for monitoring with the CO probe laser. Thus, its bond dissociation energy could not be directly determined. However, a bond dissociation energy could be estimated for this system based on the fact that though no dissociation was observed on a 500-μs time scale the compound was not stable for the few seconds necessary to obtain its FTIR spectrum. Assuming the same preexponential as measured for the $W(CO)_5(CF_2Cl_2)$ complex, $W(CO)_5(N_2O)$ has a bond dissociation energy of 22 ± 2 kcal/mol.

Clearly this study and others[25] demonstrate that the potential now exists to generate a wide variety of weakly bonded organometallic complexes using laser flash photolysis and to study them by time-resolved infrared spectroscopy. These studies hold promise of providing insights into the nature of solvent interactions with coordinatively unsaturated organometallics and quantitative information on the effects of solvation on the rates and pathways of condensed phase reactions of coordinatively unsaturated reaction centers.

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Acknowledgment. We thank the NSF for support of this work under Grant No. CHE 88-06020. We also thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

Asymmetric Aldol Reactions. A New Camphor-Derived Chiral Auxiliary Giving Highly Stereoselective Aldol Reactions of both Lithium and Titanium(IV) Enolates

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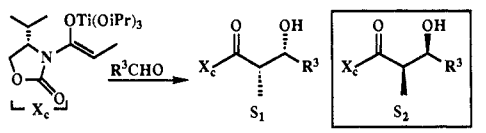
Abstract: A new, conformationally rigid camphor-derived *N*-propionyloxazolidinone effects asymmetric stereochemical control in syn-selective aldol condensations of the derived lithium and titanium(IV) enolates with a variety of aldehydes. Simple and diastereofacial selectivities of the reaction are high, and diastereomeric purities of the crude aldol adducts can be improved, usually by a single recrystallization, to levels of 98–99% in most cases. The observed facial selectivity is best explained by a transition structure in which intramolecular chelation between the oxazolidinone carbonyl oxygen and the metal induces an enolate π-facial differentiation; the major products observed are those expected from *chelation control*. Hydrolysis of the exocyclic carbonyl of the aldol adducts led to β-hydroxy-α-methylcarboxylic acids, with recovery of the chiral auxiliary. Consonant double-asymmetric induction with (*R*)-2-(benzyloxy)propanal gave the product expected from oxazolidinone chelation but nonchelation of the aldehyde benzyloxy group.

Stereoselective aldol reactions employing chiral boron enolates[1-5] and more recently chiral titanium(IV) enolates[6-11] have received significant synthetic and mechanistic attention. The discovery of the valine- and norephedrine-derived chiral *N*-propionyloxazolidinones[2] has led to their use in the synthesis of enantiomerically pure β-hydroxy-α-methylcarboxylic acids and related compounds[9,12] as well as α-amino acids.[13-16] Work in this laboratory has demonstrated that the triisopropoxytitanium enolate of the valine-derived *N*-propionyloxazolidinone (eq 1) reacts with



(1)

benzaldehyde to give the product diastereomer predicted from chelation control (S_2) with a 92% level of selectivity.[6] This sense of diastereofacial selectivity is opposite to that observed for the corresponding di-*n*-butylboron enolates[2] and is consistent with the Lewis acidity of titanium(IV), which permits metal chelation to the oxazolidinone carbonyl.[17] It appears that chelation specifically orients the oxazolidinone ring in the transition structure. This capability is very promising for stereocontrol in synthetically useful reactions.

To capitalize on the expected utility of this chemistry and to further explore the stereochemical control elements of the aldol

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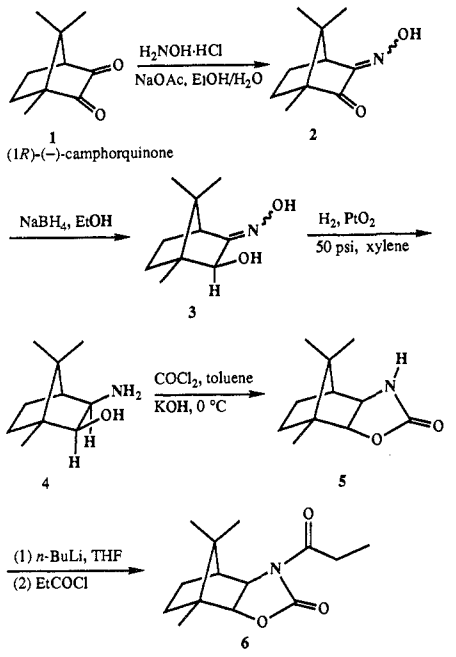
Scheme I



reaction, we sought to design a new chiral system and to compare its stereochemical influence with that of the valine-derived chiral auxiliary. For this purpose, we elected to use the camphor skeleton (readily available as either antipode in enantiomerically pure form) as our chiral source, owing to the ample precedents[18] for chiral bornyl derivatives to induce strong stereocontrol in asymmetric reactions; a camphorsulfonic acid derived boranesultam has recently given highly selective aldol reactions.[19] In this design, the *syn*-7-methyl group would extend the chiral steric influence by one extra carbon compared with the valine-derived auxiliary, and the rigid fused-ring system should locate this methyl group directly over one face of the derived enolate. Our expectations are in fact borne out by our X-ray structure of a crystalline silyl enol ether (cf. Figure 1). We also proposed that the high crystallinity associated with the camphor nucleus might be translated into the aldol products, which would provide a practical means (recrystallization) for improving optical purities of the crude aldol product mixtures. In this paper, we demonstrate the utility of this new camphor-derived chiral auxiliary in lithium- and titanium-mediated aldol reactions.

Results

We have synthesized a new camphor-based chiral auxiliary, shown that it yields crystalline aldol adducts in very high optical purities, and demonstrated that these aldol adducts can be transformed into synthetically useful chiral intermediates. Stereochemical analysis indicates chelation control for *both the lithium and titanium enolates*, on the basis of assuming the expected *Z* enolate, reacting via a chairlike transition structure to give syn product selectively. This mechanism is further supported by an X-ray crystal structure of the product of trapping the enolate, which demonstrates for the first time with an *N*-acyloxazolidinone that the *Z* enolate is indeed formed and provides a model for enolate structural features.[20,21]

Scheme II

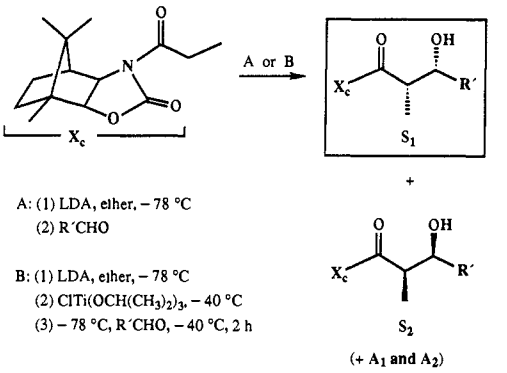


Table I. Aldol Reactions of *N*-Propionyloxazolidinone **6** with Representative Aldehydes

aldehyde	metal[a]	adduct	ratio[b] S_1:S_2:$A_{(1)}$:$A_{(2)}$
PhCHO	Li	**7**	58:2:40:0[d]
	Ti	**7**	79:2:19:0[d]
	Ti	**7**	98:2:0:0[e]
cyclo-C_6H_{11}CHO	Li	**8**	66:4:30:0[d]
	Ti	**8**	84:3:13:0[d]
EtCHO	Li	**9**	92:8:0:0[d]
	Ti	**9**	76:13:11:0[d]
	Ti	**9**	99:1:0:0[e]
t-BuCHO	Li	**10**	98:2:0:0[d]
	Ti	**10**	88:6:6:0[d]
	Ti	**10**	94:6:0:0[e]
$(CH_3)_2$CHCHO	Li	**11**	90:0:10:0[d]
	Ti	**11**	86:2:7:5[d]
	Ti	**11**	99:1:0:0[f]
trans-CH_3CH=CHCHO	Li	**12**	73:3:24:0[d]
	Ti	**12**	49:4:40:7[d]
	Ti	**12**	92:8:0:0[e]
(*R*)-2-(benzyloxy)propanal	Li[c]	**17**	92:7:1:0[d]
	Ti[c]	**17**	70:17:7:6[d]
	Li[c]	**17**	98:1:1:0[g]
(*S*)-2-(benzyloxy)propanal	Li[c]	**18**	42:52:6:0[d]

[a] Li enolate generated at −78 °C in diethyl ether; Ti enolate generated at −40 °C in diethyl ether. [b] Ratios measured by HPLC, except for PhCHO by ^{1}H NMR. Assignments of A_1 vs A_2 are based on analogy with the reaction of PhCHO with the valinol-derived reagent shown in eq 1,[2,6] and so may conceivably be reversed. [c] THF used as solvent. [d] Crude. [e] First recrystallization; yields after recrystallization, not fully optimized, 42–65% overall based on acyloxazolidinone **6**. [f] Second recrystallization. [g] After flash chromatography.

Synthesis of Camphor-Based *N*-Propionyloxazolidinone. Known *exo,exo*-amino alcohol **4**[22-26] (Scheme I) was nicely prepared in three steps from (1*R*)-(−)-camphorquinone (**1**). When camphorquinone was treated with excess hydroxylamine hydrochloride and sodium acetate in ethanol and refluxed for 10 min, monooximation occurred exclusively at C-3 of camphorquinone, affording a 5:1 mixture of anti and syn oximes **2** in 86% yield.[27] Reduction of the carbonyl of **2** with $NaBH_4$ in ethanol gave *exo*-hydroxyoxime **3** in 93% yield. Hydrogenation of **3** using PtO_2 at 3.4 atm produced the desired *exo,exo*-amino alcohol **4** in 85%

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(20) An experiment with the *tert*-butyldimethylsilyl-trapped enolate of the *N*-(α-chloroacetyl)valine-derived oxazolidinone indicated, by the absence of a ^{1}H NOE between the olefinic proton and the silylmethyl groups, a *Z* configuration.[21] However, absence of an NOE cannot be considered (and was not claimed to be) conclusive. Conclusive assignment of *Z* configuration to the silyl-trapped enolate $X_cC(=O)CHMeC(OTMS)=CHMe$, where X_c is a chiral *N*-oxazolidinone group (which is not, however, the enolate of an *N*-acyloxazolidinone), was made through a ^{1}H NMR NOE study.[9]
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yield following purification by sublimation. While previous workers[22,24] used pressures of 100 atm to reduce **3** to **4**, we found that hydrogenation in a Parr bomb at 50 psi was adequate to ensure complete reduction. Although others have reported simultaneous reduction of the carbonyl and oxime functionalities of **2** with $LiAlH_4$ in ether[25,26,28] or hydrogen and PtO_2 at ambient temperature and atmospheric pressure,[28] in our hands these methods failed to give the isomerically pure *exo,exo*-amino alcohol.

Treatment of amino alcohol **4** with a biphasic mixture of phosgene in toluene and solid KOH at 0 °C[29] afforded the tricyclic oxazolidinone **5** in 88% yield after recrystallization. N-Acylation of **5** using *n*-butyllithium and propionyl chloride led to *N*-propionyloxazolidinone **6** in 93% yield.

