Asymmetric Aldol Reactions: A Novel Model for Switching between Chelation- and Non-Chelation-Controlled Aldol Reactions

Tu-Hsin Yan,* Chang-Wei Tan, Hui-Chun Lee, Hua-Chi Lo, and Tzung-Yu Huang

Contribution from the Department of Chemistry, National Chung-Hsing University, Taichung, Taiwan 400, Republic of China

Received October 19, 1992

Abstract: A new camphor-based *N*-propionyloxazolidinethione provides remarkable levels of asymmetric induction for both chelation- and non-chelation-controlled aldol processes. While the aldol condensation of the derived di-*n*-butylboryl enolate with various aldehydes affords the "Evans" syn aldol with excellent diastereoselectivity, the chlorotitanium enolate gives the "non-Evans" syn aldol expected from chelation control. Most noteworthy is the observation that the sense of facial selectivity from the chlorotitanium enolate of propionyloxazolidinethione is opposite to that obtained from propionyloxazolidinone. This important finding illustrates the importance of increased chelating potential of the enolate ligand, ring thiocarbonyl, in maximizing the aldol π-facial discrimination. Final nondestructive chiral auxiliary removal via hydroperoxide-assisted hydrolysis and subsequent esterification provides enantiomerically pure methoxycarbonyl aldols.

Asymmetric aldol reactions are potentially of great value to synthetic chemists. Consequently, the asymmetric aldol condensation continues to stimulate much thought from a synthetic[1] and mechanistic[2,3] point of view. Over the past ten years, several chiral enolate synthon systems have been reported to exhibit high levels of diastereoselectivity in aldol reactions.[4,5] More recently, metal-assisted aldol condensations[6] have received much synthetic and mechanistic attention and shown tremendous potential in asymmetric synthesis. Its use in the preparation of chelation- and non-chelation-controlled aldol adducts has been amply demonstrated.[4-8]

However, while a reversed sense of facial selectivity was observed on aldol condensation of boron versus lithium and tin(IV) enolates derived from *N*-propionyloxazolidone[4a,c,f] and *N*-propionylsultam,[4e] both enantioselection and reaction diastereoselection were found to be dependent on the metal chosen. In numerous studies carried out in this laboratory, we found that aldol diastereoselection was excellent for the boron enolate of camphor-based acyloxazolidone and moderate for the lithium enolate.[5] Similar trends were also observed for enolates of α-haloacetyloxazolidone,[4c] acylsultam,[4e] and acyloxazolidone.[4a,f] These observations imply that the generality and synthetic utility of chelation-controlled aldol condensations are limited. These results also prompted us to explore substrate and reaction variables which could enhance intramolecular complexation, thereby conferring greater enantioselection and diastereoselection. Accordingly, we turn our attention to a redesign of the camphor-based chiral auxiliary. In this account we describe the preparation of camphor-based oxazolidinethione, compare its aldol diastereoselection with that of previously reported camphor-based chiral oxazolidone,[5] and demonstrate its enormous potential in chelation- and non-chelation-controlled aldol reactions. Information pertaining to the critical role of increased chelating potential of imide enolate ligand, ring thiocarbonyl, in aldol facial selectivity is presented.

Results and Discussion

Preparation of Substrates for Aldol Condensation Studies. The preparation of the requisite camphor-based chiral oxazolidinethione **4S** involves a straightforward, high-yield, three-step synthesis starting from ketopinic acid (**1**) (Scheme I). Previously reported isocyanate **2**[5,9] was treated successively with $NaBH_4$ in methanol and 6 N KOH to afford amino alcohol **3** in >90% yield. Treatment of amino alcohol **3** with carbon disulfide provided the desired chiral oxazolidinethione **4S** in 95–100% isolated yield. Acylation of **4S** with propionyl chloride in the presence of sodium hydride led to a nearly quantitative yield of *N*-propionyloxazolidinethione **5S**. Previously described oxazolidone **4O** was prepared in two steps from ketopinic acid (**1**).[5,9] Subsequent acylation of **4O** gave *N*-propionyloxazolidone **5O** in >90% overall

(1) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (b) Heathcock, C. H. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B, p 111. (c) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–30. (d) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976–4977.

(2) (a) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923. (b) Dubois, J. E.; Dubois, M. *Tetrahedron Lett.* **1967**, 4215. (c) Nielson, A. T.; Houlihan, W. *J. Org. React.* **1968**, *16*, 1–438. (d) Dubois, J. E.; Fort, J. F. *Tetrahedron* **1972**, *28*, 1653–1663, 1665–1675, and references cited therein. (e) Dubois, J. E.; Fellman, P. *C. R. Acad. Sci.* **1972**, *274*, 1307–1309. (f) Dubois, J. E.; Fellman, P. *Tetrahedron Lett.* **1975**, 1225–1228. (g) Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247. (h) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066–1081.

(3) (a) Evans, D. A.; Vogel, E.; Nelson, J. V. *J. Am. Chem. Soc.* **1979**, *101*, 6120–6123. (b) Evans, D. A.; Taber, T. R. *Tetrahedron Lett.* **1980**, 4675–4678. (c) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111 and references cited therein. (d) Heathcock, C. H. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon Press: Oxford, England, 1991; Vol. 11, Chapter 1, p 181.

(4) (a) Evans, D. A.; Bartrol, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127–2129. (b) Heathcock, C. H.; Arseniyadis, S. *Tetrahedron Lett.* **1985**, *26*, 6009. (c) Abdel-Magid, A.; Lendon, N. P.; Drake, S. E.; Ivan, L. *J. Am. Chem. Soc.* **1986**, *108*, 4595–4602. (d) Hsiao, C.-N.; Liu, L.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 2201–2206. (e) Oppolzer, W.; Blagg, J.; Rodriguez, I.; Walther, E. *J. Am. Chem. Soc.* **1990**, *112*, 2767–2772. (f) Bonner, M. P.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 1299–1308.

(5) Yan, T.-H.; Chu, V.-V.; Lin, T.-C.; Tseng, W.-H.; Cheng, T.-W. *Tetrahedron Lett.* **1991**, *32*, 5563–5566.

(6) (a) Evans, D. A.; McGee, L. R. *J. Am. Chem. Soc.* **1981**, *103*, 2876. (b) Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1983**, 297. (c) Imamoto, T.; Kusumoto, T.; Yokoyama, M. *Tetrahedron Lett.* **1983**, *24*, 5233. (d) Liebeskind, L. S.; Welker, M. E.; Goedken, V. *J. Am. Chem. Soc.* **1984**, *106*, 441. (e) Davies, S. G.; Dordor-Hedgecock, I. M.; Warner, P.; Jones, R. H.; Prout, K. *J. Organomet. Chem.* **1985**, *285*, 213.

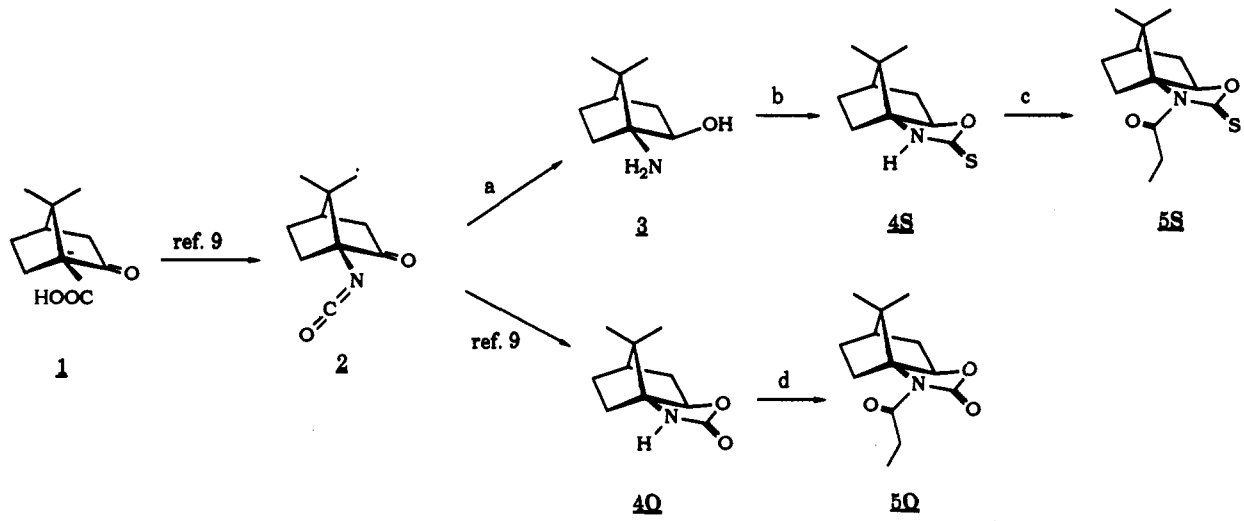
(7) (a) Reetz, M. T.; Kesseler, K.; Schmidtberger, S.; Wenderoth, B.; Steinbach, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 989. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556 and references cited therein.

(8) Heathcock, C. H. *Aldrichimica Acta* **1990**, *23*, 99–111 and references cited therein.

(9) Yan, T.-H.; Chu, V.-V.; Lin, T.-C.; Wu, C.-H.; Liu, L.-H. *Tetrahedron Lett.* **1991**, *32*, 4959–4962.

0002-7863/93/1515-2613$04.00/0 © 1993 American Chemical Society

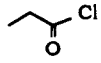
Scheme I



a. $NaBH_4$ / MeOH / $CeCl_3.7H_2O$, -78°C→ 0°C; 6N KOH

b. CS_2 / THF / NEt_3 / Δ

c. NaH / THF / 0°C; 

d. NaH / THF / 0°C → 25°C; 

yield. It is noteworthy that both **4S** and **4O** can be prepared on a 100-g scale without the need of purification by chromatography.

