6.26; N, 4.35. Found: C, 44.68, H, 6.20; N, 4.30.

Next was isolated **5f** as a solid: mp 107–109 °C (Et_2O/hexane); $[\alpha]^{25}_D$ +85.6 °C (*c*, 1.0; $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.96 (d, J = 3 Hz, 1 H), 4.65–4.24 (m, 3 H), 388 (br s, 1 H), 3.54 (dd, J = 3 and 7.5 Hz, 1 H), 2.60–2.15 (m, 1 H), 2.05–1.55 (m, 1 H), 1.089–0.86 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 170.0 (s), 152.9 (s), 75.3 (d), 63.6 (t), 58.3 (d), 48.2 (d), 31.6 (d), 27.9 (d), 18.9 (q), 17.8 (q), 14.8 (q). Anal. Calcd for $C_{12}H_{20}BrNO_4$: C, 44.73; H, 6.26; N, 4.35. Found: C, 44.65; H, 6.20; N, 4.20.

A very small amount of an epoxide was then isolated which was not fully characterized. Finally a few milligrams of **8f** were separated as an impure oil: ^1H NMR ($CDCl_3$) δ 5.73 (d, J = 9 Hz, 1 H), 4.67–3.93 (m, 4 H), 3.20 (br s, 1 H), 2.60–2.08 (m, 2 H), 1.11–0.89 (m, 12 H). No further data were obtained on this compound.

(b) Using Sn^{II} Enolate of 3b. (i) When the reaction was done in CH_2Cl_2 with $Sn(OTf)_2$ and *N*-ethylpiperidine as described previously for **3a**, the major isolated product (40%) was the dehydration product (A): mp 68–70 °C; ^1H NMR ($CDCl_3$) δ 6.27 (d, J = 9 Hz, 1 H), 4.68–4.12 (m, 3 H), 3.10–2.65 (m, 1 H), 2.63–2.15 (m, 1 H), 1.18–0.80 (m, 12 H); mass spectrum [m/z (%)] 306 (100), 304 (100), 302 (3), 290 (3), 288, (3), 227 (3), 226 (10), 225 (11), 224 (91), 177 (10), 175 (9), 130 (15), 97 (9). The remainder of the product was a mixture of the bromohydrins **5f–8f** (26%) from which the ratio was not determined.



(A)

(ii) To the lithium enolate of **3b** (2.5 mmol) in ether (25 mL) was added a solution of $Sn(OTf)_2$ (1.3 g, 3 mmol) in THF (12 mL) at −78 °C under nitrogen. After mixture was stirred for 30 min at −78 °C, isobutyraldehyde (0.2 g, 2.7 mmol) was added and the reaction was worked up as described for **3a**. A total isolated yield of 0.55 g (65%) was obtained.

(4*S*)-3-Chloroacetyl-4-(1-methylethyl)oxazolidine (9). To a solution of (4*S*)-4-(1-methylethyl)oxazolidine[10h] (11.52 g, 0.1 mol) in 1:1 CH_2Cl_2–hexane (200 mL) cooled to 0 °C was added dry triethylamine (20 mL). To the resulting solution was slowly added chloroacetyl chloride (11.2 g, 0.1 mol) over 30 min. The mixture was stirred at 0 °C for 2 h and then quenched with 10% mg of citric acid solution. The product was extracted with ether, and the ether extract was washed with water, sodium bicarbonate solution, and brine, and then dried ($MgSO_4$). Evaporation of the solvent afforded the crude product as a brownish oil (19.2 g). Distillation of this product at reduced pressure afforded the pure product as a colorless oil (bp 100–101 °C (0.5 mmHg)) (14.1 g, 73%). The oil solidified on standing to a white crystalline solid: mp 37–38 °C; $[\alpha]_D^{25}$ +33.7° (*c*, 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.18–4.95 (m, 2 H), 4.27–3.83 (m, 3 H), 2.48–1.91 (m, 1 H), 1.06–0.81 (2d, 6 H); ^{13}C NMR ($CDCl_3$) δ 163.4 (s), 78.5 (t), 67.4 (t), 59.8 (d), 41.9 (t), 28.6

(d), 18.5 (q), 16.4 (q); mass spectrum [m/z (% abundance)] 192 (M + H, 100).