Aldol Reactions of Camphor-Based *N*-Propionyloxazolidinone. With the desired camphor-based acyloxazolidinone **6** in hand, we were in position to investigate the asymmetric aldol reactions of the corresponding lithium and titanium enolates. The lithium enolate of **6** was generated at −78 °C from LDA in ether (Scheme 11) and then treated with 2 equiv of the given aldehyde. We used ether as the solvent since we had previously shown that diethyl ether enhances the apparent chelation ability of valine-derived titanium enolates.[6] The diastereomer ratios were measured by reversed-phase HPLC or high-field ^1H NMR. The triisopropoxytitanium enolate of **6** was prepared by transmetalation of the lithium enolate in diethyl ether using 3 equiv of (very inexpensive) $ClTi(OCH(CH_3)_2)_3$[30] at −40 °C; the resulting titanium enolate was treated at −78 °C with 2 equiv of aldehyde. Results of the aldol reactions of the lithium and titanium enolates of **6** with representative aldehydes are given in Table I.

The major diastereomer obtained from reactions of both the lithium and titanium enolates of **6** with the various aldehydes listed in Table I is S_1. Note that, because the absolute configuration of the camphorquinone here is opposite to that of L-valine, the same chelation mechanism predicts that it is S_1 which should be favored here (cf. eq 1). X-ray crystal structure determinations were carried out for the adducts obtained with benzaldehyde and propionaldehyde (**7** and **9**, respectively). The ORTEP diagrams[31] show that the absolute stereochemistry of the two newly formed chiral centers is syn (S_1), the stereochemistry predicted by chelation control. Absolute stereochemistries for two other major aldol adducts (**10** and **11**) were assigned as S_1 after conversion to the known β-hydroxy-α-methylcarboxylic acids by correlating the signs of the specific rotations. Adducts **8** and **12** were assigned syn stereochemistry on the basis of the similarities of the 250-MHz ^1H NMR spectra of carboxylic acids **13d** and **13e** derived by hydrolysis to those of the acids **13a–c** of known stereochemistry. In particular, the small $^3J_{H\text{-}2,H\text{-}3}$ values, 3.1 and 4.2 Hz, respectively, are indicative of syn stereochemistry.[32–34] It is not proven that the stereochemistries of **8** and **12** are S_1 and not S_2, but they are assigned as S_1 on the basis of proven S_1 stereochemistry in the four other cases.

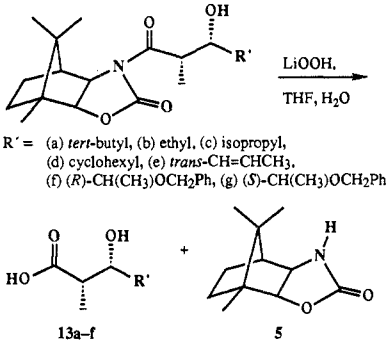
A noteworthy feature of the camphor-derived chiral auxiliary is its crystallinity, a property that was translated into all but two of the aldol adducts. As shown in Table I, the diastereomeric purity of the crude product mixtures can be significantly enhanced (92–99%) upon a single recrystallization, with 42–65% (overall yield based on acyloxazolidinone **6**; not fully optimized) chemical recovery of the S_1 isomer.

Table II. β-Hydroxycarboxylic Acids from LiOOH Hydrolysis of Syn Aldol Adducts

aldol adduct	aldehyde	acid	% yield	ratio[a] syn:anti
10	*t*-BuCHO	**13a**	93	100:0
9	EtCHO	**13b**	57	92:8
11	$(CH_3)_2CHCHO$	**13c**	65	100:0
8	*cyclo*-$C_6H_{11}CHO$	**13d**	72	91:9
12	*trans*-$CH_3CH{=}CHCHO$	**13e**	65	97:3
17	(*R*)-2-(benzyloxy)propanal	**13f**	77	100:0
18	(*S*)-2-(benzyloxy)propanal	**13g**	90	80:20

[a] Upper limits of anti isomer determined by integration of syn:anti ratios in 250-MHz ^1H NMR of carbinol proton regions.

Hydrolysis and Reduction of Adducts. To demonstrate further the synthetic utility of the camphor-derived chiral auxiliary, we have investigated the hydrolyses of syn aldol adducts **8–12** (eq 2). Good yields of the corresponding β-hydroxy-α-methyl-

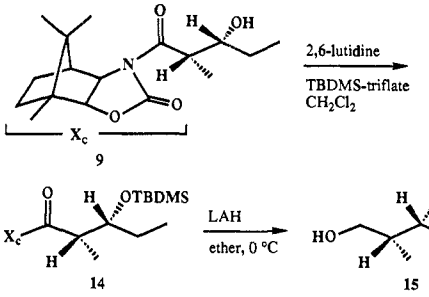


(2)

carboxylic acids were obtained by using the lithium hydroperoxide hydrolysis procedure,[35] and the unacylated oxazolidinone **5** was recovered with complete stereochemical integrity. We never detected any of the side-product which could result from hydrolysis of the endocyclic carbonyl of the oxazolidinone.

Since α-epimerization to give anti diastereomer could conceivably have occurred during hydrolysis of the syn aldol adducts, we wanted to assess the degree of anti isomer contamination. An area of absorption that was characteristic of the anti isomer was measured in the high-field ^1H NMR spectra of the total crude carboxylic acids. For two of the acids (**13a** and **13c**), the δ values for the carbinol proton anti to the α proton have been reported,[36] and the differences for the measured syn isomers and the literature anti isomers ranged between 0.2 and 0.6 ppm. For the other carboxylic acids, small absorptions within this δ range of the carbinol proton regions were integrated to determine an upper limit to the amount of contamination by anti isomer. In most cases, anti adduct was absent or only minor (Table II).

We also investigated hydride reduction of the aldol adduct derived from propionaldehyde (eq 3). Aldol adduct **9** was first



(3)

protected as its TBDMS ether with TBDMS triflate and 2,6-lutidine[37] to afford ether **14** in 75% yield. The crude silylation

(28) Beckett, A. H.; Lan, N. T.; McDonough, G. R. *Tetrahedron* **1969**, *25*, 5689–5692.
(29) Newman, M. S.; Kutner, A. *J. Am. Chem. Soc.* **1951**, *73*, 4199–4204.
(30) An excess of $ClTi(OCH(CH_3)_2)_3$ (3 molar equiv) was used since it had been previously demonstrated that the stereoselectivities of Ti-mediated aldol reactions could be dramatically improved by addition of an excess of the titanium reagent.[6–8] It was proposed that the lower selectivity observed with 1 equiv of $ClTi(OCH(CH_3)_2)_3$ might arise from interference by a lithium titanium ate enolate complex $[Li^+C{=}COTi^-Cl(OCH(CH_3)_2)_3]$.
(31) X-ray crystal structure data for compounds **7**, **9**, **18**, **19**, and **21** are available as supplementary material.
(32) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, FL, 1984; Vol. 3, pp 111–212.
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(34) Heathcock, C. H. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon Press: Oxford, 1983; pp 27–43.
(35) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144.
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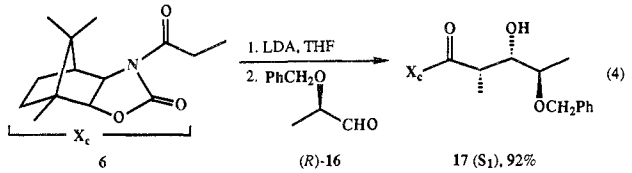
(37) Webber, S. E. Ph.D. Dissertation in Chemistry, University of Pennsylvania, Philadelphia, PA, 1986.

product was then reduced with LAH in ether, affording a mixture of hydroxy ether **15** and unacylated oxazolidinone **5**. The mixture was readily separated by flash chromatography, with **15** eluting first, followed by the more polar amide. Monoprotected diol **15** was obtained in crystalline form.

Double-Asymmetric Induction. Chelation of the ether oxygen of α-alkoxy aldehydes has been proposed for certain aldol reactions on stereochemical grounds.[17] In view of the preference for chelation products (S_1) we have observed here for **6** with achiral aldehydes (Table I), a key issue is whether these two chelation effects will behave consonantly or competitively. Consequently, we have examined double-asymmetric induction[4,38] in reactions of acyloxazolidinone **6** with (*R*)- and (*S*)-2-(benzyloxy)propanal[39] (eqs 4 and 5). Chelation of the benzyloxy oxygen could affect the S_1:S_2 diastereofacial preference or even reverse the simple stereoselection from syn to anti.



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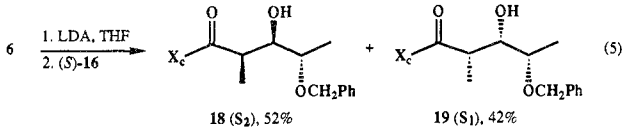


(5)

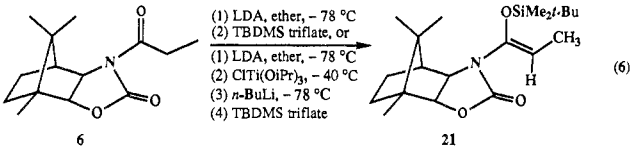
Reaction of the lithium enolate of **6** with (*R*)-2-(benzyloxy)-propanal afforded a 92:7:1 mixture of products, and the major diastereomer obtained (**17**, eq 4) was identified as S_1,[40] the product predicted from chelation of the oxazolidinone and nonchelation of the aldehyde. Because of double-asymmetric induction,[4,38] either the *R* or the *S* aldehyde will provide larger diastereofacial selectivity, acting in concert with the preferred facial selectivity of the enolate, whereas the enantiomeric aldehyde will provide lower diastereofacial selectivity, acting in opposition to the preferred facial selectivity of the enolate. Here, the reaction of oxazolidinone **6** with (*R*)-2-(benzyloxy)propanal (eq 4) gives the higher selectivity, the preferred facial selectivity of the enolate (chelation control) being reinforced by the preferred selectivity of the aldehyde (nonchelation control) and leading to predominant formation of **17**.

The titanium-mediated aldol reaction of oxazolidinone **6** with (*R*)-2-(benzyloxy)propanal was also investigated. The major product was also **17**, the adduct predicted from chelation of the oxazolidinone and nonchelation of the aldehyde. Both the simple and facial selectivities for the reaction (70:17:7:6) were lower than those observed for the lithium-mediated reaction (92:7:1:0). This tendency for the lithium enolate of **6** to exhibit higher selectivities than the corresponding titanium enolate was also observed in reactions with some achiral aldehydes (Table I).

The lithium-mediated reaction of acyloxazolidinone **6** with (*S*)-2-(benzyloxy)propanal (eq 5) exhibits opposing aldehyde and enolate selectivities, leading to a 52:42:6 mixture of products. The absolute stereochemistries of both major diastereomers obtained in the reaction (**18** and **19**, eq 5) were determined by X-ray structure analysis. We also prepared the acetate of **18** (**20**) to distinguish the C-3 and C-4 methine protons in **18**. The ^{1}H NMR spectrum of **20** showed the expected downfield shift of the C-3 proton relative to **18**. The X-ray structures also show that the alkoxy carbon stereocenter of **16** is retained as *S* during the aldol reaction, i.e., that neither adduct resulted from racemization of the chiral aldehyde under the basic conditions prior to aldol reaction.

Diastereomer **18** is the product predicted from nonchelation of the oxazolidinone and nonchelation of the aldehyde, while **19** is predicted to arise from chelation of the oxazolidinone and chelation of the aldehyde. In both reactions (eqs 4 and 5), syn diastereomers were obtained almost exclusively; even the product corresponding to aldehyde chelation was syn and not anti. These results are mechanistically significant (see Discussion).