Aldol Diastereoselection via Boron and Chlorotitanium Enolates. Perhaps the most novel and interesting mechanistic issue arising from the current studies relates to the factors governing the sense of asymmetric induction in the carbon–carbon bond formation process.[4-8] It would be instructive to develop transition-state models which correlate the effects of the metal ligand and imide enolate ligand, ring carbonyl, with the sense of asymmetric induction in the aldol bond construction process. Metal ligand effects on the π-facial discrimination are well recognized and are of considerable value in chelation- and non-chelation-controlled condensations.[3c,7b] More recently, Evans and co-workers have disclosed that both $TiCl_4$- and *n*-Bu_2BOTf-mediated aldolizations of imide enolates derived from *N*-acyloxazolidone and acylsultam afforded almost exclusively the normal "Evans" syn aldol adduct expected from nonchelation control.[10] However, directed aldol reactions of a chiral titanium imide enolate bearing isopropoxy ligands reported by Thornton and co-workers provided predominantly the "non-Evans" syn aldol diastereoisomer predicted from chelation control.[4f,11] Accordingly, titanium ligands could play a role in influencing chelating ability, thereby affecting product distributions. While chelating ability of titanium(IV) Lewis acids should be an important contributor in determining transition structure, it was of considerable interest to us to determine whether the increased chelating potential of the imide enolate ligand could maximize the π-facial differentiation of aldolization. Since there is considerable structural homology between metal enolates of **5S** and **5O**, an examination of counterion effects[4-8] might reveal the influence of the imide enolate ligand on the aldol bond construction process. In particular, it was anticipated that an increase in the chelating potential of the enolate ligand should lead to an increase in chelate effect and therefore to maximum π-facial selectivity. Since condensations of chlorotitanium enolates of acyloxazolidinethione have not been previously explored, we aimed at studying the comparative aldol condensations of the chlorotitanium and boron enolates of the camphor-based imides **5S** and **5O** (Scheme II). We first addressed the well-established boron enolate emethodology.[4a,12] Dibutylboryl enolate was generated by the sequential addition of 1.1 equiv of *n*-Bu_2BOTf (1 M in CH_2Cl_2) and diisopropylethylamine (1.2 equiv) to a cold (0 °C) solution of **5S** in methylene chloride. Condensation of the resulting boron enolate with aldehyde at −78 °C and extractive workup afforded the aldol adduct in good yield. The various aldehydes employed along with subsequent results are shown in Table I. In all cases examined, analysis of the crude aldol product revealed a single diastereomer to the detection limits of high-field NMR spectroscopy. Assignment of the erythro configuration is based on the ^1H NMR vicinal coupling using the well-established fact that J_{threo} (7–9 Hz) > $J_{erythro}$ (3–6 Hz).[13] In all cases studied, the small $J(2,3)$ values ranging from 2 to 5 Hz are indicative of the syn configuration. To confirm the absolute stereochemistry of the syn aldols, assignments were made in four cases **6a**, **6b**, **6c**, and **6d** via nondestructive removal of the chiral auxiliary **4S**. Mild lithium hydroperoxide hydrolysis[14] of syn aldols **6a**, **6b**, **6c**, and **6d** followed by methylation of the resulting β-hydroxy carboxylic acids with CH_2N_2 provided the corresponding methyl esters **14** (Scheme III). The absolute configurations of the resultant syn methoxycarbonyl aldols were determined by comparing their optical rotations with those

(10) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpi, F. *J. Am. Chem. Soc.* **1991**, *113*, 1047-1049.

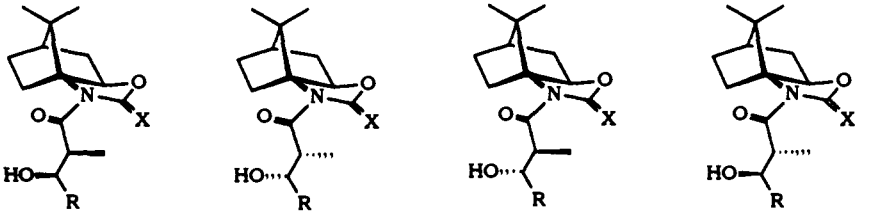
(11) Nerz-Stormes, M.; Thornton, E. R. *Tetrahedron Lett.* **1986**, *27*, 897-900.

(12) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566.

(13) (a) House, H. O.; Crumrine, D. S.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310. (b) Kleschick, W. A.; Buse, C. T.; Heathcock, C. H. *J. Am. Chem. Soc.* **1977**, *99*, 247-248. (c) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; John, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066-1081.

(14) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

Scheme II



6; X=S **7**; X=S **8**; X=S **9**; X=S

10; X=O **11**; X=O **12**; X=O **13**; X=O

a; R = C_6H_5 b; R = n-C_3H_7 c; R = $CH_3CH{=}CH$ d; R = i-C_3H_7

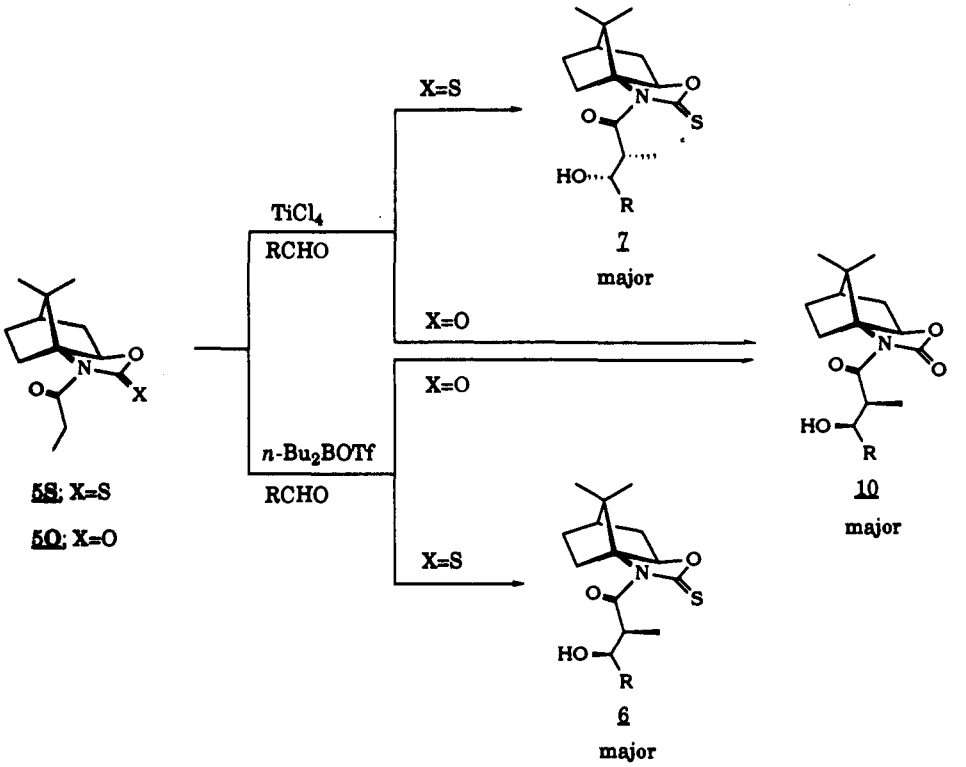


Table I. Diastereoselective Aldol Condensations of Chlorotitanium versus Di-*n*-butylboron Enolates of *5S* with Representative Aldehydes

entry	electrophile	enolates	syn:anti[a,b] (*6*+*7*:*8*+*9*)	enantioselection[a] *6*:*7*	yield[d] (%)	$[\alpha]^{25}_D$ (deg)	mp (°C)
1	PhCHO	B(*n*-Bu)$_2$	>99:1	>99:1	86	+53.4	141–142
2	PhCHO	$TiCl_4$	>99:1	13:87			
3	PhCHO[c]	$TiCl_4$	>99:1	3:97	84	+106.2[e]	139–140
4	*n*-PrCHO	B(*n*-Bu)$_2$	>99:1	>99:1	78	+48.9	63–64
5	*n*-PrCHO	$TiCl_4$	>99:1	<1:99	88	+52.4	
6	MeCH=CHCHO	B(*n*-Bu)$_2$	>99:1	>99:1	81	+70.3	
7	MeCH=CHCHO	$TiCl_4$	>99:1	<1:99	86	+82.4	
8	Me_2CHCHO	B(*n*-Bu)$_2$	>99:1	>99:1	79	+2.1	
9	Me_2CHCHO	$TiCl_4$	>99:1	2:98	85	+66.5	77–78

[a] Ratios determined by 300-MHz ^{1}H NMR. [b] None of the anti diastereomers could be detected by ^{1}H NMR. [c] Precomplexed benzaldehyde (PhCHO/$TiCl_4$) was used in place of benzaldehyde. [d] Combined isolated yield of all diastereomers. [e] Optical rotation of purified syn diastereomer *7*.

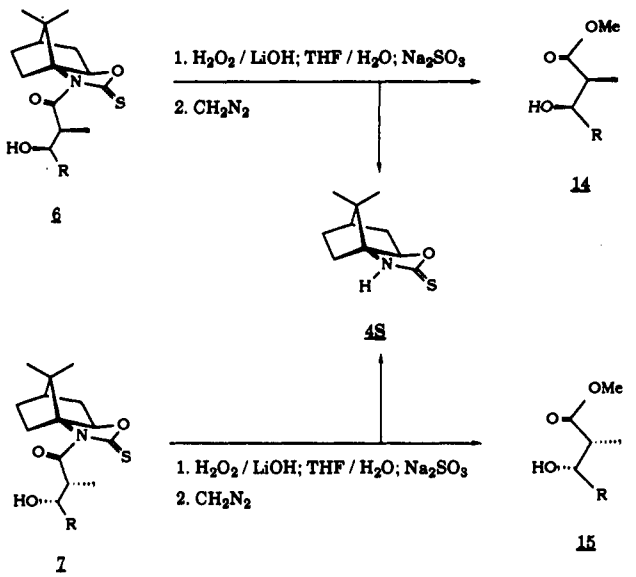
reported in the literature.[4a,c] On the basis of the above stereochemical correlation, the aldolization of the boron enolate of **5S** should give the erythro-diastereofacial selection predicted from nonchelation control, leading to the "Evans" syn aldol adduct. Quite recently, we have already made parallel observations with the boron enolate derived from propionyloxazolidone **5O**.[5] Having established the sense of asymmetric induction in the boron-mediated aldol condensations of **5S** and **5O**, we next investigated the comparative aldol condensations of chlorotitanium enolates derived from **5S** and **5O** to determine the influence of variable chelating potentials of the imide enolate ligand (exocyclic imide carbonyl). The derived chlorotitanium enolate **16S** was prepared by the successive addition of 1.1 equiv of $TiCl_4$ (1 M in CH_2Cl_2) and 1.2 equiv of diisopropylethylamine (1 M in CH_2Cl_2) to a

Table II. Diastereoselective Aldol Condensations of Chlorotitanium versus Di-*n*-butylboron Enolates of *5O* with Representative Aldehydes

entry	electrophile	enolates	syn:anti[a] (*10+11:12+13*)	product ratio[a] (*10:11:12:13*)	yield[d,e] (%)	$[\alpha]^{25}_D$ (deg)	mp (°C)
1	PhCHO	$B(n\text{-}Bu)_2$	>99:1[b]	>99:<1:0:0[c]	72 (91)	+94.8	121–122
2	PhCHO	$TiCl_4$	>99:1[b]	88:12:0:0	82	+44.2[f]	43–44[h]
3	*n*-PrCHO	$B(n\text{-}Bu)_2$	>99:1[b]	>99:<1:0:0[c]	69 (92)	+81.0	51–52
4	*n*-PrCHO	$TiCl_4$	>99:1[b]	95:5:0:0	87	+57.5[f]	56–57[h]
5	MeCH=CHCHO	$B(n\text{-}Bu)_2$	>99:1[b]	>99:<1:0:0[c]	73 (90)	+92.2	
6	MeCH=CHCHO	$TiCl_4$	82:18	70:12:18:0	84	+20.1[g]	89–90[i]
7	Me_2CHCHO	$B(n\text{-}Bu)_2$	>99:1[b]	>99:<1:0:0[c]	68 (92)	+84.6	91–92
8	Me_2CHCHO	$TiCl_4$	>99:1[b]	98:2:0:0	88	+49.0[f]	

[a] Ratios determined by 300-MHz ^{1}H NMR. [b] None of the anti diastereomers could be detected by ^{1}H NMR. [c] The syn aldol *10* was the only detected product by ^{1}H NMR. [d] Combined isolated yield of all diastereomers. [e] Those in parentheses are yields which have been normalized to account for recovered starting material *5b*. [f] Optical rotation of syn diastereomer *11*. [g] Optical rotation of anti diastereomer *12*. [h] Melting point of syn diastereomer *11*. [i] Melting point of anti diastereomer *12*.

