Electrophilic Substitution at Saturated Carbon. 52. A Model for the Proton Transfer Steps of Biological Transamination and the Effect of a 4-Pyridyl Group on the Base-Catalyzed Racemization of a Carbon Acid[1,2]

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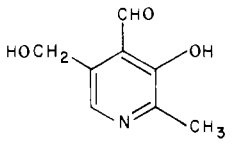
Abstract: Imines (−)-(*S*)-*N*-(α-ethoxycarbonylneopentylidene)-α-(4-pyridyl)ethylamine [(−)-**7**-H] and (−)-(*S*)-*N*-[α-(4-pyridyl)ethylidene]-α-ethoxycarbonylneopentylamine [(−)-**8**-H] were prepared in optically pure forms for study as models for the biological transamination reaction. In *tert*-butyl alcohol at 50 °C, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) catalyzed equilibration gave $K = 8/7 > 199$. Under the same conditions, isomerization of (−)-**7**-H to **8** and racemization of (−)-**7**-H occurred at comparable rates. Imine (−)-**8**-H resulted, and use of a kinetic model which corrected for concomitant racemization of (−)-**7**-H gave a value of 12% for the stereospecificity of the **7**-H to **8**-H isomerization. Likewise, with (−)-**7**-H in pyridine and in dimethyl-d_6 sulfoxide with 1,4-diazabicyclo[2.2.2]octane (Dabco) as catalyst at 101.4 °C, corrected values of 24 and 29% stereospecificity, respectively, were obtained for the isomerization of **7** to **8**. In each case the stereospecific component of the isomerization was interpreted in terms of the intermediacy of a single, inherently symmetrical aza-allylic carbanion A asymmetrically ion paired with the conjugate acid of the base. The stereospecific isomerization occurred in cis or *suprafacial* fashion across the face of carbanion A. Collapse of A favored **8** over **7** by a factor of ca. 4 ($k_5/k_6 = 0.26$) in *tert*-butyl alcohol-*O*-*d*-DBN, and in the same medium, intramolecularity in the isomerization of **7**-H to **8** was 37%. Isotopic exchange reactions of (−)-**7**-H and (−)-**8**-H were studied in *tert*-butyl alcohol-*O*-*d*-DBN, and k_e/k_α values of 0.25 and 7, respectively, resulted. Thus the isotopic exchange of **7**-H occurred with isoinversion and that of **8**-H with retention of configuration. The role of the 4-pyridyl group in the isoinversion pathway of (−)-**7**-H was analyzed by a study of the isotopic exchange reactions of (−)-(*S*)-*N*,*N*-dimethyl-α-(4-pyridyl)ethylamine [(−)-**11**-H]. Three solvent-base systems were used, *tert*-butyl alcohol-*O*-*d*-potassium *tert*-butoxide at 50.7 °C, 2:1 (v/v) hexamethylphosphoramide-*tert*-butyl alcohol-*O*-*d*-DBN at 175 °C, and methanol-*O*-*d*-potassium methoxide at 100 °C, and k_e/k_α values of 0.75, 0.42, and 1, respectively, resulted. In each of the first two solvents isoinversion was a contributing mechanistic pathway resulting from the effect of the 4-pyridyl group.

Biological transamination involves the enzyme-catalyzed isomerization of imines derived from pyridoxal (**1**) and α-amino acids and from pyridoxamine (**2**) and α-keto acids.[4] The



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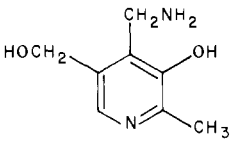