Enolate Geometry. It has been demonstrated that the degree of simple diastereoselectivity attained in the aldol reaction is a function of enolate geometry.[41,42] Although aldol reactions of *N*-acyloxazolidinones have given stereoselectivities consistent with intermediate formation of *Z* enolates, in no case has the configuration actually been determined.[20] To determine the geometric purity of the lithium and titanium enolates of our *N*-acyloxazolidinone, we trapped them as the silyl enol ether **21** (eq 6),



(6)

hoping to capitalize upon the crystallinity associated with the camphor nucleus. Treatment of the lithium enolate of **6** with *tert*-butyldimethylsilyl triflate led to the solid silyl enol ether **21** in 84% yield. The 250-MHz ^{1}H NMR spectrum of the crude silyl enol ether revealed a single quartet at δ 4.60 (J = 6.90 Hz) for the vinyl hydrogen and a single doublet at δ 1.48 (J = 6.90 Hz) for the vinyl methyl group, thus confirming the isomeric purity of the enolate. Flash chromatography afforded crystals suitable for X-ray analysis. The ORTEP diagram (Figure 1) confirms the *Z* geometry of the enolate double bond, rigorously establishing the correlation of simple stereoselectivity and acyloxazolidinone enolate geometry. We also examined the question of planarity of the oxazolidinone ring, since nonplanarity could conceivably explain the significant amounts of anti diastereomer found in certain cases, even with Ti, which has ligands that should improve upon Li. However, the ring was found to be entirely planar.

All attempts to trap directly the titanium enolate of **6**, prepared by transmetalation of the lithium enolate with $ClTi(OCH(CH_3)_2)_3$, as the silyl enol ether using *tert*-butyldimethylsilyl triflate were unsuccessful. Therefore, the titanium enolate of **6** was treated with excess *n*-butyllithium at −78 °C and then with *tert*-butyldimethylsilyl triflate just as was done for the lithium enolate. The ^{1}H NMR spectrum of the crude product obtained from this experiment revealed the same single quartet for the vinyl hydrogen of **21** at δ 4.60 (J = 6.90 Hz) as that observed for the silyl enol ether prepared from the lithium enolate. The reaction was still incomplete under these conditions, and starting material was also present in the crude product mixture. However, the homogeneity indicated by the ^{1}H NMR spectrum in the vinyl methyl region constitutes very strong evidence in support of isomerically pure *Z* silyl enol ether identical with **21**, and thus of an isomerically pure *Z* titanium enolate. The alternatives, that *Z* lithium enolate isomerized in some part to *E* titanium enolate but then isomerized back to essentially only *Z* lithium enolate before trapping or that only *Z*, but not *E*, titanium enolate reacted with *n*-butyllithium, are highly unlikely.

Discussion

We have synthesized a new, conformationally rigid, chiral oxazolidinone, **6**, from (*R*)-(−)-camphorquinone. *Both the lithium-*

(38) Reference 32, p 191.
(39) Both enantiomers can be prepared by the method of Heathcock: Takai, K.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 3247–3251.
(40) The absolute configuration for **17** was assigned by comparison of the corresponding β-hydroxy acid (**13f**) to the acid obtained from the hydrolysis of adduct **18** (**13g**). Since the absolute configuration of adduct **18** was confirmed through X-ray analysis, the enantiomeric relationship of acids **13f** and **13g** (established by the fact that their ^{1}H NMR spectra were identical) provided a rigorous assignment of absolute configuration for **17**. [**13f** and **13g** cannot be identical, since (a) they are formed from aldehydes (*R*)-**16** and (*S*)-**16** of opposite configurations and (b), in any case, their identity requires that **17** and **18** also be identical, which they are not.]
(41) Dubois, J. E.; Fellman, P. *Tetrahedron Lett.* **1975**, *16*, 1225–1228.
(42) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066–1081.

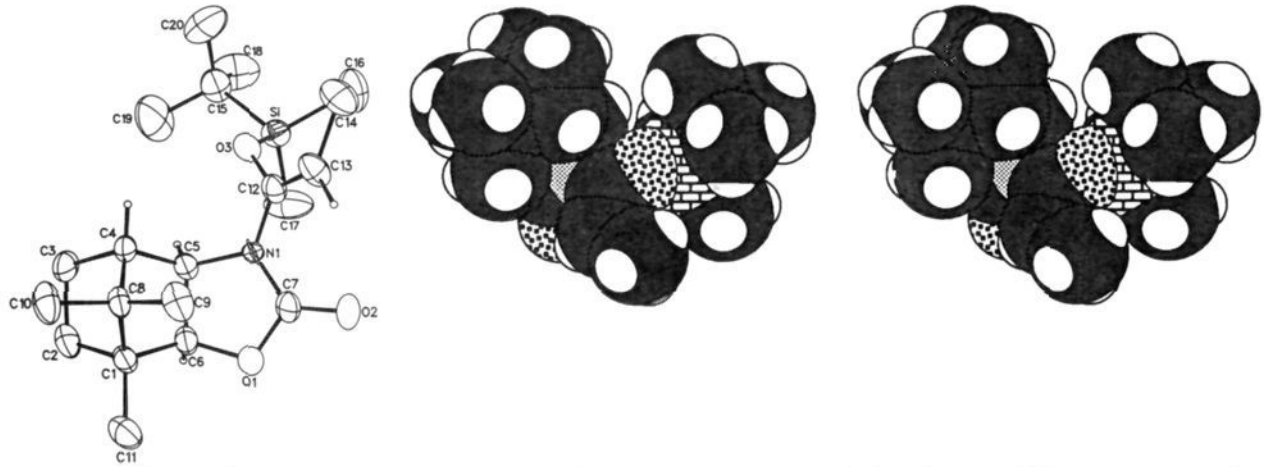


Figure 1. ORTEP drawing of enolate trapped as silyl enol ether **21**, demonstrating *Z* geometry. Also shown is a space-filling stereo representation *of this X-ray structure*, oriented so as to show the proximity of the *syn*-7-methyl group to the outer face of the *Z*-enolate β-carbon. (Small squares = carbon; white = hydrogen; large squares = oxygen; dots = nitrogen; bricks = silicon.)

and titanium-mediated aldol reactions of this system with representative aldehydes proceeded with high simple and facial diastereoselectivities, yielding a syn diastereomer as the major product. The absolute stereochemistry of the major diastereomer obtained in reactions with achiral aldehydes was confirmed as S_1, the product predicted from chelation control, by X-ray structure analysis of two representative aldol adducts. This provided a rigorous proof of stereochemistry for aldol adducts **7** and **9**, since the stereochemistry of the camphor nucleus was already known. Hydrolysis to known β-hydroxy-α-methylcarboxylic acids provided rigorous proof for two additional aldehydes.

Mechanistic Implications. The observed simple and facial stereoselectivities for these aldol reactions (Table I) can be explained by the chelated chair transition structure A (Figure 2). In transition structure A, the enolate and the reacting aldehyde are coordinated in a chair conformation, with R^3 equatorial, the widely accepted Zimmerman–Traxler[43] model for correlating metal enolate geometry and the relative stereochemistry of aldol adducts. Current theoretical[44-46] and experimental[47] studies support this model for *Z* enolates and strongly coordinating metals. Our X-ray and ^{1}H NMR data for the trapped enolate (**21**) and for aldol adducts **7**–**12** confirm the expected *Z* geometry of the enolate and the syn relative configuration of the methine and carbinol carbons of each major aldol diastereomer.

Although it has been purported that the observed syn diastereoselectivities observed in aldol reactions of acyloxazolidinones originate from *Z* enolates, it had not been rigorously established that metal enolates of these imides exist in the *Z* configuration. The enolate configuration of our camphor-derived oxazolidinone enolate was of particular interest because of the unexpected fact that lithium gave very high diastereofacial selectivities, higher than titanium, with several aldehydes. As Figure 2 shows, the chair model predicts syn product from a *Z* enolate (conversely, *E* enolates should favor anti products). The X-ray data for the silyl-trapped enolate **21** (Figure 1) confirm the *Z* geometry of the enol ether moiety and thus the *Z* geometry of the metal enolates. The *Z* geometry in turn indicates that the source of our observed stereoselectivities must be sought in chairlike transition structures.

This X-ray structure is necessarily of a nonchelated conformation, but it illustrates concretely how the conformationally rigid camphor nucleus provides a highly chiral steric environment, which

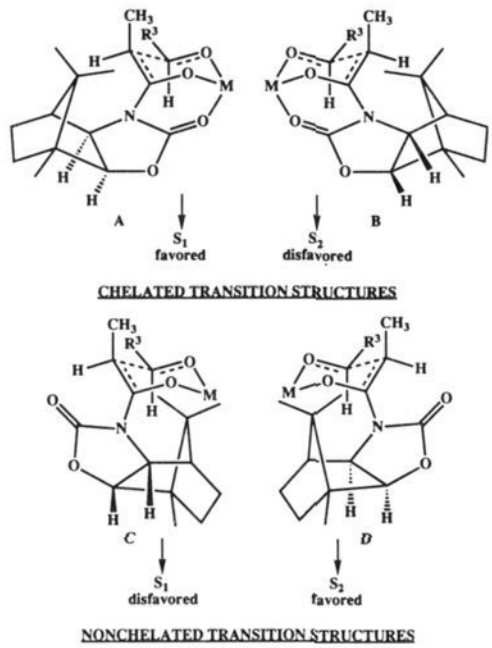


Figure 2. Chelated and nonchelated transition structures for aldol reactions of *Z*-titanium enolate of camphor-based *N*-propionyloxazolidinone.

would be sensed by a chelated conformation as well. Consideration of the trajectory of approach of the aldehyde to the enolate emphasizes the difficulty of attack on the hindered face. According to arguments derived for the aldehyde, the preferred angle of C–C bond formation will be tipped away from the R group and toward the H of RCHO.[48] Similarly, the preferred angle *at the enolate carbon* should be tipped away from the *Z*-methyl group and toward the H. As can be seen in Figure 1, *such a tip moves the aldehyde directly toward the syn-7-methyl group of the camphor unit* (cf. Figure 2C). Likewise, in the chelated conformation, the tipping of the aldehyde away from the *Z*-methyl group would move it directly toward the camphor nucleus (Figure 2B).

Consequently, we believe that the camphor-derived chiral auxiliary constitutes a structurally organized unit with an extremely well defined facial bias. Extra stabilization and rigidity can be derived from chelation between the metal (Li or Ti) and the oxazolidinone carbonyl oxygen in the form of a six-membered ring. This metal–oxygen chelation is proposed to be the source

(43) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.
(44) Li, Y.; Paddon-Row, M. N.; Houk, K. N. *J. Org. Chem.* **1990**, *55*, 481–493.
(45) Leung-Toung, R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1990**, *112*, 1042–1048.
(46) Bernardi, A.; Capelli, A. M.; Gennari, C.; Goodman, J. M.; Paterson, I. *J. Org. Chem.* **1990**, *55*, 3576–3581.
(47) Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1989**, *111*, 8032–8034.
(48) Nguyên, Trong, Anh; Bui Tho Thanh. *Nouv. J. Chim.* **1986**, *10*, 681–683.

of the enolate π-facial differentiation. As depicted in chelated transition structure A (Figure 2), the *syn*-7-methyl group of the camphor substructure is rigidly directed toward the proximal face of the enolate π-bond, so the aldehyde attacks the distal face to give the S_1 diastereomer. The diastereomeric chelated transition structure that would lead to S_2 (Figure 2B) would be destabilized relative to A, since here the aldehyde is attacking the same (distal) enolate π face which is so highly congested by the rigid directionality of the *syn*-7-methyl group.