Scheme III



precooled (0 °C) solution of **5S** (0.5 M in CH_2Cl_2). In all cases the aldehyde was added to the solution containing the enolate at −78 °C. The rather surprising results are summarized in Table I. With the exception of benzaldehyde, the aldolizations from chlorotitanium enolate **16S** exhibited excellent diastereoselection (≤2:98). In fact, the crude products usually consisted of a single aldol diastereomer within high-field ^{1}H NMR (200 or 300 MHz) detection limits. The modest level of diastereoselection (13:87) observed with benzaldehyde was surprising. In an effort to confer greater stereoselectivity in the condensation of enolate **16S** with benzaldehyde, we have examined the condensation of **16S** with the 1:1 benzaldehyde/$TiCl_4$ complex. With such a modification, the resultant aldol diastereoselectivity observed with benzaldehyde was greatly improved (Table I, entry 3, 3:97). Confirmation of the syn configuration in each case was based on the consideration of the carbinol resonances in the ^{1}H NMR spectra.[13] The stereochemical identities of the syn aldol stereomers were confirmed, as before, by conversion of the aldol adducts **7a**, **7b**, **7c**, and **7d** to the corresponding methoxycarbonyl aldols **15**, whose specific rotations are equal in magnitude and opposite in sign to those obtained from syn aldols **6a**, **6b**, **6c**, and **6d** (Table III). On the basis of the above stereochemical comparisons, it is significant that $TiCl_4$-mediated aldol reactions of **5S** give the "non-Evans" syn aldols resulting from chelation control[4,7] or the open transition state.[8] These results are in marked contrast to those of Evans and co-workers in their investigations with the chlorotitanium enolate derived from *N*-acyloxazolidone.[10] To get further insight into the influence of the imide enolate ligand on the π-facial discrimination and diastereoselectivity of aldol condensation, the comparative aldolizations of the chlorotitanium enolate of **5O** were carried out with representative aldehydes. In a similar fashion, chlorotitanium enolate **16O** was generated by the method of Evans[10] and subsequently subjected to condensation with aldehyde at −78 °C. Diastereoselection in the comparative $TiCl_4$-mediated condensation was found to be dependent on the structure of the aldehydes (Table II). The resultant aldol diastereoselectivities observed with alkyl carboxaldehydes were excellent (≥95:5). Benzaldehyde is somewhat less stereoselective (~88:12). The resultant aldol diastereoselection observed with crotonaldehyde is relatively low (Table II, entry 6). More significantly, ^{1}H NMR studies indicated that the major syn aldols obtained from titanium enolate **16O** were the same as those observed in the corresponding boron-mediated aldol condensation of **5O**.[5] Considering titanium's desire for hexacoordination[7] and considerable structural homology between **16S** and **16O** (Scheme IV), it would be expected that chlorotitanium enolates **16S** and **16O** give similar erythro-diastereofacial selection in their aldol condensations. However, they differ dramatically in their corresponding aldol π-facial discriminations (Scheme II). These initial findings were intriguing, since they pointed out that the sense of facial selectivity could be controlled not only by the selected counterion but also by the enolate ligand. What is not so evident from this comparison is why changing the enolate ligand from ring carbonyl to ring thiocarbonyl had a significant effect on the stereochemistry of aldol condensation. Although the interpretation of the above observations is complicated by our lack of knowledge concerning the effect of the metal ligand on chelating ability of the metal ion,[4f,7,11] we believe that the origin of this marked difference in behavior may lie in the chelating potential difference between ring thiocarbonyl and ring carbonyl. On the basis of the known preference of 1,4-thioxane to coordinate to the methyltitanium trichloride Lewis acid through sulfur,[15] it is reasonable to anticipate that thiocarbonyl coordination to chlorotitanium compares very favorably with carbonyl coordination. We surmise that the chelate effect obtained by the intramolecular complexation of $TiCl_4$ with thiocarbonyl is relatively large compared to that obtained with ring carbonyl. Although chelation to $TiCl_4$ could stabilize the chlorotitanium chelates **16S** and **16O**,[16] the dipolar repulsions developed in the aldol bond construction process might disrupt the ordered chelated form.

On the basis of the well-established Zimmerman/Traxler pericyclic chair like transition-state model,[2,3] it can be envisioned that aldehyde carbonyl coordination to chelate **16S** or **16O** may result in two monomeric 1:1 chlorotitanium enolate/aldehyde complexes with octahedrally hexacoordinated titanium atoms (Scheme IV).[16-18] In the chelated octahedral 1:1 complex represented by *Ta*, the aldehyde carbonyl oxygen is cofacial with two imide carbonyl oxygens, encountering two severe dipolar repulsions: between aldehyde carbonyl and enolate carbonyl and between aldehyde and exocyclic imide carbonyl. When the aldehyde carbonyl competes favorably with the ring carbonyl as a ligand for titanium, there is, however, only one dipole–dipole

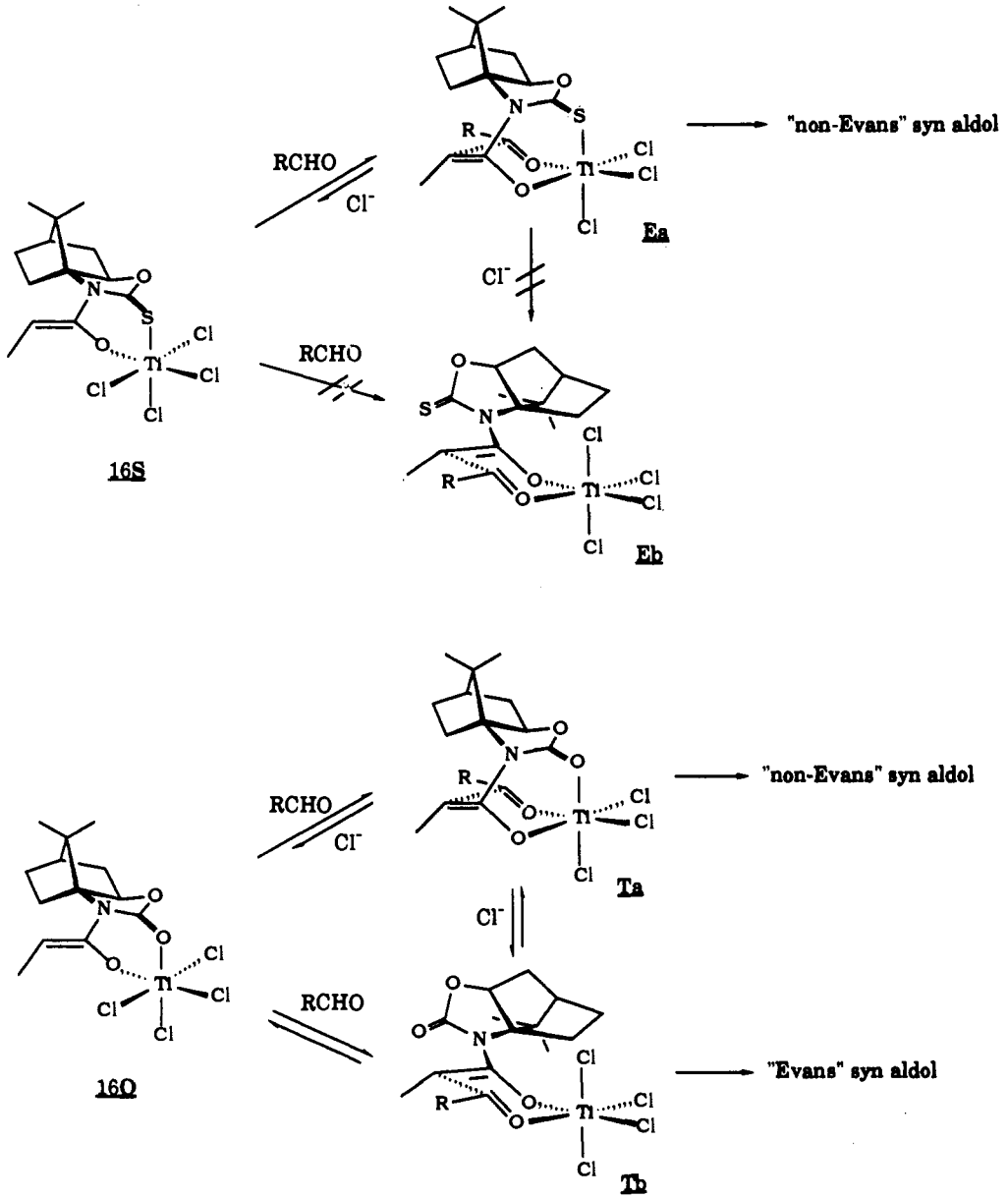
(15) Fowles, G. W. A.; Rice, D. A.; Wilkins, J. D. *J. Chem. Soc.* **1971**, 1920–1923.

Table III. Consecutive Hydroperoxide-Assisted Hydrolysis and Esterification *6* → *4S* + *14* and *7* → *4S* + *15*

			α-methyl-β-hydroxy ester				
entry	carboximide	R	ester product[a]	config	yield (%)	$[\alpha]^{25}_D$[b] (deg)	$[\alpha]^{25}_D$ (lit. ref)
1	*6a*	C_6H_5	*14a*	(2*S*,3*S*)	79	−22.5	−23.1(4a), −20.8(4e)
2	*7a*	C_6H_5	*15a*	(2*R*,3*R*)	87	**23.6**	+23.2(4a), +23.5(4e)
3	*6b*	*n*-C_3H_7	*14b*	(2*S*,3*R*)	76	+12.6	+12.1(4e)
4	*7b*	*n*-C_3H_7	*15b*	(2*R*,3*S*)	92	−13.4	
5	*6c*	MeCH=CH	*14c*	(2*S*,3*R*)	79	+11.1	+11.5(4e)
6	*7c*	MeCH=CH	*15c*	(2*R*,3*S*)	87	−12.3	
7	*6d*	*i*-C_3H_7	*14d*	(2*S*,3*R*)	82	−7.8	−7.1 (4e)
8	*7d*	*i*-C_3H_7	*15d*	(2*R*,3*S*)	86	+7.1	+7.7(4a), +7.5(4e)

[a] The chiral auxiliary *5a* was recovered in >90% yield. [b] Measured in CH_2Cl_2.