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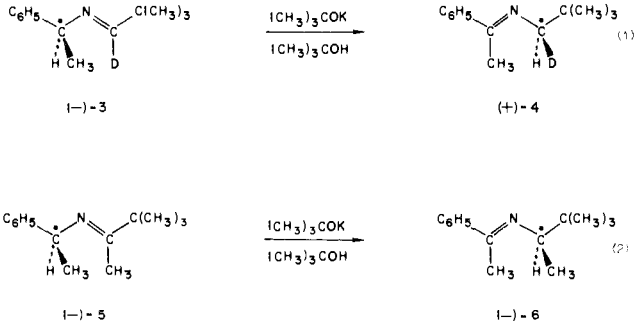
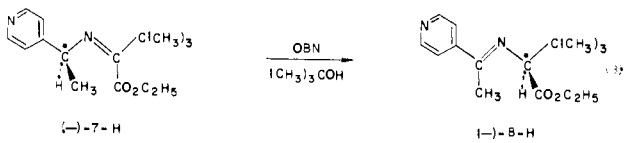
isomerization is stereospecific, and with some enzymes containing the phosphate ester of pyridoxal the proton (or isotope) transfer occurs intramolecularly.[5,6] In a related reaction, enzymes containing pyridoxal catalyze the isotopic exchange of α hydrogens of L-amino acids with high retention of configuration.[7] Previous models for the imine isomerization step of biological transmination have included the systems of eq 1 and 2.[8,9] Both the **3** to **4** and **5** to **6** isomerizations were stereospecific as indicated. Furthermore, in potassium *tert*-butoxide-*tert*-butyl alcohol-*O*-*d*, intramolecularity was demonstrated for the former isomerization,[8] and the benzyl hydrogens of **3** and **5** underwent isotopic exchange with high retention of configuration.[8,9]



(−)-3 (+)-4 (1)

(−)-5 (−)-6 (2)

We report herein a study of the isomerization of **7** to **8** (eq 3), which was undertaken for several reasons. (1) With respect



(−)-7-H (−)-8-H (3)

to the **3**,**4** and **5**,**6** systems, the substituents of the **7**,**8** system more closely approximate those of the imines involved in biological transamination. (2) The absolute configurations of α-(4-pyridyl)ethylamine (**9**)[10] and ethyl 2-amino-3,3-dimethylbutanoate (**10**) are known, and therefore those of **7** and **8** could be determined simply by synthesis. (3) Both **7** and **8** proved chemically and optically stable to and preparatively separable by GLC. (4) Imine **8** was found to be favored in equilibrium mixtures of **7** and **8**, and isomerizations of **7** could be carried out under conditions such that **8**, once formed, did not react further to a significant extent. (5) The bulk of the *tert*-butyl and pyridyl groups was expected to enforce conformational homogeneity for both **7** and **8** and for the intermediate aza-allylic anion. In order to assess the effect of the 4-pyridyl group on the stereochemical fate of carbanions generated from **7** and **8**, the base-catalyzed isotopic exchange reactions of *N*,*N*-dimethyl-α-(4-pyridyl)ethylamine (**11**) were studied also.

Results

Starting Materials. Racemic **9**-H was resolved with *d*-tartaric acid in aqueous methanol to give optically pure (−)-**9**-H, $[\alpha]_{546}^{25}$ −31.5° (*c* 1.53, absolute C_2H_5OH), of established *S* configuration.[10] Condensation of this material with ethyl tri-

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Table I. DBN-Catalyzed Equilibrations of Imines 7 and 8 in *tert*-Butyl Alcohol at 50.0 ± 0.1 °C

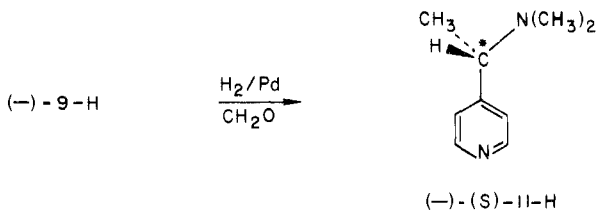
run	substrate nature	substrate concn, M	DBN concn, M	time, h	% 8[a]
1	7-H	0.40	0.50	811	99.5
2	8-H	0.085	0.57	231	>99.9[b]

[a] Of the 7-8 mixture as determined by GLC analysis. [b] No 7 was detected (limit of 0.1%).