Conversely, nonchelated transition structures with the oxazolidinone ring rotated 180° (C and D, Figure 2), which have been postulated to explain the observed stereochemistry with boron enolates (nonchelating metal) of other oxazolidinones,[2] reverse the congestion encountered and are not capable of explaining the stereoselectivities observed here with lithium and titanium. Chelation of the metal (Li or Ti) with the carbonyl of the oxazolidinone would thus reverse enolate π facial differentiation as compared with boron. The observed reversal constitutes strong evidence that chelation is involved in the present reactions of both the lithium and titanium enolates.

Double-Asymmetric Induction. The product stereochemistry *expected* from chelation (or nonchelation) corresponds to attack at the *less hindered face* of the aldehyde or enolate conformation characteristic of chelation (or nonchelation). Our experimentally observed stereochemistries can thus be classified as those expected from chelation or nonchelation, first, at the enolate oxazolidinone carbonyl and, second, at the aldehyde benzyloxy oxygen.

We observed double stereodifferentiation in the lithium-mediated reaction of **6** with (*R*)-2-(benzyloxy)propanal, providing a 92:7:1 mixture of products. The major diastereomer obtained (**17**) has the stereochemistry expected from chelation of the oxazolidinone but nonchelation of the aldehyde (Figure 3A). The selectivities of the substrate and the aldehyde reagent are acting in concert, and high diastereofacial selectivity is observed.

Almost no selectivity is observed, however, in the Li-mediated reaction of **6** with the enantiomeric aldehyde, (*S*)-2-(benzyloxy)propanal, which gave only a 1.3:1 diastereomeric mixture, where the major product is that expected from nonchelation of both the aldehyde and the oxazolidinone, the minor one, from chelation of both the aldehyde and the oxazolidinone. The low selectivity here, compared with the high selectivity for (*R*)-2-(benzyloxy)propanal above, shows that, while the enolate prefers chelation, the aldehyde prefers nonchelation. This result is in turn nicely consistent with our recent measurements of relative reactivities of α-alkoxy ketones, which show directly that chelation is not the source of their high reactivities in aldol reactions with a lithium enolate.[49]

In Figure 3, the nonchelation conformation of the aldehyde is drawn as in the Cornforth dipolar model[49,50] (OCH_2Ph group antiperiplanar to the aldehyde C=O), but a Felkin–Anh conformation[48,51] (OCH_2Ph group perpendicular to the aldehyde O=CHC plane) predicts that the same face would be less hindered, too.

To obtain **18** or **19** through a chairlike nonchelation aldehyde/chelation oxazolidinone transition structure requires attack on the hindered face of the enolate or aldehyde, respectively. Consequently, the *only* chairlike transition structures that give syn product stereochemistry and still correspond to attack on the less hindered faces of both the aldehyde and enolate are B (nonchelation aldehyde/nonchelation oxazolidinone), leading to **18**, and C (chelation aldehyde/chelation oxazolidinone), leading to **19**. However, both B and C require that the preference, as shown by the favored stereochemistry (A), of either the aldehyde or the enolate be forsaken. Maintaining reaction at the less hindered face of both the aldehyde and enolate can otherwise only be achieved in a transition structure analogous to D having the aldehyde chain in the hindered, axial position—which would,

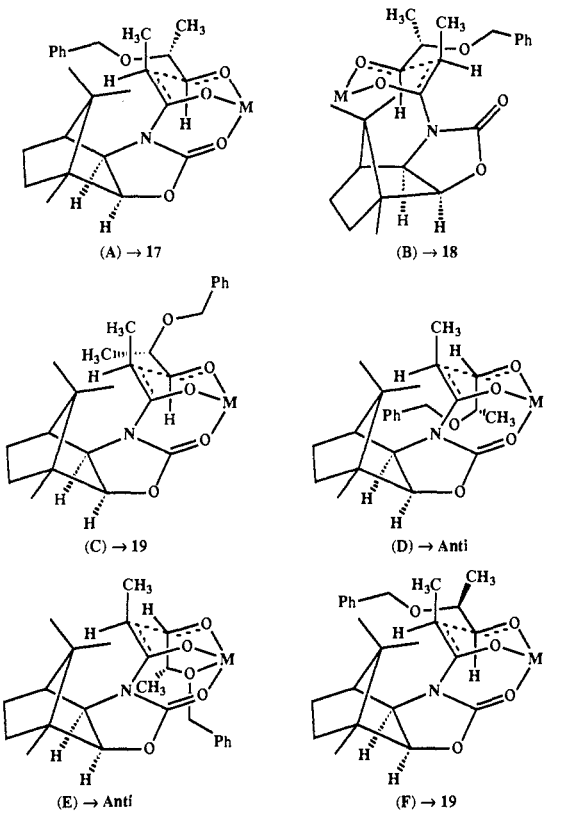


Figure 3. Possible transition structures for double-asymmetric induction in aldol reactions of camphor-derived *N*-propionyloxazolidinone enolates with (*R*)- and (*S*)-2-(benzyloxy)propanal. (A) Reaction of *R* aldehyde (major product): nonchelation aldehyde/chelation oxazolidinone. (**B**) Reaction of *S* aldehyde (major product); nonchelation aldehyde/nonchelation oxazolidinone. (C) Reaction of *S* aldehyde (minor product): chelation aldehyde/chelation oxazolidinone (favorable chair, but no chelation of aldehyde ether oxygen with metal actually possible). (D) Reaction of *S* aldehyde: nonchelation aldehyde/chelation oxazolidinone, but leading to anti, not syn, product. (E) Reaction of *R* aldehyde: chelation aldehyde/chelation oxazolidinone, *with* aldehyde ether oxygen chelated to metal, but leading to anti, not syn, product. (F) Reaction of *S* aldehyde (minor product): *conformations* as in (A) (nonchelation aldehyde/chelation oxazolidinone), but giving the same product as (C), via attack of enolate on *more hindered* face of aldehyde.

however, give an anti adduct stereochemistry, not syn as observed. The experimental preference for **18** over **19** indicates that transition structure B (Figure 3) is preferred over C and thus provides evidence that the free energy preference for the nonchelation conformation of the aldehyde[49] outweighs that for chelation of the enolate!

Alkoxy chelation to the metal requires that the alkoxy-bearing aldehyde chain be axial, as shown in Figure 3E, but anti adduct stereochemistry would result. Both the *R* and *S* aldehydes give almost exclusively syn, not anti, products, showing that the alkoxy-bearing chain prefers not to be oriented axially in spite of the possibility for chelation. On the other hand, the chelation aldehyde/chelation oxazolidinone transition structure providing the syn adduct (Figure 3C), though by definition having the aldehyde in a conformation *appropriate for chelation*, actually places the alkoxy oxygen so far from the metal that it is incapable of any actual chelation interaction. Though this lithium enolate is quite hindered, it may be aggregated,[52] and, if so, the aldehyde in a transition structure such as that in Figure 3C could be chelated to a second lithium within the aggregate. It is also possible that **19** arises from a transition structure as in Figure 3F, which involves attack at the *more hindered* face of the aldehyde when it is in a Cornforth-like (nonchelation) conformation to give the same product (**19**) expected from attack on the *less hindered* face of the aldehyde when it is in its chelation conformation (as in Figure

(49) Das, G.; Thornton, E. R. *J. Am. Chem. Soc.* **1990**, *112*, 5360–5362.
(50) Cornforth, J. W.; Cornforth, R. H.; Mathew, K. K. *J. Chem. Soc.* **1959**, 112–127.
(51) Nguyên, Trong Anh. *Top. Curr. Chem.* **1980**, *88*, 145–162.
(52) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624–1654.

Table III. X-ray Crystal Data[a]

compd	7	9	18	19	21
formula	$C_{21}H_{27}NO_4 \cdot {}^1/_2H_2O$	$C_{17}H_{27}NO_4$	$C_{24}H_{33}NO_5$	$C_{24}H_{33}NO_5 \cdot H_2O$	$C_{20}H_{35}NO_3Si$
formula wt	366.46	309.49	415.24	433.55	365.59
cryst class	monoclinic	orthorhombic	orthorhombic	monoclinic	orthorhombic
space gp	$P2_1$	$P2_12_12_1$	$P2_12_12_1$	$P2_1$	$P2_12_12_1$
cell constants	$Z = 4$	$Z = 4$	$Z = 8$	$Z = 2$	$Z = 4$
a, Å	11.224(3)	6.958(2)	10.664(2)	12.826(3)	8.835(2)
b, Å	6.909(1)	10.762(3)	10.961(2)	7.055(1)	11.691(2)
c, Å	25.035(2)	22.713(3)	39.332(5)	13.056(1)	21.291(5)
β, deg	96.58(1)			97.58(1)	
μ, cm^{-1}	6.65	6.55	6.4	6.8	1.18
D(calc), g/cm^3	1.262	1.208	1.198	1.230	1.104
θ range, deg	2–65	2–65	2–65	2–65	2–25
no. of reflns measd	7569	1714	4437	2285	4358
no. of reflns used in refinement	3351 ($I > 3\sigma$)	1190 ($I > 3\sigma$)	3301 ($I > 3\sigma$)	2006 ($I > 3\sigma$)	1409 ($I > 3\sigma$)
R	0.048	0.051	0.059	0.049	0.050
R_w	0.064	0.062	0.095	0.072	0.068
S		1.78		1.90	

[a] The reflections were measured with an automatic four-circle diffractometer equipped with Cu Kα radiation (1.541 84 Å). The structure was solved with a multisolution tangent formular approach and difference Fourier analysis and refined by using full-matrix least-squares techniques.

3C). A boatlike transition structure that could permit chelation of both the aldehyde and the oxazolidinone is also a possibility. *Nonetheless, these double-asymmetric induction results demonstrate that the aldehyde consistently prefers a nonchelated conformation.*

Synthetic Utility. Hydrolytic and reductive removal and recovery of the chiral auxiliary, with the production of carboxylic acids and primary alcohols, produces useful chiral intermediates. Single recrystallizations of the crude aldol adducts usually lead to nearly optically pure samples. Since the (*S*)-camphor-derived acyloxazolidinone would necessarily proceed by the same mechanism, the chelated chair transition structure would readily provide the S_2 aldol adducts.

Conclusions

We have shown that both the lithium- and titanium-mediated aldol reactions of *N*-acyloxazolidinone **6** with representative aldehydes occur with high diastereofacial selectivities. All of the aldol adducts studied were crystalline, except **8**[53] and **17**, and a single recrystallization of the crude product mixtures usually afforded products of high enantiomeric purity (92–99% S_1). Stereochemical analysis of aldol adducts, including X-ray crystal structures of four, revealed that the stereochemistry is S_1, indicating chelation control, in all cases except that involving opposed double-asymmetric induction to give **18**. This possibility of enriching optical purities up to such high levels without the need for sample derivatization or chromatography enhances the usefulness of **6** in large-scale applications.

Hydrolysis of the exocyclic imide bond of the aldol adducts afforded the corresponding β-hydroxy-α-methylcarboxylic acids, and the chiral auxiliary could be recovered and recycled.

Experimental Section

Materials and Methods. Reagents and solvents were dried and/or purified before use.[54] Diisopropylamine was distilled from CaH_2. THF and diethyl ether were distilled from sodium benzophenone ketyl immediately prior to use. $ClTi(OCHMe_2)_3$ was distilled under reduced pressure. Benzaldehyde was dried with anhydrous Na_2CO_3, filtered and distilled under reduced pressure from zinc dust. Propionaldehyde, isobutyraldehyde, and pivalaldehyde were dried with $CaSO_4$, filtered, and distilled immediately prior to use. All reactions and distillations were conducted under argon; glassware was oven-dried (160 °C) and then flame-dried under a stream of argon.