(4S)-3-(2'-Chloro-3'-hydroxy-4'-methylpentanoyl)-4-(1-methylethyl)-oxazolidines 10, 11, 12, and 13. (a) From the Lithium Enolate of 9. To a cooled (−78 °C) solution of lithium enolate of **9** (2.5 mmol) in ether (15 mL) under nitrogen was added isobutyraldehyde (0.18 g, 2.5 mmol), and the mixture was stirred for 30 min. The reaction was quenched with 5% aqueous citric acid solution, and the product was extracted with ether. The GC analysis of the crude product (0.52 g) indicated the formation of **10**, **11**, **12**, and **13** in the ratio of 51:27:4:18, respectively. Flash column chromatography with 10% ether in hexane as an initial eluent gave **10** as a solid: mp 81–83 °C (hexane); $[\alpha]^{25}_D$ +31.0° (*c*, 0.9; $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.13–4.92 (M, 2 H), 4.60–3.65 (m, 6 H), 2.43–2.27 (m, 1 H), 2.03–1.86 (m, 1 H), 1.12–0.84 (m, 12 H); ^{13}C NMR ($CDCl_3$)[44] δ 167.9, 166.9 (s), 79.5, 78.9 (t), 76.0, 75.7 (d), 68.6, 67.7 (t), 60.8, 59.9 (d), 56.6, 55.0 (d), 31.6, 30.0 (d), 30.0, 28.5 (d), 19.4, 18.8 (q), 18.8, 18.7 (q), 18.7, 18.5 (q), 17.5, 16.6 (q). Anal. Calcd for $C_{12}H_{22}ClNO_3$: C, 54.64: H, 8.41; N, 5.31; Cl, 13.44. Found: C, 54.88; H, 8.33; N, 5.18; Cl, 13.48. Further elution provided **11** as a solid: mp 95–97 °C (hexane); $[\alpha]^{25}_D$ −14.9° (*c*, 0.9; $CHCl_3$); ^1H NMR ($CDCl_3$) δ [5.22 (d, *J* = 3.85 Hz), 5.11 (d, J = 5 Hz), 4.94 (d, *J* = 3.85 Hz) total of 2 H], 4.27–3.64 (m, 6 H), 3.33–2.13 (m, 1 H), 2.0–1.83 (m, 1 H), 1.05–0.88 (m, 12 H); ^{13}C NMR ($CDCl_3$)[44] δ 168.0, 166.5 (s), 79.9, 78.9 (t), 76.6, 76.3 (d), 68.3, 67.9 (t), 61.1, 60.3 (d), 57.4, 56.3 (d), 30.7, 30.2 (d), 29.5, 29.1 (d), 19.0 (q), 18.9 (q), 17.7 (q), 16.9 (q). Anal. Calcd for $C_{12}H_{22}ClNO_3$: C, 5464; H, 8.41; N, 5.31; Cl, 13.44. Found: C, 54.64; H, 8.48; N, 56.38; Cl, 13.58. Further elution gave **13** as a solid: mp 119–120 °C; $[\alpha]^{25}_D$ +89.7° (*c*, 1.0; $CHCl_3$); ^1H NMR ($CDCl_3$) δ 5.25–4.92 (m, 2 H), 4.26–3.37 (m, 6 H), 2.39–1.95 (m, 2 H), 1.06–0.88 (m, 12 H); ^{13}C NMR ($CDCl_3$)[44] δ 166.8, 1664 (s), 79.7, 78.8 (t), 75.5, 75.4 (d), 68.5, 67.9 (t), 60.7, 60.1 (d), 54.6, 53.8 (d), 31.6, 29.2 (d), 28.7, 28.3 (d), 19.9, 19.4 (q), 19.1, 18.8 (q), 17.3, 16.7 (q), 16.7, 14.6 (q); mass spectrum (EI) [m/z (% abundance)] 263 (15). High-resolution mass spectrum calculated for $C_{12}H_{22}ClNO_3$ 263.129, found 263.129. The absolute stereochemistry of **10**, **11**, and **13** was confirmed by X-ray crystallography.[45] The last fraction provided **12**: $[\alpha]^{25}_D$ −23.4° (*c*, 1.1, $CHCl_3$), ^1H NMR ($CDCl_3$) δ 5.22–4.93 (m, 2 H), 4.32–3.61 (m, 6 H), 2.32–2.03 (m, 2 H), 1.06–0.087 (m, 12 H); ^{13}C NMR ($CDCl_3$)[44] δ 167.6, 165.8 (s), 79.7, 78.7 (t), 76.0 (d), 68.4, 68.0 (t), 60.9, 60.4 (d), 54.8, 54.7 (d), 30.9, 29.1 (d), 28.8, 28.3 (d), 19.8, 19.7 (q), 19.2, 19.0 (q), 16.9, 16.4 (q), 15.2, 14.1 (q); mass spectrum (EI) [m/z (% abundance)] 263 (10). High-resolution mass spectrum calculated for $C_{12}H_{22}ClNO_3$ 263.129, found 263.128.

(b) Using Zr Enolate of 9. To the lithium enolate of **9** (2.5 mmol) in ether (15 mL) cooled to −78 °C under nitrogen was added a solution of bis(cyclopentadienyl)zirconium dichloride (0.9 g, 2.5 mmol) in dry THF (10 mL). The mixture was stirred while it was allowed to warm up to 0 °C and then cooled again to −78 °C and isobutyraldehyde (0.18 g, 2.5 mmol) added. After 20 min, the reaction was quenched with 5% aqueous citric acid solution and the product was extracted with ether. The crude product contained the chlorohydrins **10**, **11**, **12**, and **13** in the ratio of 80:6:11:3, respectively.