Scheme IV



interaction between the aldehyde carbonyl and the enolate carbonyl is present in the nonchelated octahedral complex *Tb*. On this basis, the latter would be favored. In accord with this model, the aldol condensations of **16O** should proceed mainly via nonchelation control, leading to the "Evans" syn aldol adduct. In contrast to **16O**, aldolizations of **16S** proceed via chelated complex *Ea*, resulting from displacement of chloride anion, rather than the nonchelated complex *Eb*, arising by displacing thiocarbonyl.

(16) The observations that in solution titanium-derived Lewis acids prefer to form 1:1 chelated adducts have been documented.[17] Another noticeable feature of the chelated structures is that they are all monomeric. Presumably, this was due to the ability of the bidentate ligand to satisfy titanium's desire for hexacoordination and octahedral geometry. Thus the crystal structures of $TiCl_4$ chelated by acetic anhydride,[18a] acryloylmethyl lactate,[18b] or 3,3-dimethyl-2,4-pentanedione[18c] show a 1:1 stoichiometry with two carbonyls cis to one another around the octahedrally coordinated titanium atom. In view of these observations, we believe that in solution **16a**, **16b**, and their subsequent transition structures are all monomeric 1:1 complexes with hexacoordinated titanium atom.

(17) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986.

(18) (a) Viard, B.; Poulain, M.; Grandjean, D.; Anandrut, J. *J. Chem. Res., Synop.* **1983**, 850. (b) Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 112. (c) Maier, G.; Seipp, U. *Tetrahedron Lett.* **1987**, *28*, 4515.

This is reasonable on two grounds. First, thiocarbonyl showed strong affinity toward association with chlorotitanium. Second, the relatively small dipole moment of thioketones[19] compared to the corresponding ketones suggests that the dipolar repulsion between aldehyde carbonyl and thiocarbonyl is relatively unimportant. Although the above analysis is purely speculative, it can be anticipated that further studies will provide evidence for the enhanced preference of the 1:1 chelated adduct *Ea* in the aldol bond construction process.

Conclusion

In summary, we demonstrate a novel model for switching between chelation- and non-chelation-controlled aldol reactions. The remarkable chelate effect obtained through the ring thiocarbonyl chelation to a chlorotitanium Lewis acid uncovered in this study should find application in other acid/enolate systems. Significantly, acyloxazolidinethione **5S** provides remarkable levels of asymmetric induction for both chelation- and non-chelation-controlled aldol reactions. In fact both the "Evans" syn aldol and "non-Evans" syn aldol[8] can be obtained with exceptional quality of stereocontrol by employing **4S**. The methodology described herein, therefore, compares favorably with existing approaches to these two syn aldol adducts. Finally, the remarkable ease of preparation of **4S** on a 100-g scale together with nondestructive chiral auxiliary removal further enhances its importance as a practical chiral auxiliary in asymmetric synthesis.

Experimental Section

General Experimental Methods. Diisopropylethylamine and dichloromethane were dried by distillation under N_2 from calcium hydride. Di-*n*-butylboryl triflate and titanium tetrachloride were purchased from Aldrich Chemical Co. as 1.0 M solutions in CH_2Cl_2. All aldehydes were freshly distilled prior to use. Flash chromatography was done as previously described[20] on E. Merck silica gel 60 (230–400 mesh). Melting points were measured on a Büchi 535 capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Hitachi 270-30 infrared spectrophotometer. Optical rotations were obtained on an Optical Activity AA-100 polarimeter.

^1H and ^{13}C NMR spectra were recorded on either a Varian VXR-300 or a Gemini-200 spectrometer at ambient temperature. High-resolution mass spectra were determined on a Jeol JMS-HX 110 spectrometer. Unless otherwise noted, all nonaqueous reactions were carried out under a dry nitrogen atmosphere with oven-dried glassware.

(1*S*,2*R*,3*R*)-1-Amino-2-*exo*-hydroxy-7,7-dimethylbicyclo[2.2.1]heptane (3). To a solution of 17.9 g (100 mmol) of isocyanate **2** in 600 mL of methanol at 0 °C was added solid $CeCl_3 \cdot 7H_2O$ (3.72 g, 10 mmol). After 10 min the mixture was cooled to −78 °C and solid $NaBH_4$ (5.29 g, 140 mmol) was added portionwise over 20 min. The reaction mixture was stirred at −50 to −36 °C for 2 h and then allowed to warm to 25 °C over 30 min. The methanol was removed by rotary evaporation, and 6 N KOH (45 mL) was added to the remaining slurry (ca. 50 mL). The reaction mixture was heated to reflux for 3 h, diluted with 600 mL of ether, and washed successively with 10% K_2CO_3 and then saturated aqueous sodium chloride. The organic layer was dried over potassium carbonate, filtered, and concentrated in vacuo to give 14.5 g (94%) of a white solid, which was used directly without further purification: mp 220–221 °C; IR (KBr) 3536, 3372, 2956, 1566, 1390, 1054 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.65 (dd, 1 H, J = 5.2, 5.0 Hz, C*H*O), 1.78–1.08 (m, 7 H, $CH_2CH_2CHCH_2$), 0.97 and 0.81 (2 s, 6 H, $C(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 76.58, 64.59, 45.47, 42.49, 38.92, 32.85, 26.68, 19.63, 19.23; $[\alpha]^{25}_D$ −16.2° (*c* 9.0, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_9H_{17}NO$ 155.1310, found 155.1315. Analysis of the aminoalcohol was performed through its hydrochloride salt. Anal. Calcd for $C_9H_{18}NOCl$: C, 56.42; H, 9.47; N, 7.31. Found: C, 55.95; H, 9.40; N, 7.28.

(1*S*,5*R*,7*R*)-10,10-Dimethyl-3-thioxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (4S). The oxazolidinethione **4S** was prepared by a modification of the published procedure for an analogous oxazolidinethione.[4d] A solution of 7.75 g (50 mmol) of **3** in 200 mL of dry THF was treated successively with 15 mL (250 mmol) of carbon disulfide and 27.8 mL (200 mmol) of triethylamine. The resulting solution was heated at reflux for 15 h. THF, carbon disulfide, and NEt_3 were removed by rotary evaporation. The resultant slurry was diluted with CH_2Cl_2 (300 mL) and water (30 mL). The layers were shaken and separated, and the aqueous layer was extracted with CH_2Cl_2 (60 mL). The combined organic layers were washed with saturated aqueous sodium chloride, dried over magnesium sulfate, filtered, and concentrated in vacuo to give 9.85 g (100%) of **4S** as a white solid. A small portion was recrystallized from hexane/dichloromethane for analysis: mp 174–175 °C; IR (KBr) 3168, 2960, 1510, 1266, 1244, 1220, 1190, 1174, 1150, 1126 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.55 (b s, 1 H, N*H*), 4.58 (dd, J = 8.4, 4.5 Hz, 1 H, C*H*O), 2.42–1.2 (m, 7 H, $CH_2CH_2CHCH_2$), 1.03 and 0.97 (2 s, 6 H, $C(CH_3)_2$); ^{13}C NMR (75.5 MHZ, $CDCl_3$) δ 191.6, 92.8, 73.6, 48.6, 42.3, 35.4, 26.2, 25.4, 19.2, 19.1; $[\alpha]^{25}_D$ +6.8° (*c* 4.0, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{10}H_{15}NOS$ 197.0875, found 197.0876. Anal. Calcd for $C_{10}H_{15}NOS$: C, 60.94; H, 7.67; N, 7.11. Found: C, 60.80; H, 7.60; N, 7.13.

***N*-Propionyl-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (5S).** To a solution of sodium hydride (1.8 g, 75 mmol) in 150 mL of anhydrous THF, stirred at 0 °C under dry N_2, was added via cannula a precooled (0 °C) solution of 9.85 g (50 mmol) of **4S** in 100 mL of dry THF. The mixture was stirred at 0 °C for 25 min, and 5.2 mL (5.55 g, 60 mmol, 1.2 equiv) of propionyl chloride was added dropwise over 10 min. The solution was stirred at that temperature for 30 min, and the reaction was quenched with acetic acid (1.43 mL, 25 mmol). THF was removed by rotary evaporation, the resultant slurry was diluted with CH_2Cl_2 (300 mL), and the CH_2Cl_2 solution was washed with two 50-mL portions of saturated aqueous sodium bicarbonate and 50 mL of brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo to give 12.52 g (99%) of the title compounds as a white solid. An analytical sample was prepared by recrystallization from dichloromethane/hexane to afford a colorless, crystalline solid: mp 73–74 °C; IR (KBr) 2976, 1708, 1486, 1456, 1376, 1302, 1284, 1248, 1228, 1184, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.39 (dd, J = 7.8, 3.9 Hz, 1 H, C*H*O), 3.42 (m, 1 H, $CH_3CHHC{=}O$), 3.0 (m, 1 H, $CH_3CHHC{=}O$), 2.85–1.15 (m, 7 H, $CH_2CH_2CHCH_2$), 1.107 (t, J = 7.2 Hz, 3 H, CH_3CH_2), 1.07 and 0.978 (2 s, 6 H, $C(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 187.8, 176.1, 89.4, 49.0, 42.3, 34.5, 32.0, 25.8, 25.1, 21.4, 19.1, 8.6; $[\alpha]^{25}_D$ + 52.4° (*c* 12.1, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{13}H_{19}NO_2S$ 253.1126, found 253.1134. Anal. Calcd for $C_{13}H_{19}NO_2S$: C, 61.69; H, 7.57; N, 5.53. Found: C, 61.34; H, 7.46; N, 5.67.