Solvent systems are described as volume:volume ratios before mixing. Baker or Whatman silica gel (40 μm average particle size) was used for flash chromatography. Baker glass-backed TLC plates (with fluorescence) were used for analysis of reactions and fractions.

Melting points were determined on a Thomas–Hoover melting point apparatus and are reported uncorrected. Infrared spectra were calibrated with the 1601 cm^{-1} resonance of polystyrene. Abbreviations accompanying IR frequencies are defined as follows: br, broad; s, strong. All NMR spectra are reported in parts per million on the δ scale relative to internal tetramethylsilane for proton and carbon NMR. NMR data are presented in the following manner: chemical shift (δ) [multiplicity (abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak), coupling constant in hertz, integration, and assignment].

High-resolution mass spectra (CI, chemical ionization, using NH_3 as CI gas) were obtained from the University of Pennsylvania Mass Spectrometry Facility of the Chemistry Department. Single-crystal X-ray structure determination (Table III) was performed by Dr. P. Carroll of the University of Pennsylvania X-ray Crystallography Facility of the Chemistry Department with an Enraf-Nonius CAD-4 automatic diffractometer.

Eluent compositions for flash chromatography[55] follow each column description. Fractions were analyzed by TLC with visualization by either fluorescence or staining with 2.3% ethanolic phosphomolybdic acid or 1.5% ethanolic/acidic *p*-anisaldehyde.

Rotary evaporation refers to removal of volatile components, including solvent, under water aspirator pressure on a Büchi rotavapor evaporator at ≤30 °C.

(1*R*,4*S*)-3-(Hydroxyimino)-2-oxo-1,7,7-trimethylbicyclo[2.2.1]heptane (2). To a solution of hydroxylamine hydrochloride (1.2 g, 16.6 mmol) and sodium acetate (2.1 g, 26.1 mmol) in water (8 mL) was added (1*R*,4*S*)-(−)-camphorquinone (980 mg, 5.9 mmol) in absolute ethanol (16 mL). The solution was refluxed gently for 10 min, after which time analysis by TLC indicated the complete disappearance of starting material. The solution was cooled, ethanol was removed by rotary evaporation, and water (5 mL) was added to the remaining aqueous slurry. The slurry was cooled (ice bath), and the solid that precipitated was collected in a sintered glass funnel with vacuum filtration. The solid was dried under high vacuum for 2 h to yield an off-white solid, **2** (930 mg, 86%), which was used without further purification. An analytical sample was recrystallized from hexane–ethanol to give an off-white solid, **2**: mp 142–143 °C; $[\alpha]^{24}_D$ +178° (*c* 3.5, CH_2Cl_2);[56] IR ($CHCl_3$) 3540, 3275 (br), 2950, 2820, 1730 (s), 1690 (s), 1640, 1590, 1440, 1380, 1090, 1060, 990 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3/D_2O$) δ 3.23 and 2.72 [2d, J = 4.4 and 4.1, 0.83 H and 0.17 H, respectively, C*H*C=NOD of anti and syn (anti/syn assignments not certain) oximes], 2.18–1.50 (m, 4 H, C-5 and C-6 *H*), 1.04, 1.02, 1.00, 0.93, 0.88 (5s, C-1 and C-7 CH_3 of anti and syn oximes); ^{13}C NMR (125.8 MHz, $CDCl_3$) mixture of anti and syn oximes, δ (major isomer) 204.5 (*C*=O), 159.4 (*C*=N), 58.4, 46.5, 44.8, 30.6, 23.7, 20.6, 17.5, 8.8 (C-1 and C-4–C-10 *C*); (minor isomer) 204.5, 156.1, 59.5, 49.5, 46.4, 29.8, 24.9, 20.5, 17.9, 8.4. Anti/syn

(53) The aldol reaction of acyloxazolidinone **6** with cyclohexanecarboxaldehyde always afforded an oil as the crude product mixture, which did not solidify even upon trituration with hexane.

(54) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon: Oxford, 1980.

(55) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

(56) The optical rotation of **2**, +178° (*c* 3.5, CH_2Cl_2), was nearly identical with the value reported by Liu,[24] +179° (*c* 0.22, $CHCl_3$). A higher specific rotation value, +231° (*c* 1.0, CH_2Cl_2), was measured for the material prepared according to the procedure of Forster and Rao.[27] This product existed as a 3:2 mixture of anti and syn oximes, and the product obtained by the monooximation of camphorquinone existed as a 1:5 mixture of anti and syn oximes (anti/syn assignments not certain).

assignment is indirect and based on that for the reduction product **3**, by assuming that the major isomer of both **2** and **3** has the same configuration. Cl MS: *m/e* 182.1199 $(M + H)^+$. Calcd for $C_{10}H_{16}NO_2$: *m/e* 182.1181.

(1*R*,2*S*,4*S*)-2-*exo*-Hydroxy-3-(hydroxyimino)-1,7,7-trimethylbicyclo[2.2.1]heptane (3). The hydroxyoxime was prepared by a previous procedure.[22] To the α-oximoketone **2** (12.9 g, 71 mmol) in absolute ethanol (80 mL) was added solid $NaBH_4$ (1.55 g, 41 mmol), portionwise over 10 min at 0 °C (ice bath). After stirring at 0 °C for 1 h, the reaction mixture was stirred at ca. 25 °C for 20 h. The reaction mixture was cooled to 0 °C, and solid $NaBH_4$ (1.55 g, 41 mmol) was added portionwise over 10 min. The mixture was stirred at ca. 25 °C for 15 h. The ethanol was removed by rotary evaporation, and water (200 mL) was added to the remaining solid. The aqueous slurry was acidified carefully to pH 4 with 6 N H_2SO_4 at 0 °C. The aqueous solution was extracted three times with ether (150 mL). The ether layers were washed twice with saturated, aqueous sodium bicarbonate (150 mL) and once with saturated, aqueous NaCl (150 mL). The organic layer was dried with $MgSO_4$, vacuum filtered, and concentrated by rotary evaporation to yield an off-white solid, **3** (12.1 g, 93%): mp 116–118 °C, which was used without further purification; $[\alpha]^{24}_D$ +64° (*c* 0.90, CH_2Cl_2); IR ($CHCl_3$) 3545, 3245, 2925, 2855, 1460, 1445, 1380, 1365, 1340, 1270, 1070 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.28 and 3.94 [2s, 0.8 H and 0.2 H, respectively, C*H*OH of anti and syn (anti/syn assignments not certain) oximes], 3.51 (br, 1 H, C=NO*H*), 3.05 and 2.33 (2d, *J* = 4.3 and 4.4, 0.8 H and 0.2 H, respectively, CH_2CHC=NOH of anti and syn oximes), 1.94–1.05 (m, 5 H, C-5 and C-6 *H* and O*H*), 1.09 and 1.06 (2s, 3 H, C-1 CH_3 of anti and syn oximes), 0.99 and 0.88 (2s, 6 H, C-7 CH_3); ^{13}C NMR (125.8 MHz, $CDCl_3$) mixture of anti and syn oximes, δ (major isomer) 170.4 (*C*=N), 77.6 (*C*HOH), 49.5, 47.7, 47.0, 33.7, 22.9, 21.3, 19.0, 10.8 (C-1 and C-4–C-10 *C*); (minor isomer) 170.0, 76.7, 50.8, 49.6, 48.1, 33.5, 24.1, 21.0, 19.3, 10.3. Anti/syn assignment for **3**, and by implication for **2**, is based on the closeness of our mp (116–118 °C) to that reported for the anti isomer (114 °C).[27] CI MS: *m/e* 184.1319 $(M + H)^+$. Calcd for $C_{10}H_{18}NO_2$: *m/e* 184.1337.

(1*R*,2*S*,3*R*,4*S*)-3-*exo*-Amino-2-*exo*-hydroxy-1,7,7-trimethylbicyclo[2.2.1]heptane (4). To hydroxyoxime **3** (11.7 g, 64 mmol) in xylene (80 mL) was added crystalline PtO_2 (1.0 g, 4.41 mmol). The mixture was stirred for 9 h under 3.4 atm of H_2 pressure at ca. 25 °C. The reaction mixture was filtered through a sintered glass funnel, and PtO_2 was recycled. Xylene was removed by evaporation (H_2O aspirator) while heating to 50 °C. The residue was purified by sublimation at 100 °C (0.1 mmHg) to yield a flaky white solid, **4** (9.21 g, 85%): mp 190–194 °C (lit.[22] mp 198–200 °C); $[\alpha]^{22}_D$ −1.3° (*c* 1.43, MeOH); IR ($CHCl_3$) 3510, 3245, 2960, 2925, 2900, 2860, 1490, 1470, 1400, 1380, 1210 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3/D_2O$) δ 3.35 (d, *J* = 7.4, 1 H C*H*OD), 3.06 (d, *J* = 7.4, 1 H, C*H*ND_2), 1.8–1.1 (m, 4 H, C-5, and C-6 *H*), 1.56 (d, *J* = 4.5, 1 H, C-4 *H*), 1.06 (s, 3 H, C-1 CH_3), 0.95 and 0.79 (2s, 6 H, C-7 CH_3). Cl MS: *m/e* 170.1558 $(M + H)^+$. Calcd for $C_{10}H_{20}NO$: *m/e* 170.1545.

(1*R*,2*S*,6*R*,7*S*)-1,10,10-Trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0^{2,6}]decane (5). The oxazolidinone **5** was prepared by a modification of a literature procedure[29] for an analogous oxazolidinone. To amino alcohol **4** (6.0 g, 35.4 mmol) in toluene (50 mL) was added (dropwise, via cannula and addition funnel) a 20% solution of phosgene in toluene (36.0 mL, 70.9 mmol) at 0 °C (ice bath) over 30 min. The reaction mixture was stirred at 0 °C for an additional 40 min. The unreacted phosgene was removed under vacuum (H_2O aspirator) and collected in a trap at −78 °C. [The collected phosgene was later treated with 10% NaOH (200 mL) and allowed to hydrolyze slowly before disposal.] The remaining solution was diluted with ethyl acetate (300 mL) and extracted with water (50 mL). The aqueous layer was extracted twice more with ethyl acetate (150 mL), and the combined organic layers were dried with $MgSO_4$, vacuum filtered, and concentrated by rotary evaporation to yield a pale yellow solid, **5** (6.7 g, 97%). Recrystallization from hexane–ether yielded **5** (6.1 g, 88%) as an off-white solid: mp 138–140 °C; $[\alpha]^{22}_D$ −33° (*c* 0.625, CH_2Cl_2); IR ($CHCl_3$) 3450, 3250 (br), 2950, 2880, 1760, 1500, 1480, 1435, 1415, 1390, 1380, 1225, 1120, 1080 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.96 (br, 1 H, N*H*), 4.39 and 3.77 (2d, *J* = 8.1, 8.1, 2 H, C*H*N, C*H*O), 1.86 (d, *J* = 4.5, 1 H, C-7 *H*), 1.9–1.4 (m, 4 H, C-8 and C-9 *H*), 1.11 (s, 3 H, C-1 CH_3), 1.04 and 0.91 (2s, 6 H, C-10 CH_3). Cl MS: *m/e* 196.1380 $(M + H)^+$. Calcd for $C_{11}H_{18}NO_2$: *m/e* 196.1337.