(44) The proton and carbon resonances of these compounds were seen in duplicate because of conformational isomerism resulting from restricted rotation about the amide carbonyl–nitrogen bond.

(45) The stereochemistry of the products of these reactions was confirmed by X-ray structure determination of **10**, **11**, and **12**. For details see: Eggleston, D.; Abdel-Magid, A.; Pridgen, L.; Lantos, I. *Acta. Crystallogr.*, submitted for publication.

Benzyl (+)-(2*R*,3*R*)-2,3-Epoxy-4-methylpentanoate (14). To a solution of benzyl alcohol (0.295 g, 2.72 mmol) in THF (10 mL) cooled to −78 °C under nitrogen was added *n*-butyllithium (2.72 mmol). To the resulting solution was added **5f** (0.44 g, 1.36 mmol) in THF (10 mL), and the solution was stirred while it was slowly warmed to −20 °C. The reaction was quenched with 5% aqueous citric acid solution, and the product was extracted with ether. The combined ether extract was dried ($MgSO_4$) and evaporated in vacuo to leave the crude product. Flash column chromatography with 8% ether in hexane gave the pure cis epoxide **14** (0.225 g, 74%) as a colorless liquid: $[\alpha]^{25}_D$ +35.7° (*c*, 1.0; $CHCl_3$); FT-IR (neat) 3067, 3035, 2967, 2871, 1755, 1731, 1498, 1468, 1456, 1433, 1392, 1385, 1366, 1299, 1274, 1253, 1197, 1182, 1134, 1100, 1052, 974, 925, 907, 885, 842, 802, 755, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (s, 5 H), 5.22 (s, 2 H), 3.54 (d, *J* = 5 Hz, 1 H), 2.80 (dd, *J* = 5 and 9 Hz, 1 H), 1.86–1.30 (m, 1 H), 1.06 (d, *J* = 7 Hz, 3 H), 0.76 (d, *J* = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.3 (s), 135.4 (s), 128.7 (d), 67.2 (t), 63.3 (d), 53.3 (d), 27.1 (d), 20.2 (q), 18.3 (q); mass spectra [m/z (% abundance)] 221 (0.6), 203 (1), 175 (2), 131 (4), 129 (2), 113 (2), 107 (2), 98 (2), 92 (7), 91 (100), 81 (2). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.63; H, 7.34.

Reaction of 5a with $PhCH_2OLi$. To a solution of benzyl alcohol (0.22 g, 2 mmol) in ether (10 mL) cooled to −78 °C under nitrogen was added *n*-butyllithium (2 mmol). To the resulting solution was added **5a** (0.31 g, 1 mmol) in ether (7 mL). The reaction was quenched after 10 min with 5% aqueous citric acid solution, and the product was extracted with ether. Flash column chromatography with 5% ether in hexane gave **22** (0.24 g, 84%): ^1H NMR ($CDCl_3$) δ 7.37 (s, 5 H), 5.23 (s, 2 H), 4.35 (d, *J* = 5 Hz, 1 H), 4.20–3.98 (m, 1 H), 2.72 (br s, 1 H), 1.63–1.11 (m, 8 H), 0.89 (t, 3 H). No epoxide was detected under these conditions.

When the reaction was repeated on 0.62 g of **5a** (2 mmol) and allowed to warm up to room temperature before quenching, it afforded a mixture of the olefin **24a** (56 mg, 12%) and the trans epoxide **23a** (0.13 g, 27%). ^1H NMR ($CDCl_3$) δ 7.31 (s, 5 H), 7.13 (t, *J* = 7 Hz, 1 H), 5.29 (s, 2 H), 2.52–2.11 (m, 2 H), 1.71–1.20 (m, 6 H), 0.89 (t, 3 H); mass spectra [m/z (% abundance)] 265 (0.36), 213 (3), 211 (4), 178 (2), 177 (29), 176 (11), 174 (100). $[\alpha]^{25}_D$ +15.4° (*c*, 1.0, $CHCl_3$); FT-IR (neat) 3067, 3035, 2957, 2932, 2872, 2860, 1752, 1498, 1456, 1380, 1340, 1282, 1250, 1189, 1003, 902, 891, 750, 741, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36 (s, 5 H), 5.21 (s, 2 H), 3.30–3.08 (d, *J* = 1.5 Hz and m, 2 H), 1.69–1.14 (m, 8 H), 0.85 (t, 3 H); mass spectra [m/z (% abundance)] 277 (54), 178 (6), 177 (48), 158 (10), 157 (100), 151 (9). None of the cis epoxide was isolated.

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Supplementary Material Available: General experimental procedures, additional X-ray data, synthesis preparations, and spectral data for **3b–8b**, **5c–8c**, **5d–8d**, **5e–8e**, and **15–19**; reactions of **5c** and **6e** with lithium benzyloxide (29 pages). Ordering information is given on any current masthead page.