***N*-Propionyl-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (5O).** To a solution of sodium hydride (1.8 g, 75 mmol) in 200 mL of anhydrous THF at 0 °C was added a solution of (9.05 g, 50 mmol) oxazolidinone **4O** in 100 mL of dry THF. The mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature for an additional 5 h, and then recooled to 0 °C. To the above solution was added via cannula a solution of 5.2 mL (60 mmol) of propionyl chloride in 30 mL of dry THF. The resulting solution was stirred at 0 °C for 1 h and 25 °C for 2 h. The reaction mixture was recooled to 0 °C and quenched with 2 N HCl (15 mL). Following removal of the THF in vacuo on the rotary evaporator, the residue was diluted with 300 mL of dichloromethane and 50 mL of water. The organic extract was washed successively with saturated aqueous sodium bicarbonate and brine, dried ($MgSO_4$), and concentrated in vacuo to yield **5O** (11.6 g, 98%) as a viscous oil, which was used without purification. A small portion was purified by flash chromatography on silica gel for analysis: R_f 0.35 (30% hexane/dichloromethane); IR (neat) 2968, 1786, 1710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.2 (dd, J = 7.8, 5.0 Hz, 1 H, C*H*O—C=O), 3.2–1.2 (m, 9 H, CH_3CH_2—C=O, CH_2CH_2-$CHCH_2$), 1.127 (t, J = 10.8 Hz, 3 H, CH_3CH_2). 1.11 and 0.99 (2 s, 6 H, $C(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 175.1, 154.8, 84.4, 71.9, 47.9, 42.1, 34.4, 29.7, 25.7, 25.5, 21.3, 18.9, 8.1; $[\alpha]^{25}_D$ +58.4° (*c* 13.CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{13}H_{19}NO_3$ 237.1365, found 237.1365. Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.85; H, 8.07; N, 5.91. Found: C, 65.63; H, 8.03; N, 5.92.

General Procedure for the Aldol Condensation of Di-*n*-butylboron Enolates. Di-*n*-butylboryl triflate (1 M in CH_2Cl_2, 1.1 mmol) was added dropwise to a stirred solution of the *N*-acyloxazolidinethione **5S** or *N*-acyloxazolidinone **5O** (1 mmol) in 4 mL of dichloromethane at 0 °C. After the mixture was stirred at 0 °C for 10 min, 0.21 mL (155 mg, 1.2 mmol) of diisopropylethylamine in 1 mL of CH_2Cl_2 was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and was then recooled

(19) Duus, F. *Comprehensive Organic Chemistry; Thiocarbonyl Compounds.* In Barton, D., Ollis, W. D., Eds.; Pergamon Press: Oxford, England, 1979; Vol. 3, p 376.

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

to −78 °C. To the above enolate solution was added a solution of freshly distilled aldehyde (1.2–2.0 mmol) in 2 mL of CH_2Cl_2. The reaction mixture was stirred at −78 °C for 20 min, allowed to warm to 0 °C, and then quenched with a mixture of 6 mL of methanol, aqueous phosphate buffer (pH = 7, 4 mL), and 4 mL of 28% H_2O_2. The aqueous layer was extracted with two portions of CH_2Cl_2. The combined organic extracts (16 mL) were washed with saturated aqueous NH_4Cl and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was subjected to NMR analysis and purification by flash chromatography or recrystallization.

***N*-[(2*S*,3*S*)-3-Hydroxy-2-methyl-3-phenylpropionyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (6a).** As described above, propionyloxazolidinethione **5S** (506 mg, 2 mmol) and benzaldehyde (0.25 mL, 260 mg, 2.4 mmol) provided a crude reaction mixture. Diastereomer analysis of the unpurified product revealed the presence of a single diastereomer. Purification by recrystallization from hexane/CH_2Cl_2 afforded **6a** (618 mg, 86%) as a colorless, crystalline solid: mp 141.4–142.4 °C; IR (KBr) 3472, 2936, 1694, 1464, 1116 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.2 (m, 5 H, C_6H_5), 4.79 (dq, J = 5.7, 2.4 Hz, 1 H, CH_3CHC=O), 4.78 (d, J = 2.4 Hz, 1 H, C_6H_5CHOH), 4.0 (dd, J = 8.4, 3.9 Hz, 1 H, CHO—C=S), 2.75 (b s, 1 H, O*H*), 2.35–1.65 (m, 5 H, camphor ring-*H*), 1.35–1.331 (d, J = 5.7 Hz, 3 H, CH_3CHC=O), 1.16–1.036 (m, 1 H, camphor ring-*H*), 1.035 and 0.952 (2 s, 6 H, $C(CH_3)_2$), 0.34–0.25 (m, 1 H, camphor ring-*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 187.7, 177.7, 141.5, 128.3, 127.8, 126.6, 89.8, 78.8, 48.9, 46.4, 42.3, 34.4, 25.6, 23.8, 21.2, 19.1, 12.6; $[\alpha]^{25}_D$ +53.4° (*c* 2.3, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{20}H_{25}NO_3S$ 359.1553, found: 359.1548. Anal. Calcd for $C_{20}H_{25}NO_3S$: C, 66.89; H, 7.02; N, 3.90. Found: C, 66.61; H, 7.02; N, 4.10.

***N*-[(2*S*,3*R*)-3-Hydroxy-2-methylhexanoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (6b).** As described above, 253 mg (1 mmol) of **5S** and *n*-butyraldehyde (0.11 mL, 88 mg, 1.2 mmol) gave a crude reaction mixture. Diastereomer analysis by 300-MHz ^{1}H NMR of the unpurified product indicated the presence of essentially a single aldol adduct. The pale-yellow oil was purified by flash chromatography on silica gel (20% ethyl acetate/hexane) to afford 253 mg (78%) of **6b** as a white solid: mp 63–64 °C; IR (KBr) 3500, 2924, 1786, 1168 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.54–4.61 (m, 2 H, CHO—C=S and CH_3CHC=O), 3.86 (dt, J = 7.8, 3.9 Hz, 1 H, CHOH), 2.81–1.82 (m, 6 H, camphor ring-*H* and O*H*), 1.55–1.16 (m with d at 1.27, J = 6.9 Hz, 9 H, CH_3CHC=O, CH_2CH_2CHOH, and camphor ring-*H*), 1.148 and 1.057 (2 S, 6 H, $C(CH_3)_2$), 0.926 (t, J = 7.2 Hz, 3 H, CH_3CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 188, 179.6, 90.0, 89.9, 72.5, 49.3, 44.1, 42.6, 36.5, 34.7, 25.9, 25.1, 21.6, 19.3, 19.1, 14.0, 10.3; $[\alpha]^{25}_D$ +48.9° (*c* 4.2, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{17}H_{27}NO_3S$ 325.1718, found 325.1719. Anal. Calcd for $C_{17}H_{27}NO_3S$: C, 62.79; H, 8.37; N, 4.31. Found: C, 62.51; H, 8.30; N, 4.55.

***N*-[(2*S*,3*R*)-3-Hydroxy-2-methyl-4-hexenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (6c).** As described above, **5S** (506 mg, 2 mmol) and crotonaldehyde (0.21 mL, 178 mg, 2.5 mmol) gave a crude reaction mixture. Diastereomer analysis (^{1}H NMR) of the unpurified aldol adduct revealed the presence of essentially a single syn aldol. The mixture was purified by flash chromatography (silica gel, 25% ethyl acetate/hexane) to afford 523 mg (81%) of **6c** as a clear colorless oil: IR (neat) 3456, 2968, 1708, 1184 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.69 (ddq, J = 15.4, 10.2, 1.2 Hz, 1 H, CH_3CH=CH), 5.45 (ddq, J = 15.4, 6.0, 1.2 Hz, 1 H, CH_3CH=C*H*), 4.52 (dq, J = 7.0, 2.4 Hz, 1 H, CH_3CHC=O), 4.45 (dd, J = 8.2, 4.0 Hz, 1 H, CHO—C=S), 4.28 (m, 1 H, CHOH), 2.76–1.5 (m with d at 1.69, J = 10.0, 1.2 Hz, 9 H, CH_3CH=C, O*H*, camphor ring-*H*), 1.4–1.12 (m with s at 1.14 and d at 1.27, J = 7.2 Hz, 8 H, CH_3—C—CH_3, CH_3CHC=O, camphor ring-*H*), 1.045 (s, 3 H, CH_3=C=CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 188.4, 178.7, 130.7, 128.6, 90.2, 77.3, 74.4, 49.1, 44.9, 42.5, 34.5, 25.8, 24.7, 21.3, 19.1, 17.5, 11.6; $[\alpha]^{25}_D$ +77.5° (*c* 3.0, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{17}H_{25}NO_3S$ 323.1556, found 323.1559. Anal. Calcd for $C_{17}H_{25}NO_3S$: C, 63.19; H, 7.79; N, 4.33. Found: C, 62.94; H, 7.77; N, 4.33.

***N*-[(2*S*,3*R*)-3-Hydroxy-2,4-dimethylpentanoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (6d).** As described above, **5S** (506 mg, 2 mmol) and isobutyraldehyde (0.27 mL, 216 mg, 3 mmol) afforded a crude reaction mixture. Diastereomer analysis (300-MHz ^{1}H NMR) of the crude product indicated the presence of a single aldol adduct. Purification by flash chromatography (20% ethyl acetate/hexane, silica gel) yielded 514 mg (79%) of **6d** as a colorless oil: IR (neat) 3490, 2968, 1712, 1184 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.69 (dq, J = 8.6, 2.6 Hz, 1 H, CH_3CHC=O), 4.45 (dd, J = 8.2, 4.0 Hz, 1 H, CHO—C=S), 3.45 (dd, J = 6.6, 2.6 Hz, 1 H, CHOH), 2.81–1.13 (m with d at 1.22, J = 9.2 Hz, 12 H, CH_3CHC=O, $CH(CH_3)_2$, O*H*, $CH_2CH_2CHCH_2$), 1.126 and 1.036 (2 s, 6 H, $C(CH_3)_2$), 0.974 (d, J = 9.6 Hz, 3 H, CH_3—$CHCH_3$), 0.88 (d, J = 10.2 Hz, 3 H, CH_3CH—CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 187.8, 179.0, 89.8, 77.8, 77.2, 49.2, 42.6, 41.8, 34.6, 31.2, 25.9, 24.9, 21.5, 19.3, 19.0, 18.7, 9.9; $[\alpha]^{25}_D$ +2.04° (*c* 2.25, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{17}H_{27}NO_3S$ 325.1712, found 325.1703. Anal. Calcd for $C_{17}H_{27}NO_3S$: C, 62.79; H, 8.37; N, 4.31. Found: C, 62.70; H, 8.31; N, 4.42.