***N*-Propionyl-(1*R*,2*S*,6*R*,7*S*)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0^{2,6}]decane (6).** To oxazolidinone **5** (3.8 g, 19.5 mmol) in THF (60 mL) was added *n*-butyllithium solution in hexanes (1.27 M, 21.5 mmol, 16.9 mL), with external cooling (dry ice–acetone bath). Propionyl chloride (2.03 mL, 23.4 mmol) was then added dropwise, via syringe at −60 to −65 °C (internal temperature). The reaction mixture was stirred at −70 °C for 1 h and then allowed to warm to ca. 25 °C over 30 min. Saturated, aqueous ammonium chloride (35 mL) was added slowly with stirring. THF was removed by rotary evaporation to give an aqueous slurry, which was extracted three times with CH_2Cl_2 (150 mL). The combined organic layers were washed twice with 5% NaOH (75 mL) and then twice with saturated, aqueous NaCl (75 mL). The organic layer was dried with $MgSO_4$, vacuum filtered, and concentrated by rotary evaporation to yield 4.55 g (93%) of a pale yellow solid, **6**, mp 76–78 °C, which was used without further purification. An analytical sample was recrystallized from hexane–ether to give an off-white solid, **6**: mp 78–80 °C; $[\alpha]^{22}_D$ −80° (*c* 2.00, CH_2Cl_2); IR ($CHCl_3$) 2980, 2900, 1780 (s), 1715, 1490, 1470, 1385, 1340, 1240, 1100, 1070, 1040 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.22 and 4.13 (2d, *J* = 8.1, 8.1, 2 H, C*H*N, C*H*O), 2.84 and 2.82 (2dq, *J* = 10.5, 7.4, and 10.4, 7.3, respectively, 2 H, CH_2CH_3), 2.22 (d, *J* = 4.6, 1 H, C-7 *H*), 1.8–1.1 (m, 4 H, C-8 and C-9 *H*), 1.08 (apparent t, *J* = 7.4, 3 H, CH_2CH_3), 0.99 (s, 3 H, C-1 CH_3), 0.91 and 0.83 (2s, 6 H, C-10 CH_3). Cl MS: *m/e* 252.1565 $(M + H)^+$. Calcd for $C_{14}H_{22}NO_3$: *m/e* 252.1600.

General Procedure for Formation and Aldol Reactions of Lithium Enolate of *N*-Propionyl-(1*R*,2*S*,6*R*,7*S*)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0^{2,6}]decane (6). Reactions were carried out in a septum-capped, 25-mL, flame-dried flask under argon. All reagents were added via oven-dried hypodermic syringes. To diisopropylamine (1.1 equiv based on **6**) in diethyl ether (0.16 M based on imide **6**) at 0 °C (ice bath) was added *n*-butyllithium solution in hexanes (1.1 equiv based on **6**). The solution was stirred for 15 min and then cooled to −78 °C (dry ice–acetone bath). *N*-Propionyloxazolidinone **6** (1 equiv) in diethyl ether (0.16 M based on **6**) was added dropwise over 5 min, and the reaction was stirred for 1 h at −78 °C. The aldehyde (2.0 equiv based on **6**) was added neat, and the reaction was quenched after 15 min by adding saturated, aqueous ammonium chloride solution (2 mL/mmol of **6** used). The solution was allowed to warm to ca. 25 °C, and then the mixture was extracted with diethyl ether three times. The organic layer was dried ($MgSO_4$), vacuum filtered, concentrated by rotary evaporation, and then placed under high vacuum (ca. 0.10 mmHg) for at least 2 h. The residue was refrigerated to yield a crude solid.

General Procedure for Formation and Aldol Reactions of Titanium Enolate of *N*-Propionyl-(1*R*,2*S*,6*R*,7*S*)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0^{2,6}]decane (6). The lithium enolate was generated as described above. At −78 °C (dry ice–acetone bath), $ClTi(OCH(CH_3)_2)_3$ (3.5 equiv, neat) was added dropwise with stirring over 3 min. After 5 min, the solution turned from clear pale yellow to clear bright red-orange. The solution was transferred to a constant-temperature bath set at −40 °C and kept there for 2 h. After 1 h, a white solid began to precipitate from the solution and the bright red-orange color faded to pale orange. After the solution was cooled to −78 °C, the aldehyde (2 equiv) was added dropwise. The reaction mixture was then transferred back to the −40 °C constant-temperature bath and kept there for 2 h. The reaction mixture was quenched by adding saturated, aqueous ammonium fluoride (2 mL/mmol of **6** used). The solution was allowed to warm to ca. 25 °C, and the mixture was extracted with diethyl ether three times. The organic layers were washed with small portions of saturated, aqueous NaCl and dried with $MgSO_4$. After vacuum filtration and concentration by rotary evaporation, the residue was placed under high vacuum for at least 2 h. The remaining oil was refrigerated to yield a crude solid.

***N*-[(2*S*,3*S*)-3-Hydroxy-2-methyl-3-phenylpropionyl]-(1*R*,2*S*,6*R*,7*S*)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0^{2,6}]decane (7):** crude yield 92% (Ti); mp 165–167 °C; IR ($CHCl_3$) 3450, 3060, 2960, 2920, 2890, 1780, 1700, 1690, 1620, 1520, 1470, 1396, 1150, 1120, 1070 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.43–7.28 (m, 5 H, C_6H_5), 5.12 [m (collapses to d in $CDCl_3/D_2O$, *J* = 4.5), 1 H, C*H*OH], 4.29 and 4.19 (2d, *J* = 8.1, 8.1, 2 H, C*H*N, C*H*OC=O), 4.11 (qd, *J* = 6.8, 4.6, 1 H, C*H*CH_3), 2.77 (d, *J* = 2.9, O*H*), 2.15 (d, *J* = 4.6, 1 H, C-7 *H*), 1.8–1.0 (m, 4 H, C-8 and C-9 *H*), 1.13 (d, *J* = 6.9, 3 H, CH_3CH), 1.04 (s, 3 H, C-1 CH_3), 0.85 and 0.81 (2s, 6 H, C-10 CH_3). Cl MS: *m/e* 358.2050 $(M + H)^+$. Calcd for $C_{21}H_{28}NO_4$: *m/e* 358.2018.

***N*-[(2*S*,3*R*)-3-Cyclohexyl-3-hydroxy-2-methylpropionyl]-(1*R*,2*S*,6*R*,7*S*)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0^{2,6}]decane (8):** colorless oil; IR ($CHCl_3$) 3510, 2925, 2850, 1780, 1690, 1440, 1390, 1150, 1120, 1070, 925 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3/D_2O$) δ 4.29 and 4.21 (2d, *J* = 8.1, 8.1, 2 H, C*H*N, C*H*OC=O), 4.05 (qd, *J* = 6.8, 2.8, 1 H, C*H*CH_3), 3.55 (dd, *J* = 6.3, 2.8, 1 H, C*H*OD), 2.26 (d, *J* = 4.6, 1 H, C-7 *H*), 2.1–1.1 (m, 15 H, C-8, C-9, and cyclohexyl *H*), 1.15 (d, *J* = 6.9, 3 H, CH_3CH), 1.06 (s, 3 H, C-1 CH_3), 0.99 and 0.91 (2s, 6 H, C-10 CH_3). Cl MS: *m/e* 364.2453 $(M + H)^+$. Calcd for $C_{21}H_{34}NO_4$: *m/e* 364.2488.

***N*-[(2*S*,3*R*)-3-Hydroxy-2-methylpentanoyl]-(1*R*,2*S*,6*R*,7*S*)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0^{2,6}]decane (9):** crude yield 90% (Ti); mp 118–120 °C: $[\alpha]^{22}_D$ −69° (*c* 1.12, CH_2Cl_2); IR ($CHCl_3$) 3500, 2960, 2880, 1780, 1695, 1490, 1465, 1390, 1145 cm^{-1}; ^1H NMR

(250 MHz, $CDCl_3$) δ 4.30 and 4.20 (2d, J = 8.0, 8.0, 2 H, C*H*N, C*H*OC=O) 3.85 (m, 2 H, C*H*OH and C*H*CH_3) 2.66 (d, J = 2.8, 1 H, O*H*), 2.28 (d, J = 4.6, 1 H, C-7 *H*), 1.2–0.8 (m, 9 H, C-8 and C-9 *H*, CH_2CH_3), 1.17 (d, J = 6.8, 3 H, CH_3CH), 1.07 (s, 3 H, C-1 CH_3), 0.99 and 0.91 (2s, 6 H, C-10 CH_3). CI MS: m/e 310.2042 $(M + H)^+$. Calcd for $C_{17}H_{28}NO_4$: m/e 310.2018.

***N*-[(2*S*,3*S*)-3-Hydroxy-2,4,4-trimethylpentanoyl]-(1*R*,2*S*,6*R*,7*S*)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0^{2,6}]decane (10)**: crude yield 87% (Li), 71% (Ti); mp 142–144 °C; IR ($CHCl_3$) 3450, 2950, 2880, 1780 (s), 1690, 1490, 1470, 1390, 1145, 1125 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3/D_2O$) δ 4.30 and 4.20 (2d, J = 8.0, 8.0, 2 H, C*H*N, C*H*OC=O), 4.14 (m, 1 H, C*H*CH_3), 3.62 (d, J = 3.5, 1 H, C*H*OD), 2.25 (d, J = 4.5, 1 H, C-7 *H*), 1.8–1.0 (m, 4 H, C-8 and C-9 *H*), 1.20 (d, J = 6.9, 3 H, CH_3CH), 1.06 (s, 3 H, C-1 CH_3), 0.97 and 0.90 (2s, 6 H, C-10 CH_3), 0.96 (s, 9 H, *tert*-butyl *H*). CI MS: m/e 338.2351 $(M + H)^+$. Calcd for $C_{19}H_{32}NO_4$: m/e 338.2331.

***N*-[(2*S*,3*R*)-3-Hydroxy-2,4-dimethylpentanoyl]-(1*R*,2*S*,6*R*,7*S*)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0^{2,6}]decane (11)**: crude yield 86% (Ti), 77% (Li); mp 95–96 °C; $[\alpha]^{22}_D$ −54° (c 0.75, CH_2Cl_2); IR ($CHCl_3$) 3500, 2920, 2880, 1780, 1695, 1410, 1290, 1240, 1220, 1145, 1120, 920 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3/D_2O$) δ 4.30 and 4.22 (2d, J = 8.0, 8.0, 2 H, C*H*N, C*H*OC=O), 4.02 (qd, J = 6.9, 3.4, 1 H, COC*H*CH_3), 3.50 (dd, J = 8.1, 3.5, 1 H, C*H*OD), 2.26 (d, J = 4.6, 1 H, C-7 *H*), 1.9–0.7 [m, 5 H, C-8 and C-9 *H*, C*H*$(CH_3)_2$], 1.15 (d, J = 6.9, 3 H, COCHC*H*$_3$), 1.06 (s, 3 H, C-1 CH_3), 1.01 and 0.92 [2d, J = 6.6, 6.1, 6 H, CH$(CH_3)_2$], 0.99 and 0.90 (2s, 6 H, C-10 CH_3). CI MS: m/e 324.2122 $(M + H)^+$. Calcd for $C_{18}H_{30}NO_4$: m/e 324.2175.