***N*-[(2*S*,3*S*)-3-Hydroxy-2-methyl-3-phenylpropionyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (10a).** As described above, **5O** (237 mg, 1 mmol) and benzaldehyde (0.13 mL, 135 mg, 1.3 mmol) afforded a crude reaction mixture. Diastereomer analysis (300-MHz ^{1}H NMR) of the unpurified product indicated the presence of a single diastereomer. The mixture was purified by recrystallization (hexane/CH_2Cl_2) to give 49 mg of **5O** and 247 mg (72%) of **10a** as a colorless, crystalline solid: mp 121–122 °C; IR (KBr) 3468, 2972, 1784, 1694, 1488 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.25 (m, 5 H, C_6H_5), 4.985 (dd, J = 4.2, 1.2 Hz, 1 H, CHOH), 4.05 (dq, J = 7.2, 4.2 Hz, 1 H, CH_3CHC=O), 4.04 (dd, J = 8.4, 4.2 Hz, 1 H, CHO=C=O), 3.07 (d, J = 2.4 Hz, 1 H, O*H*), 2.86–1.73 (m, 5 H, camphor ring-*H*), 1.33–1.18 (m with d at 1.247, J = 6.9 Hz, 4 H, CH_3CHC=O, camphor ring-*H*), 1.112–0.95 (m with 2 s at 1.112 and 0.995, 7 H, $C(CH_3)_2$, camphor ring-*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.1, 154.7, 141.5, 128.3, 127.6, 126.4, 84.7, 74.7, 72.3, 48.2, 45.5, 42.4, 34.6, 25.9, 25.5, 21.5, 19.1, 11.4; $[\alpha]^{25}_D$ +94.8° (*c* 12.6, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{20}H_{25}NO_4$ 343.1783, found 343.1763. Anal. Calcd for $C_{20}H_{25}NO_4$: C, 70.00; H, 7.34; N, 4.08. Found: C, 70.03; H, 7.31; N, 4.06.

***N*-[(2*S*,3*R*)-3-Hydroxy-2-methylhexanoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (10b).** As described above, **5O** (474 mg, 2 mmol) and *n*-butyraldehyde (0.22 mL, 176 mg, 2.4 mmol) afforded a crude reaction mixture. Analysis (300-MHz ^{1}H NMR) of the unpurified product indicated the presence of a single aldol adduct. Purification by recrystallization (CH_2Cl_2/hexane) yielded 118 mg of **5O** and 426 mg (69%) of **10b** as a white solid: mp 51–52 °C; IR (KBr) 3460, 2960, 1782, 1690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.257 (dd, J = 8.4, 4.5 Hz, 1 H, CHO—C=O), 3.39 (m, 1 H, CHOH), 3.70 (dq, J = 6.9, 3.0 Hz, 1 H, CH_3CHC=O), 3.02–1.22 (m, 12 H, $CH_2CH_2CHCH_2$, CH_2CH_2CHOH), 1.21 (d, J = 6.9 Hz, 3 H, CH_3CHC=O), 1.15 and 0.99 (2 s, 6 H, $C(CH_3)_2$), 0.89 (t, J = 7.2 Hz, 3 H, CH_3CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.3, 154.7, 84.6, 72.3, 71.5, 48.2, 42.8, 42.3, 36.0, 34.6, 25.9, 25.8, 21.5, 19.1, 19.0, 13.9, 10.3; $[\alpha]^{25}_D$ +81° (*c* 10.1, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{17}H_{27}NO_4$ 309.1940, found 309.1928. Anal. Calcd for $C_{17}H_{27}NO_4$: C, 66.04; H, 8.80; N, 4.53. Found: C, 65.80; H, 8.69; N, 4.63.

***N*-[(2*S*,3*R*)-3-Hydroxy-2-methyl-4-hexenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (10c).** As described above, **5O** (474 mg, 2 mmol) and crotonaldehyde (0.21 mL, 178 mg, 2.5 mmol) gave a crude reaction mixture. Analysis (300-MHz ^{1}H NMR) of the unpurified product indicated the presence of essentially a single aldol adduct. Purification by flash chromatography (silica gel, 17% ethyl acetate/hexane) provided 90 mg of **5O** and 448 mg (73%) of **10c** as a colorless oil: IR (neat) 3520, 2972, 1776, 1708, 1080, 970 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (ddq, J = 15.6, 9.6, 0.9 Hz, 1 H, CH_3CH=CH), 5.45 (ddq, J = 15.6, 6.3, 1.2 Hz, 1 H, CH_3CH=C*H*), 4.34 (ddd, J = 6.0, 3.9, 1.2 Hz, 1 H, C=CH—CHOH), 4.25 (dd, J = 8.4, 4.2 Hz, 1 H, CHOC=O), 3.794 (dq, J = 6.9, 3.9 Hz, 1 H, CH_3CHC=O), 3.06–1.63 (m with d at 1.695, J = 6.3 Hz, 9 H, CH_3CH=C, O*H*, camphor ring-*H*), 1.40–1.17 (m with d at 1.24, J = 6.9 Hz, 5 H, CH_3CHC=O, camphor ring-*H*), 1.132 and 1.024 (2 s, 6 H, $C(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.9, 154.7, 130.4, 127.7, 84.5, 73.1, 72.2, 48.0, 43.6, 42.2, 34.5, 25.5, 21.4, 18.9, 17.5, 11.3; $[\alpha]^{25}_D$ +92.2° (*c* 15.8, CH_2Cl_2); high-resolution MS *m/e* calcd for $C_{17}H_{25}NO_4$ 307.1784, found 307.1772. Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.47; H, 8.20; N, 4.56. Found: C, 66.40; H, 8.24; N, 4.57.

***N*-[(2*S*,3*R*)-3-Hydroxy-2,4-dimethylpentanoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (10d).** As described above, **5O** (237 mg, 1 mmol) and isobutyraldehyde (0.18 mL, 144 mg, 2 mmol) gave a crude reaction mixture. Analysis (300-MHz ^{1}H NMR) of the unpurified product revealed the presence of a single aldol adduct. Purification by flash chromatography (silica gel, 17% ethyl acetate/hexane) yielded 61.5 mg of **5O** and 210 mg (68%) of **10d** as a white solid: mp 91–92 °C; IR (KBr) 3512, 2976, 1778, 1690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24 (dd, J = 8.4, 3.9 Hz, 1 H, CHO—C=O), 3.90 (dq, J = 6.9, 2.7 Hz, 1 H, CH_3CHC=O), 3.464 (dt, J = 8.4, 3.3 Hz, 1 H, CHOH), 2.98–1.23 (m with d at 2.823, J = 3.3 Hz, 9 H, O*H*, $CH(CH_3)_2$,

$CH_2CH_2CHCH_2$), 1.21 (d, J = 7.2 Hz, 3 H, $CH_3CHC{=}O$), 1.11 and 1.008 (2 s, 6 H, $C(CH_3)_2$), 0.997 and 0.878 (2 d, J = 6.9 Hz, 6 H, $CH(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.5, 154.6, 84.6, 77.1, 72.3, 48.2, 42.4, 40.4, 40.3, 34.6, 30.8, 25.8, 21.6, 19.1, 19.0, 18.8, 10.0; $[\alpha]^{25}_D$ + 84.6° (c 8.8, CH_2Cl_2); high-resolution MS m/e calcd for $C_{17}H_{27}NO_4$ 309.1941, found 309.1923. Anal. Calcd for $C_{17}H_{27}NO_4$: C, 66.04; H, 8.80; N, 4.53. Found: C, 66.04; H, 8.89; N, 4.47.

General Procedure for the Aldol Condensation of Chlorotitanium Enolates. To a solution of **5S** or **5O** (1 mmol) in 4 mL of CH_2Cl_2 cooled to 0 °C was added 1.1 mL (1 M in CH_2Cl_2, 1.1 mmol, 1.1 equiv) of $TiCl_4$. After stirring at 0 °C for 10 min, slow addition of diisopropylethylamine (1 M in CH_2Cl_2, 1.2 mL, 1.2 mmol), and further stirring for 20 min at 0 °C, the reaction mixture was cooled to −78 °C. To the above enolate solution was slowly added a solution of freshly distilled aldehyde (1.2–3.0 mmol) in 2 mL of CH_2Cl_2. The reaction mixture was stirred at −78 °C for 1 h, allowed to warm to 0 °C, and then quenched with 6 mL of a 1:2 mixture of saturated aqueous ammonium chloride and aqueous phosphate buffer (pH = 7). The aqueous layer was extracted with 15 mL of CH_2Cl_2. The combined organic extracts were washed with saturated aqueous NH_4Cl (4 mL) and brine (4 mL), dried ($MgSO_4$), and concentrated in vacuo.

***N*-[(2*R*,3*R*)-3-Hydroxy-2-methyl-3-phenylpropionyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (7a).** **Method A.** As described above, 253 mg (1 mmol) of propionyloxazolidinethione **5S** was converted to its chlorotitanium enolate. Condensation with benzaldehyde (0.13 mL, 135 mg, 1.3 mmol) and workup afforded a crude product mixture. Diastereomer analysis [300-MHz ^1H NMR integration of the C-2 and/or C-3 methine protons ($CH(OH)C_6H_5$ and $CH_3CHC{=}O$)] of the unpurified adduct revealed the presence of two syn aldols **6a** and **7a** in the ratio of 13:87. **Method B.** In an experiment otherwise identical with that described above, the chlorotitanium enolate was treated with a solution of 1:1 benzaldehyde/$TiCl_4$ complex (1.2 mmol) in 1.2 mL of CH_2Cl_2. Workup and ^1H NMR diastereomer analysis gave a 3:97 ratio of syn aldol adducts **6a** and **7a**. The mixture was recrystallized from hexane/CH_2Cl_2 to afford 301 mg (84%) of **7a** as a colorless crystalline solid: mp 139–140 °C; IR (KBr) 3528, 2980, 1682, 1452, 1172 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.51–7.23 (m, 5 H, C_6H_5), 5.36 (d, J = 3.0 Hz, 1 H, C_6H_5CHOH), 5.10 (dq, J = 7.2, 3.0 Hz, 1 H, $CH_3CHC{=}O$), 4.46 (dd, J = 8.4, 4.2 Hz, 1 H, $CHO{-}C{=}S$), 3.35 (b s, 1 H, OH), 2.83–1.2 (m, 7 H, camphor ring-H), 1.12 and 1.05 (2 s, 6 H, $C(CH_3)_2$), 1.075 (d, J = 7.2 Hz, 3 H, $CH_3CHC{=}O$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 187.9, 180.4, 141.2, 128.2, 127.2, 126.0, 89.9, 77.0, 72.2, 49.2, 45.2, 42.6, 34.7, 25.9, 25.0, 21.4, 19.3, 11.2; $[\alpha]^{25}_D$ + 106.2° (c 2.7, CH_2Cl_2); high-resolution MS m/e calcd for $C_{20}H_{25}NO_3S$ 359.1551, found 359.1548. Anal. Calcd for $C_{20}H_{25}NO_3S$: C, 66.89; H, 7.02; N, 3.90. Found: C, 66.58; H, 6.99; N, 4.10.

***N*-[(2*R*,3*R*)-3-Hydroxy-2-methylhexanoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (7b).** As described above, 253 mg (1 mmol) of **5S** was converted to its chlorotitanium enolate. Condensation with n-butyraldehyde (0.18 mL, 144 mg, 2 mmol) and workup gave a crude reaction mixture. Analysis by 300-MHz ^1H NMR revealed the presence of a single syn aldol. The mixture was purified by flash chromatography on silica gel (17% ethyl acetate/hexane) to provide 286 mg (88%) of **7b** as a colorless oil: IR (KBr) 3436, 2964, 1698, 1144 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.70 (dq, J = 7.5, 2.4 Hz, 1 H, $CH_3CHC{=}O$), 4.65 (dd, J = 8.1, 3.9 Hz, 1 H, $CHO{-}C{=}S$), 4.15 (m, 1 H, CH_2CHOH), 2.91 (b s, 1 H, OH), 2.82–1.19 (m, 11 H, CH_2CH_2-CHOH, camphor ring-H), 1.175 (d, J = 7.2 Hz, 3 H, $CH_3CHC{=}O$), 1.153 and 1.068 (2 s, 6 H, $C(CH_3)_2$), 0.96 (t, J = 7.2 Hz, 3 H, $CH_3CH_2CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 187.9, 180.4, 92.9, 89.7, 70.4, 49.1, 42.9, 42.5, 35.7, 34.5, 25.8, 24.8, 21.4, 19.2, 19.0, 13.9, 10.9; $[\alpha]^{25}_D$ + 52.4° (c 2.55, CH_2Cl_2); high-resolution MS m/e calcd for $C_{17}H_{27}NO_3S$ 325.1711, found 325.1707. Anal. Calcd for $C_{17}H_{27}NO_3S$: C, 62.79; H, 8.37; N, 4.31. Found: C, 62.52; H, 8.29; N, 4.55.

***N*-[(2*R*,3*S*)-3-Hydroxy-2-methyl-4-hexenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (7c).** As described above, 253 mg (1 mmol) of **5S** was converted to its chlorotitanium enolate. Condensation with crotonaldehyde (0.11 mL, 93 mg, 1.3 mmol) and workup afforded a crude product mixture. Diastereomer analysis (200-MHz ^1H NMR) of the unpurified mixture revealed the presence of essentially a single syn aldol. Purification by flash chromatography (20% ethyl acetate/hexane, silica gel) yielded 278 mg (86%) of **7c** as a colorless oil: IR (neat) 3463, 2972, 1708, 1172 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.73 (ddq, J = 15.4, 10.0, 1.0 Hz, 1 H, $CH_3CH{=}C$), 5.5 (ddq, J = 15.4, 6.2, 1.4 Hz, 1 H, $CH_3CH{=}CH$), 4.75 (dq, J = 7.0, 3.4 Hz, 1 H, $CH_3CHC{=}O$), 4.53 (m, 1 H, $CHOH$), 4.393 (dd, J = 8.2, 4.0 Hz, 1 H, $CHO{-}C{=}S$), 2.95 (b s, 1 H, OH), 2.86–1.16 (m with dd at 1.69, J = 10.1, 1.3 Hz, 10 H, $CH_3CH{=}CH$, $CH_2CH_2CHCH_2$), 1.126 (d, J = 7.0 Hz, 3 H, $CH_3CHC{=}O$), 1.108 and 1.02 (2 s, 6 H, $C(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 188.8, 180.1, 130.9, 128.5, 90.1, 77.6, 72.7, 49.6, 44.0, 42.8, 34.9, 26.2, 25.4, 21.7, 19.4, 17.9, 12.1; $[\alpha]^{25}_D$ + 82.4 (c 1.5, CH_2Cl_2); high-resolution MS m/e calcd for $C_{17}H_{25}NO_3S$ 323.1556, found 323.1559. Anal. Calcd for $C_{17}H_{25}NO_3S$: C, 63.18; H, 7.79; N, 4.33. Found: C, 62.90; H, 7.73; N, 4.39.

***N*-[(2*R*,3*S*)-3-Hydroxy-2,4-dimethylpentanoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-thioxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (7d).** As described above, 506 mg (2 mmol) of **5S** was converted to its chlorotitanium enolate. Condensation with isobutyraldehyde (0.27 mL, 216 mg, 3 mmol) provided a crude reaction mixture. Diastereomer analysis [300-MHz ^1H NMR integration of the C-2 and/or C-3 methine protons ($CHOH$ and $CH_3CHC{=}O$)] of the unpurified adduct revealed the presence of a 2:98 ratio of **6d** and **7d**. Purification by flash chromatography (25% ethyl acetate/hexane, silica gel) afforded 540 mg (83%) of **7d** as a white solid: mp 77–78 °C; IR (KBr) 3520, 2968, 2884, 1707, 1461, 1173 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.91 (dq, J = 7.5, 2.4 Hz, 1 H, $CH_3CHC{=}O$), 4.45 (dd, J = 7.8, 3.9 Hz, 1 H, $CHO{-}C{=}S$), 3.69 (dd, J = 7.2, 2.4 Hz, 1 H, $CHOH$), 3.1 (b s, 1 H, OH), 2.82–1.19 (m, 8 H, $CH(CH_3)_2$, $CH_2CH_2CHCH_2$), 1.163 (d, J = 7.2 Hz, 3 H, $CH_3CHC{=}O$), 1.15 (s, 3 H, $CH_3{-}C{-}CH_3$), 1.076 (d, J = 6 Hz, 3 H, $CH_3{-}CHCH_3$), 1.066 (s, 3 H, $CH_3{-}C{-}CH_3$), 0.922 (d, J = 6.9 Hz, 3 H, $CH_3CH{-}CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 187.9, 181.1, 89.7, 77.2, 75.7, 49.2, 42.6, 40.7, 34.6, 30.7, 25.9, 24.9, 21.5, 19.6, 19.3, 18.7, 10.7; $[\alpha]^{25}_D$ + 66.5° (c 1.1, CH_2Cl_2); high-resolution MS m/e calcd for $C_{17}H_{27}NO_3S$ 325.1712, found 325.1703. Anal. Calcd for $C_{17}H_{27}NO_3S$: C, 62.79; H, 8.37; N, 4.31. Found: C, 62.67; H, 8.30; N, 4.42.

***N*-[(2*R*,3*R*)-3-Hydroxy-2-methyl-3-phenylpropionyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (11a).** As described above, 237 mg (1 mmol) of **5O** was converted to its chlorotitanium enolate. Condensation with benzaldehyde (0.21 mL, 216 mg, 2.0 mmol) gave a crude reaction mixture. Diastereomer analysis [300-MHz ^1H NMR integration of the C-2 and/or C-3 methine protons ($CHOH$ and $CH_3CHC{=}O$)] of the unpurified product revealed the presence of two isomers **10a** and **11a** in the ratio of 88:12. **11a**:[5] mp 43–44 °C; IR (KBr) 3468, 2972, 1784, 1694, 1488 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.20 (m, 5 H, C_6H_5), 5.145 (t, J = 3.6 Hz, 1 H, $CHOH$), 4.23 (dq, J = 7.2, 4.2 Hz, 1 H, $CH_3CHC{=}O$), 4.22 (dd, J = 7.8, 4.5 Hz, 1 H, $CHO{-}C{=}O$), 3.04 (d, J = 3 Hz, 1 H, OH), 2.98–1.18 (m, 7 H, $CH_2CH_2CHCH_2$), 1.13 (d, J = 6.9 Hz, 3 H, $CH_3CHC{=}O$), 1.026 and 0.878 (2 s, 6 H, $C(CH_3)_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.9, 154.7, 141.5, 128.1, 127.5, 127.4, 84.4, 73.6, 72.4, 48.1, 44.9, 42.3, 34.6, 25.8, 25.7, 21.3, 18.8, 11.4; $[\alpha]^{25}_D$ + 44.2° (c 2.4, CH_2Cl_2); high-resolution MS m/e calcd for $C_{20}H_{25}NO_4$ 343.1783, found 343.1763. Anal. Calcd for $C_{20}H_{25}NO_4$: C, 70.00; H, 7.34; N, 4.08. Found: C, 69.97, H, 7.28; N, 4.05.

***N*-[(2*R*,3*S*)-3-Hydroxy-2-methylhexanoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (11b).** As described above, 237 mg (1 mmol) of **5O** was converted to its chlorotitanium enolate. Condensation with n-butyraldehyde (0.18 mL, 144 mg, 2.0 mmol) gave a crude reaction mixture. Diastereomer analysis [300-MHz ^1H NMR integration of the C-2 and/or C-3 methine protons ($CHOH$ and $CH_3CHC{=}O$)] of the unpurified product indicated the presence of two isomers **10b** and **11b** in the ratio of 95:5. **11b**:[5] mp 56–57 °C; IR (KBr) 3460, 2960, 1782, 1694 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.25 (dd, J = 8.4, 4.2 Hz, 1 H, $CHO{-}C{=}O$), 4.01 (m, 1 H, $CHOH$), 3.87 (dq, J = 6.9, 2.4 Hz, 1 H, $CH_3CHC{=}O$), 3.0–1.21 (m with d at 2.834, J = 2.4 Hz, 12 H, CH_2CH_2CHOH, $CH_2CH_2CHCH_2$), 1.17 (d, J = 6.9 Hz, 3 H, $CH_3CHC{=}O$), 1.15 and 1.13 (2 s, 6 H, $C(CH_3)_2$), 0.95 (t, J = 6.9 Hz, 3 H, CH_3CH_2); $[\alpha]^{25}_D$ + 57.5° (c 5.0, CH_2Cl_2); high-resolution MS m/e calcd for $C_{17}H_{27}NO_4$ 309.1940, found 309.1928. Anal. Calcd for $C_{17}H_{27}NO_4$: C, 66.04; H, 8.80; N, 4.53. Found: C, 65.80; H, 8.68; N, 4.62.