***N*-[(2*S*,3*R*)-*trans*-3-Hydroxy-2-methylhex-4-enoyl]-(1*R*,2*S*,6*R*,7*S*)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0^{2,6}]decane (12)**: crude yield 92% (Ti); mp 143–144 °C; $[\alpha]^{22}_D$ −69° (c 0.95, CH_2Cl_2); IR ($CHCl_3$) 3500, 3000, 2960, 2880, 1790, 1710, 1690, 1480, 1460, 1380, 1340, 1285, 1230, 1070, 980 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.9–5.3 (m, 2 H, C*H*=C*H*), 4.35–4.1 (m, 3 H, C*H*N, C*H*OC=O, COC*H*CH_3), 3.87 (m, 1 H, C*H*OH), 2.6 (br, 1 H, O*H*), 2.20 (m, 1 H, C-7 *H*), 1.82–0.95 (m, 4 H, C-8 and C-9 *H*), 1.72 (d, J = 6.4, 3 H, CH=CHC*H*$_3$), 1.17 (d, J = 6.9, 3 H, COCHC*H*$_3$), 1.07 (s, 3 H, C-1 CH_3), 0.99 and 0.88 (2s, 6 H, C-10 CH_3). CI MS: m/e 322.2042 $(M + H)^+$. Calcd for $C_{18}H_{28}NO_4$: m/e 322.2018.

General Procedure for Formation of β-Hydroxy-α-methylcarboxylic Acids Using Lithium Hydroperoxide.[35] The purified aldol product (1 equiv) was dissolved in a 3:1 THF–H_2O solution (total volume 0.05 M in aldol adduct) at 0 °C (ice bath). A solution of 30% H_2O_2 (5 equiv) was added dropwise followed by solid lithium hydroxide (2 equiv). The ice bath was removed, and the mixture was stirred at 0–25 °C until the disappearance of starting material was noted by TLC (5 min–1 h). The reaction mixture was then cooled to 0 °C (ice bath), and the excess peroxide was quenched by adding small portions of solid sodium sulfite, until potassium starch iodide paper (pretreated with 5% acetic acid) indicated the complete disappearance of peroxide. The sample was then buffered with saturated sodium bicarbonate to pH 10. THF was removed from the aqueous solution by rotary evaporation. The remaining slurry was diluted with water (8 mL/mmol of aldol adduct used) and extracted with CH_2Cl_2 three times. The CH_2Cl_2 layers were dried ($MgSO_4$) and concentrated by rotary evaporation to yield recovered unacylated oxazolidinone **5**. The original aqueous layer was carefully acidified to pH 2 with 3 M HCl at 0 °C and then extracted three times with EtOAc. The EtOAc layers were dried ($MgSO_4$) and concentrated by rotary evaporation to yield the carboxylic acid.

(2*S*,3*S*)-3-Hydroxy-2,4,4-trimethylpentanoic Acid (13a): crude yield 93%; mp 100–102 °C; $[\alpha]^{22}_D$ −17° (c 0.50, CH_2Cl_2); IR ($CHCl_3$) 3620, 3000 (br), 2970, 2870, 1710, 1150, 1125 (s), 920 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.35 (br, 2 H, CO_2H and O*H*), 3.71 (d, J = 3.9, 1 H, C*H*OH),[57] 2.76 (qd, J = 7.1, 3.9, 1 H, C*H*CH_3), 1.27 (d, J = 7.1, 3 H, CHC*H*$_3$), 0.97 (s, 9 H, *tert*-butyl *H*). CI MS: m/e 161.1175 $(M + H)^+$. Calcd for $C_8H_{17}O_3$: m/e 161.1177.

(2*S*,3*R*)-3-Hydroxy-2-methylpentanoic Acid (13b): crude yield 57%, colorless oil; IR (CH_2Cl_2) 3575, 3450, 3200 (br), 2950, 2875, 1700, 1460, 1410, 1380, 1330, 1220, 1000, 980, 960, 940 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.6 (br, 2 H, CO_2H and O*H*), 3.88 (ddd, J = 7.8, 5.0, 3.5, 1 H, C*H*OH), 2.55 (qd, J = 7.2, 3.5, 1 H, C*H*CH_3), 1.45 (m, 2 H, CH_2CH_3), 1.15 (d, J = 7.2, 3 H, CHC*H*$_3$), 0.92 (dd, J = 7.4, 7.4, 3 H, CH_2CH_3). CI MS: m/e 133.0869 $(M + H)^+$. Calcd for $C_6H_{13}O_3$: m/e 133.0864.

(2*S*,3*R*)-3-Hydroxy-2,4-dimethylpentanoic Acid (13c): crude yield 65%, colorless oil; $[\alpha]^{22}_D$ −8° (c 0.90, CH_2Cl_2);[58] IR (CH_2Cl_2) 3590, 3480, 3150 (br), 2950, 2880, 1770 (w), 1700 (s), 1460, 1410, 1385, 1080, 1050, 1040, 1000, 980, 970, 960 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, D_2O) δ 3.63 (dd, J = 8.2, 3.5, 1 H, C*H*OD), 2.71 (qd, J = 7.2, 3.4, 1 H, C*H*CH_3), 1.71 [m, 1 H, C*H*$(CH_3)_2$], 1.20 (d, J = 7.1, 3 H, CHC*H*$_3$), 1.02 and 0.89 [2d, J = 6.7, 6.6, 6 H, CH$(CH_3)_2$]. CI MS: m/e 147.1027 $(M + H)^+$. Calcd for $C_7H_{15}O_3$: m/e 147.1021.

(2*S*,3*R*)-3-Cyclohexyl-3-hydroxy-2-methylpropanoic Acid (13d): crude yield 72%, colorless oil; $[\alpha]^{22}_D$ −4° (c 0.60, CH_2Cl_2); IR (CH_2Cl_2) 3580, 3475, 3100 (br), 2920, 2850, 1700, 1460, 1440, 1000, 980, 960 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.92 (br, 2 H, CO_2H and O*H*), 3.70 (dd, J = 8.4, 3.1, 1 H, C*H*OH), 2.71 (qd, J = 7.2, 3.1, 1 H, C*H*CH_3), 2.1–0.7 (m, 11 H, cyclohexyl *H*), 1.18 (d, J = 7.2, 3 H, CHC*H*$_3$). CI MS: m/e 187.1291 $(M + H)^+$. Calcd for $C_{10}H_{19}O_3$: m/e 187.1334.

(2*S*,3*R*)-*trans*-3-Hydroxy-2-methyl-4-hexenoic Acid (13e): crude yield 65%, colorless oil; $[\alpha]^{22}_D$ +3° (c 1.75, CH_2Cl_2); IR (CH_2Cl_2) 3580, 3100, 2900, 1750 (w), 1705 (s), 1490, 1380, 1220, 1140, 1110, 1000, 970 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3/D_2O$) δ 5.35–5.90 (m, 2 H, C*H*=C*H*), 4.36 (m, 1 H, C*H*OD), 2.85 (qd, J = 7.2, 4.2, 1 H, COC*H*CH_3), 1.74 (d, J = 6.6, 3 H, CH=CHC*H*$_3$), 1.18 (d, J = 7.2, 3 H, COCHC*H*$_3$). CI MS: m/e 162.1134 $(M + NH_4)^+$. Calcd for $C_7H_{16}NO_3$: m/e 162.1130.

***N*-[(2*S*,3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpentanoyl]-(1*R*,2*S*,6*R*,7*S*)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0^{2,6}]decane (14)**: crude yield 75%; mp 88–92 °C, $[\alpha]^{25}_D$ −36° (c 0.25, CH_2Cl_2); IR (CH_2Cl_2) 2920, 2900, 2870, 2840, 2820, 1740, 1665, 1435, 1450, 1350, 1180, 1105, 1080, 1030, 980 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.22 and 4.16 (2d, J = 8.1, 8.1, 2 H, C*H*N, C*H*OCO), 3.95 (m, 1 H, C*H*CH_3), 3.85 (m, 1 H, C*H*OSi), 2.18 (d, J = 4.4, 1 H, C-7 *H*), 1.8–0.8 (m, 9 H, C-8 and C-9 *H*, CH_2CH_3), 1.10 (d, J = 6.7, 3 H, CH_3CH), 1.01 (s, 3 H, C-1 CH_3), 0.96 and 0.84 (2s, 6 H, C-10 CH_3), 0.85 (s, 9 H, *tert*-butyl *H*), 0.01 and 0.00 (2s, 6 H, CH_3Si). CI MS: m/e 424.2861 $(M + H)^+$. Calcd for $C_{23}H_{42}NO_4Si$: m/e 424.2883.

(2*R*,3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-methylpentan-1-ol (15): colorless oil; ^1H NMR (250 MHz, $CDCl_3/D_2O$) δ 3.57 (m, 2 H, CH_aH_bOD and C*H*OSi), 3.45 (m, 1 H, CH_aH_bOD), 1.8 (m, 1 H, C*H*CH_3), 1.42 (m, 2 H, CH_2CH_3), 0.90 (m, 3 H, CH_2CH_3), 0.83 (s, 9 H, *tert*-butyl *H*), 0.74 (d, J = 7.1, 3 H, CHC*H*$_3$), 0.22 and 0.001 [2s, 6 H, $(CH_3)_2$Si].

(*S*)-2-(Benzyloxy)propanal (16). (*S*)-2-(Benzyloxy)propanal was prepared in three steps according to a literature procedure.[39] Protection of ethyl (*S*)-lactate as the benzyl ether, followed by reduction of the resulting benzyloxy ester with lithium aluminum hydride, provided the monoprotected diol, which was oxidized under Swern conditions[59] to provide aldehyde **16** as a colorless oil: ^1H NMR (250 MHz, $CDCl_3$) δ 9.65 (d, J = 1.7, 1 H, C*H*O), 7.30 (m, 5 H, C_6H_5), 4.65 and 4.60 (2d, J = 11.7, 11.7, 2 H, CH_2Ph), 3.90 (qd, J = 6.9, 1.7, 1 H, C*H*CH_3), 1.33 (d, J = 6.9, 3 H, CHC*H*$_3$).

***N*-[(2*S*,3*S*,4*R*)-4-(Benzyloxy)-3-hydroxy-2-methylpentanoyl]-(1*R*,2*S*,6*R*,7*S*)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0^{2,6}]decane (17)**: colorless oil; $[\alpha]^{25}_D$ −49° (c 4.25, CH_2Cl_2); IR (CH_2Cl_2) 3560, 3040, 2980, 2880, 1780, 1695, 1455, 1380, 1210, 1060, 1000, 910 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.35 (m, 5 H, C_6H_5), 4.63 and 4.48 (2d, J = 11.8, 11.8, 2 H, CH_2Ph), 4.28 and 4.17 (2d, J = 8.0, 8.1, 2 H, C*H*N, C*H*OCO), 4.09 (m, 1 H, COC*H*CH_3), 3.95 (dd, J = 6.0, 4.7, 1 H, C*H*OD), 3.48 (m, 1 H, C*H*OCH_2Ph), 2.17 (d, J = 4.5, 1 H, C-7 *H*), 1.85–1.08 (m, 4 H, C-8 and C-9 *H*), 1.24 [d, J = 6.2, 3 H, CH(CH_3)O], 1.16 (d, J = 6.9, 3 H, COCHC*H*$_3$), 1.05 (s, 3 H, C-1 CH_3), 0.92 and 0.87 (2s, 6 H, C-10 CH_3). CI MS: m/e 433.2688 $(M + NH_4)^+$. Calcd for $C_{24}H_{37}N_2O_5$: m/e 433.2702.

(2*S*,3*S*,4*R*)-4-(Benzyloxy)-3-hydroxy-2-methylpentanoic Acid (13f): colorless oil; $[\alpha]^{25}_D$ −34° (c 1.5, CH_2Cl_2); IR (CH_2Cl_2) 3590 (br), 3490 (br), 3100, 3060, 3040, 3000 (br), 2990, 2940, 2890, 1710, 1608, 1500, 1460, 1380, 1140, 1110 (s), 1080, 1035 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3/D_2O$) δ 7.32 (m, 5 H, C_6H_5), 4.63 and 4.43 (2d, J = 11.6, 11.6, 2 H, CH_2Ph), 3.94 (dd, J = 6.4, 5.0, 1 H, C*H*OD), 3.54 (m, 1 H, C*H*OCH_2Ph), 2.83 (qd, J = 7.2, 5.0, 1 H, COC*H*CH_3), 1.28 (d, J = 6.2, 3 H, CHC*H*$_3$OCH$_2$Ph), 1.20 (d, J = 7.2, 3 H, COCHC*H*$_3$). CI MS: m/e 256.1546 $(M + NH_4)^+$. Calcd for $C_{13}H_{22}NO_4$: m/e 256.1549.

***N*-[(2*R*,3*R*,4*S*)-4-(Benzyloxy)-3-hydroxy-2-methylpentanoyl]-(1*R*,2*S*,6*R*,7*S*)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0^{2,6}]decane (18)**: crude yield 87%; mp 95–96 °C (after recrystallization); IR (CH_2Cl_2) 3550 (br), 2975, 2925, 2850, 1770, 1690, 1605, 1465, 1455,

(57) The δ value (ppm) and coupling constant (Hz) for the carbinol proton of *erythro*-3-hydroxy-2,4,4-trimethylpentanoic acid were reported: ^1H NMR ($CDCl_3$, 60 MHz) 3.62 (1 H, d, J = 3). Pirrung, M. C. Ph.D. Dissertation in Chemistry, University of California, Berkeley, 1980, p 195.

(58) The specific rotation for (2*R*,3*S*)-3-hydroxy-2,4-dimethylpentanoic acid (the enantiomer of **13c**) was reported to be +9.30° (c 2.56, CH_2Cl_2): McGee, L. R. Ph.D. Dissertation in Chemistry, California Institute of Technology, 1982, p 114.

(59) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480–2482.

1380, 1335, 1240, 1210, 1140, 1110 (s), 1060, 1015, 1005 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3/D_2O$) δ 7.35 (m, 5 H, C_6H_5), 4.68 and 4.38 (2d, J = 11.3, 11.3, 2 H, CH_2Ph), 4.15 (m, 1 H, $COCHCH_3$), 4.06 and 4.00 (2d, J = 8.0, 8.0, 2 H, CHN, $CHOC{=}O$), 3.85 (dd, J = 7.5, 4.9, 1 H, $CHOD$), 3.48 (m, 1 H, $CHOCH_2Ph$), 2.20 (d, J = 4.5, 1 H, C-7 H), 1.85-1.08 (m, 4 H, C-8 and C-9 H), 1.30 [d, J = 7.1, 3 H, $CH(CH_3)O$], 1.15 (d, J = 7.1, 3 H, $COCHCH_3$), 1.03 (s, 3 H, C-1 CH_3), 0.96 and 0.88 (2s, 6 H, C-10 CH_3). CI MS: m/e 416.2422 $(M + H)^+$. Calcd for $C_{24}H_{34}NO_5$: m/e 416.2437.

(2*R*,3*R*,4*S*)-4-(Benzyloxy)-3-hydroxy-2-methylpentanoic Acid (13g): colorless oil; IR (CH_2Cl_2) 3580 (br), 3490 (br), 3080, 3030, 2975, 2940, 2890, 1705, 1605, 1495, 1460, 1380, 1140, 1110 (s), 1080, 1035 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3/D_2O$) δ 7.32 (m, 5 H, C_6H_5), 4.63 and 4.43 (2d, J = 11.5, 11.5, 2 H, CH_2Ph), 3.94 (dd, J = 6.4, 5.0, 1 H, $CHOD$), 3.51 (m, 1 H, $CHOCH_2Ph$), 2.82 (qd, J = 7.1, 5.0, 1 H, $COCHCH_3$), 1.28 [d, J = 6.2, 3 H, $CH(CH_3)O$], 1.20 (d, J = 7.1, 3 H, $COCHCH_3$). CI MS: m/e 239.1253 $(M + H)^+$. Calcd for $C_{13}H_{19}O_4$: m/e 239.1283.

***N*-[(2*S*,3*S*,4*S*)-4-(Benzyloxy)-3-hydroxy-2-methylpentanoyl]-(1*R*,2*S*,6*R*,7*S*)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0^{2,6}]-decane (19)**: mp 75-76 °C (after recrystallization); ^1H NMR (250 MHz, $CDCl_3$) δ 7.38 (m, 5 H, C_6H_5), 4.67 and 4.47 (2d, J = 11.3, 11.3, 2 H, CH_2Ph), 4.33 and 4.29 (2d, J = 8.2, 8.1, 2 H, CHN, $CHOC{=}O$), 4.03 (m, 1 H, $COCHCH_3$), 3.85 (dd, J = 6.2, 4.6, 1 H, $CHOD$), 3.58 (m, 1 H, $CHOCH_2Ph$), 2.24 (d, J = 4.5, 1 H, C-7 H), 1.6-1.1 (m, 4 H, C-8 and C-9 H), 1.28 [d, J = 6.2, 3 H, $CH(CH_3)O$], 1.17 (d, J = 6.91, 3 H, $COCHCH_3$), 1.05 (s, 3 H, C-1 CH_3), 0.97 and 0.86 (2s, 6 H, C-10 CH_3). CI MS: m/e 416.2496 $(M + H)^+$. Calcd for $C_{24}H_{34}NO_5$: m/e 416.2437.

***N*-[(2*R*,3*R*,4*R*)-3-Acetoxy-4-(benzyloxy)-2-methylpentanoyl]-(1*R*,2*S*,6*R*,7*S*)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0^{2,6}]-decane (20)**: colorless oil; IR (CH_2Cl_2) 2950, 2875, 1760(s), 1735, 1685, 1480, 1450, 1375, 1360, 1330, 1240, 1210, 1060, 1010, 1000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.32 (m, 5 H, C_6H_5), 5.44 (dd, J = 8.1, 6.9, 1 H, $CHOAc$), 4.61 and 4.38 (2d, J = 11.3, 11.3, 2 H, CH_2Ph), 4.18 (m, 1 H, $COCHCH_3$), 3.78 and 3.67 (2d, J = 7.9, 7.9, 2 H, CHN, $CHOC{=}O$), 3.55 (m, 1 H, $CHOCH_2Ph$), 2.15 (d, J = 4.4, 1 H, C-7 H), 2.10 (s, 3 H, $COCH_3$), 1.75-1.40 (m, 4 H, C-8 and C-9 H), 1.20 (d, J = 6.2, 3 H, $CHCH_3OCH_2Ph$), 1.10 (d, J = 6.9, 3 H, $COCHCH_3$), 0.99 (s, 3 H, C-1 CH_3), 0.91 and 0.84 (2s, 6 H, C-10 CH_3). CI MS: m/e 458.2533 $(M + H)^+$. Calcd for $C_{26}H_{36}NO_6$: m/e 458.2542.

***N*-[(*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-1-propenyl]-(1*R*,2*S*,6*R*,7*S*)-1,10,10-trimethyl-4-oxo-5-aza-3-oxatricyclo[5.2.1.0^{2,6}]-decane (21)**. To diisopropylamine (175 μL, 1.25 mmol) in THF (2.0 mL) was added n-butyllithium solution in hexanes (1.23 M, 1.02 mL, 1.25 mmol) dropwise at 0 °C (ice bath). After stirring for 15 min, the solution was cooled to -78 °C (dry ice-acetone bath), N-propionyloxazolidinone **6** (286 mg, 1.14 mmol) in THF (2.0 mL) was added dropwise over 5 min, and the reaction mixture was stirred for 1 h at -78 °C. A solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate (265 μL, 1.14 mmol) was then added dropwise over 2 min. The dry ice-acetone bath was removed, and the solution was allowed to warm to ca. 25 °C over 1 h. A solution of pH 7 phosphate buffer (2.0 mL) was added, and the mixture was extracted twice with ether (100 mL each). The ether layers were dried ($MgSO_4$), vacuum-filtered, concentrated by rotary evaporation, and placed under high vacuum (ca. 0.1 mmHg) for 2 h to yield an off-white solid, **21**: mp 110-111 °C (348 mg, 84%); was purified by flash chromatography (9:1, petroleum ether-diethyl ether), R_f = 0.19; $[\alpha]^{24}_D$ +37° (c 0.75, CH_2Cl_2); IR ($CHCl_3$) 2990, 2950, 2875, 2850, 1745 (s), 1690, 1470, 1465, 1420, 1350, 1340, 1260, 1150, 1120, 1060 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.60 (q, J = 6.9, 1 H, $C{=}CHCH_3$), 4.08 and 3.75 (2d, J = 8.2, 8.2, 2 H, CHN, $CHOC{=}O$), 1.85 (d, J = 4.5, 1 H, C-7 H), 1.48 (d, J = 6.9, 3 H, $C{=}CHCH_3$), 1.7-0.8 (m, 4 H, C-8 and C-9 H), 0.88 (s, 6 H, C-10 CH_3), 0.81 (s, 9 H, *tert*-butyl H), 0.74 (s, 3 H, C-1 CH_3), 0.044 and 0.00 (2s, 6 H, CH_3Si). CI MS: m/e 366.2459 $(M + H)^+$. Calcd for $C_{20}H_{36}NO_3Si$: m/e 366.2464.

Acknowledgment. We thank Dr. Patrick Carroll, X-ray Diffraction Facility, Dr. George Furst, NMR Facility, and Dr. John Dykins, Mass Spectrometry Facility, for their splendid assistance, and Dr. D. R. Reddy of this laboratory for sharing his observations on selective reactions of camphorquinone. We gratefully acknowledge support by the University of Pennsylvania Research Fund and by the National Institutes of Health.

Supplementary Material Available: Tables of refined atomic positional and thermal parameters for the five X-ray structures reported and ORTEP diagrams for compounds **7**, **9**, **18**, **19**, and **21** (47 pages). Ordering information is given on any current masthead page.

An Electron Donor-Acceptor Complex and a Thermal Triplex as Intermediates in the Cycloaddition Reaction of *N*-Vinylcarbazole with Dimethyl 2,2-Dicyanoethylene-1,1-dicarboxylate

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Abstract: The formation of dimethyl 1-(carbazol-9-yl)-2,2-dicyanocyclobutane-3,3-dicarboxylate through a tetramethylene zwitterionic intermediate (T) by the reaction of *N*-vinylcarbazole (NVCZ) and dimethyl 2,2-dicyanoethylene-1,1-dicarboxylate in nonpolar and moderately polar solvents was studied kinetically. Two competitive formation paths of T were found: (a) unimolecular transformations of the electron donor-acceptor (EDA) complex and (b) bimolecular reaction between the EDA complex and free NVCZ. Contributions of these two reactions to the overall reaction are influenced by the solvent and the concentration of NVCZ. The third-order kinetics is explained on the basis that the contribution of the cation-radical form to the transition state can be enhanced by an additional donor molecule through charge resonance in a thermal triplex. This may be a general mode of catalysis for reactions of electron-rich unsaturated molecules with electrophiles.

Introduction

Even though the reactions of electrophilic olefins with nucleophilic olefins have been studied by many investigators, detailed kinetic studies have been rather infrequent. Huisgen studied in detail the reaction of vinyl ethers and of vinyl sulfides with tetracyanoethylene (TCNE).[1] The reactions were reported to follow second-order kinetics in all cases. Although electron donor-acceptor (EDA) complexes were observed in these reactions, the question of their participation in the cycloaddition reactions was left open. In Bartlett's review,[2] the cycloaddition of *p*-meth-

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0002-7863/91/1513-1308$02.50/0