***N*-[(2*R*,3*S*)-3-Hydroxy-2-methyl-4-hexenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (11c) and *N*-[(2*S*,3*S*)-3-Hydroxy-2-methyl-4-hexenoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (12c).** As described above, 237 mg (1.0 mmol) of **5O** was converted to its chlorotitanium enolate. Condensation with crotonaldehyde (0.13 mL, 107 mg, 1.5 mmol) and workup afforded a crude product mixture. Diastereomer analysis (300-MHz ^1H NMR) of the unpurified aldols indicated the presence of three diastereomers in the ratio of 70:12:18. Purification by flash chromatography (15% ethyl acetate/hexane, silica gel) yielded 211 mg (69%) of a mixture

of **10c** and **11c** (85:15 ratio by NMR) and 47 mg (15%) of **12c**[21] as a colorless, crystalline solid: mp 89–90 °C; IR (KBr) 3520, 2972, 1776, 1708 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.73 (ddq, J = 15.4, 6.6, 0.8 Hz, ^{1}H, CH_3CH=CH), 5.51 (ddq, J = 15.4, 6.6, 1.4 Hz, 1 H, CH_3-CH=C*H*), 4.20 (dd, J = 8.2, 4.2 Hz, 1 H, C*H*O—C=O), 4.07 (dd, J = 7.2, 7.0 Hz, 1 H, C*H*OH), 3.91 (quintet, J = 7.0 Hz, 1 H, CH_3CHC=O), 3.05–1.15 (m with d at 1.69, J = 6.6 Hz, 11 H, C*H*$_3$-CH=CH, O*H*, $CH_2CH_2CHCH_2$), 1.12 (d, J = 6.8 Hz, 3 H, C*H*$_3$-CHC=O), 1.1 and 1.0 (2 s, 6 H, C(C*H*$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.5, 156.1, 132.4, 128.8, 84.9, 76.1, 73.1, 48.7, 44.1, 42.6, 34.9, 26.3, 26.1, 21.7, 19.1, 17.9, 15.0; $[\alpha]^{25}$D +20.1° (c 2.2, CH_2Cl_2); high-resolution MS m/e calcd for $C_{17}H_{25}NO_4$ 307.1984, found 307.1970. Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.47; H, 8.20; N, 4.56. Found: C, 66.23; H, 8.07; N, 4.48. Syn aldol **11c** gave rise to two additional signals at δ 4.41 (ddd, J = 6.0, 4.2, 0.9 Hz, 1 H, C=CHC*H*OH) and 3.96 (dq, J = 6.9, 3.9 Hz, 1 H, CH_3C*H*C=O).

***N*-[(2*R*,3*S*)-3-Hydroxy-2,4-dimethylpentanoyl]-(1*S*,5*R*,7*R*)-10,10-dimethyl-3-oxo-2-aza-4-oxatricyclo[5.2.1.0^{1,5}]decane (11d).** As described above, 237 mg (1 mmol) of **5O** was converted to its chlorotitanium enolate. Condensation with isobutyraldehyde (0.13 mL, 104 mg, 1.4 mmol) afforded a crude reaction mixture. Diastereomer analysis (300-MHz ^{1}H NMR) of the unpurified product indicated the presence of two aldol adducts **10d** and **11d** in the ratio of 98:2. Purification by flash chromatography (silica gel, 20% ethyl acetate/hexane) afforded 265 mg (86%) of **10d** as a colorless oil. **11d**:[5] IR (neat) 3512, 2976, 1778, 1690 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.262 (dd, J = 8.4, 4.2 Hz, 1 H, C*H*O—C=O), 4.086 (dq, J = 6.9, 2.4 Hz, 1 H, CH_3C*H*C=O), 3.61 (dt, J = 8.7, 3.0 Hz, 1 H, C*H*OH), 3.01–1.20 (m with d at 2.808, J = 3.0 Hz, 9 H, O*H*, C*H*(CH$_3$)$_2$, $CH_2CH_2CHCH_2$), 1.174 (d, J = 7.5 Hz, 3 H, C*H*$_3$CHC=O), 1.151 and 1.052 (2 s, 6 H, C(C*H*$_3$)$_2$), 1.07 and 0.948 (2 d, J = 6.9 Hz, 6 H, CH(C*H*$_3$)$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 179.4, 154.6, 84.5, 77.2, 72.4, 48.2, 42.4, 40.2, 34.6, 30.7, 25.9, 25.7, 21.5, 19.3, 19.1, 18.7, 10.2; $[\alpha]^{25}$D +49.0° (c 4.0, CH_2Cl_2); high-resolution MS m/e calcd for $C_{17}H_{27}NO_4$ 309.1941, found 309.1923. Anal. Calcd for $C_{17}H_{27}NO_4$: C, 66.04; H, 8.80; N, 4.53. Found: C, 66.13; H, 8.87; N, 4.51.

General Procedure for the Hydroperoxide-Assisted Saponification/Esterification. Methoxycarbonyl Aldols 14 and 15. To a solution of aldol adduct **6** or **7** (1 equiv) in THF/H_2O (3:1, 0.16 M) at 0 °C was added a solution of LiOH (2 equiv) in 6 equiv of 28% H_2O_2. The resulting mixture was stirred at 0 °C for 0.5–3 h and treated with a solution of 8 equiv of Na_2SO_3 in H_2O. Following removal of the THF in vacuo on the rotary evaporator, the aqueous residue was diluted with H_2O and extracted with three portions of CH_2Cl_2. The combined CH_2Cl_2 extracts were dried ($MgSO_4$) and evaporated in vacuo to give recovered auxiliary **5S**. The aqueous phase was acidified with 3 N HCl and extracted with three portions of ether. The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a colorless oil, which was cooled to 0 °C and treated with a solution of CH_2N_2 (excess) in ether. After the reaction mixture was stirred at 0 °C for 0.5–1 h, it was concentrated in vacuo to afford pure α-methyl-β-hydroxy ester **14** or **15**.

(2*S*,3*S*)-Methyl 2-Methyl-3-hydroxy-3-phenylpropanoate (14a). IR (neat) 3514, 3070, 2956, 1728, 1608, 1551, 1497, 1455 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31–7.12 (m, 5 H, C$_6$H$_5$), 5.0 (d, J = 4.0 Hz, 1 H, C*H*OH), 3.58 (s, 3 H, OC*H*$_3$), 2.9 (b s, 1 H, O*H*), 2.7 (dq, J = 7.2, 4.2 Hz, 1 H, CH_3C*H*C=O), 1.03 (d, J = 7.4 Hz, 3 H, C*H*$_3$CHC=O); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.5, 141.9, 128.5, 127.8, 126.2, 73.9, 51.9, 46.6, 10.8; $[\alpha]^{25}$D –23.5° (c 0.7 CH_2Cl_2) [lit.[4e] $[\alpha]^{25}$D –20.8° (c 1.3, $CHCl_3$)]; high-resolution MS m/e calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0943.

(2*R*,3*R*)-Methyl 2-Methyl-3-hydroxy-3-phenylpropanoate (15a). IR, ^{1}H NMR, and ^{13}C NMR are identical with those of **14a**. $[\alpha]^{25}$D +23.6° (c 1.6, CH_2Cl_2) [lit.[4a] $[\alpha]^{25}$D +23.2° (c 3.2, $CHCl_3$); lit.[4e] $[\alpha]^{25}$D +23.5° (c 3.2, $CHCl_3$)].

(2*S*,3*R*)-Methyl 2-Methyl-3-hydroxyhexanoate (14b). IR (neat) 3460, 2962, 1740, 1464, 1440, 1176, 1140 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.86 (dt, J = 8.0, 3.6 Hz, 1 H, C*H*OH), 3.67 (s, 3 H, OC*H*$_3$), 2.48 (dq, J = 7.2, 3.6 Hz, 1 H, CH_3C*H*C=O), 1.6–1.2 (m, 4 H, CH_2CH_2), 1.14 (d, J = 7.2 Hz, 3 H, C*H*$_3$CHC=O), 0.89 (t, J = 7.2 Hz, 3 H, C*H*$_3$CH$_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.8, 71.4, 51.6, 44.1, 35.8, 18.9, 13.7, 10.4; $[\alpha]^{25}$D +12.6° (c 0.47, CH_2Cl_2) [lit.[4e] $[\alpha]^{25}$D +12.1° (e 1.9, $CHCl_3$)].

(2*R*,3*S*)-Methyl 2-Methyl-3-hydroxyhexanoate (15b). IR, ^{1}H NMR, and ^{13}C NMR are identical with those of **14b**. $[\alpha]^{25}$D –13.4° (c 1.0, CH_2Cl_2).

(2*S*,3*R*)-Methyl 2-Methyl-3-hydroxy-(*E*)-4-hexenoate (14c). IR (neat) 3484, 2956, 1736, 1458, 1440, 968 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.69 (ddq, J = 15.4, 6.4, 1.0 Hz, 1 H, CH_3CH=CH), 5.43 (ddq, J = 15.4, 6.8, 1.6 Hz, 1 H, CH_3CH=C*H*), 4.26 (dd, J = 5.0, 4.8 Hz, 1 H, C*H*OH), 3.65 (s, 3 H, OC*H*$_3$), 2.57 (dq, J = 7.0, 4.8 Hz, 1 H, CH_3CHC=O), 1.66 (dd, J = 6.6, 1.0 Hz, 3 H, C*H*$_3$CH=CH), 1.13 (d, J = 7.0 Hz, 3 H, C*H*$_3$CHC=O); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 176.0, 130.4, 128.4, 73.2, 51.6, 44.9, 17.5, 11.3; $[\alpha]^{25}$D +11.1° (c 2.5, CH_2Cl_2) [lit.[4e] $[\alpha]^{25}$D +11.5° (c 0.8, $CHCl_3$)]; high-resolution MS m/e calcd for $C_8H_{14}O_3$ 158.0953, found 158.0943.

(2*R*,3*S*)-Methyl 2-Methyl-3-hydroxy-(*E*)-4-hexenoate (15c). IR, ^{1}H NMR, and ^{13}C NMR are identical with those of **14c**. $[\alpha]^{25}$D –12.3° (c 3.0, CH_2Cl_2).

(2*S*,3*R*)-Methyl 2,4-Dimethyl-3-hydroxypentanoate (14d). IR (neat) 3508, 2968, 1740, 1464 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.67 (s, 3 H, OC*H*$_3$), 3.53 (dd, J = 7.8, 3.6 Hz, 1 H, C*H*OH), 2.64 (dq, J = 7.0, 3.6 Hz, 1 H, CH_3CHC=O), 1.74 (octet, J = 6.6 Hz, 1 H, (CH$_3$)$_2$C*H*), 1.14 (d, J = 7.2 Hz, 3 H, C*H*$_3$CHC=O), 0.97 and 0.84 (2 d, J = 6.6 Hz, 6 H, (C*H*$_3$)$_2$CH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 177.4, 77.0, 51.9, 41.8, 30.6, 19.0, 18.5, 10.1; $[\alpha]^{25}$D –7.8° (c 1.2, CH_2Cl_2) [lit.[4e] $[\alpha]^{25}$D –7.1° (c 1.2, $CHCl_3$)].

(2*R*,3*S*)-Methyl 2,4-Dimethyl-3-hydroxypentanoate (15d). IR, ^{1}H NMR, and ^{13}C NMR are identical with those of **14d**. $[\alpha]^{25}$D +7.1° (c 1.3, CH_2Cl_2) [lit.[4a] $[\alpha]^{25}$D +7.7° (c 5.4, $CHCl_3$); lit.[4e] $[\alpha]^{25}$D +7.5° (c 2.5, $CHCl_3$)].

Acknowledgment. Support from the National Science Council of the Republic of China (NSC 81-0208-M005-18) is gratefully acknowledged.

(21) Assignment of **12c** is based on analogy with the reaction of aldehydes with the lithium enolate derived from **5O**.[5]