methylpyruvate (**12**) in tetrahydrofuran (THF) in the presence of molecular sieves[11] gave (−)-**7**-H, $[\alpha]_{546}^{25}$ −93.3° (*c* 0.570, absolute C_2H_5OH). Amino ester **10** was resolved with dibenzoyl-*d*-tartaric acid to give optically pure (+)-(*S*)-**10**, $[\alpha]_{546}^{25}$ +58.3° (*c* 0.64, $CHCl_3$), which yielded (−)-*tert*-leucine of *S* configuration[12] on acid-catalyzed hydrolysis. That (+)-**10** was optically pure was demonstrated by its mild hydrolysis and conversion to (+)-(*S*)-*N*-*p*-toluenesulfonyl-*tert*-leucine, $[\alpha]_{546}^{25}$+51.3° (*c* 1.02, absolute C_2H_5OH). Independent resolution of the racemate with brucine gave identical material. Condensation[11] of optically pure (+)-(*S*)-**10** with methyl 4-pyridyl ketone (**13**)[13] afforded (−)-**8**-H, $[\alpha]_{546}^{25}$ −53.2° (*c* 0.410, $CHCl_3$). No racemization occurred in the preparations of (−)-**7**-H and (−)-**8**-H since acid-catalyzed hydrolyses of these materials produced optically pure (−)-**9**-H and (+)-**10**, respectively. The α protium of (±)-**9**-H was exchanged for deuterium in a refluxing solution of deuterium oxide, trifluoroacetic acid-*O*-*d*, and paraformaldehyde, and the resulting (±)-**9**-D (0.98 atom of D at the α position by ^{1}H NMR) was converted to (±)-**7**-D.

By ^{1}H NMR (ambient probe temperature ca. 40 °C) and GLC analyses, **7** and **8** were geometrically homogeneous, and it is assumed that they were in the anti configurations as indicated in eq 3. Furthermore, molecular models (Corey-Pauling-Koltun, CPK) of these anti forms can be assembled whereas those of the corresponding syn forms cannot.

Reductive methylation[14] of optically pure (−)-**9**-H gave (−)-(*S*)-**11**-H, $[\alpha]_{546}^{25}$ −60.6° (*c* 0.80, $CHCl_3$), of undetermined optical purity. Attempts to resolve (±)-**11** to optical purity by fractional crystallization of diastereomeric salt derivatives proved unsuccessful with six different resolving agents.



Equilibria. Table I summarizes the results of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) catalyzed equilibrations of **7** and **8** in *tert*-butyl alcohol at 50 °C. The reaction times of runs 1 and 2 were equivalent to about 8 and 3 half-lives, respectively, for the isomerization of **7** to **8**. The equilibrium constant, K = **8**/**7**, is >199 at 50 °C and almost certainly higher valued at 25 °C, the temperature of runs 3 and 9.

DBN-Catalyzed Isomerization of Imine 7 to 8. Tables II and III summarize the DBN-catalyzed isomerizations of (−)-**7**-H and (±)-**7**-D to **8** in *tert*-butyl alcohol and *tert*-butyl alcohol-*O*-*d*. Runs 3 and 9 were made at 25 °C and all others at 50 °C. In run 8 in *tert*-butyl alcohol-*O*-*d*, the reaction mixture contained DBN hydriodide.

Each reaction mixture was prepared by mixing reagents in a nitrogen-flushed volumetric flask. The resulting solution then was transferred to a nitrogen-flushed tube, which was degassed and sealed under vacuum (ca. 0.02 mm). After the reaction period in the appropriate constant-temperature bath, the tube was opened and the extent of isomerization of **7** to **8** was determined immediately by ^{1}H NMR analysis of the reaction mixture. For quantitation, the separated AA′XX′ patterns for the aromatic protons of **7** and **8** were integrated.[15a] After subsequent isolation, the **7**-**8** mixture was separated by preparative GLC, and **7** and **8** were analyzed polarimetrically and for deuterium content as required. For deuterium analysis, mass spectrometry was used for the former and ^{1}H NMR for the latter. A control demonstrated that (−)-**7** does not undergo thermal racemization or isomerization to **8** in *tert*-butyl alcohol at 50 °C without added DBN. An additional control demonstrated that **7** and **8** were optically stable to the procedures used for their isolation from reaction mixtures.

One-point pseudo-first-order (base concentration remained constant) and second-order rate constants for isomerization, k_i and k_i', respectively, are listed in Table III. These values were calculated from the ^{1}H NMR analyses with the assumption that, once formed, **8** did not return to **7**. This is an excellent assumption in view of the very large value of K. Use of a hydrocarbon internal standard in a control analyzed by GLC demonstrated that under the conditions of run 5, >99% of starting material could be accounted for in the form of **7** and **8**.

In run 13 (see Experimental Section) the isomerization of **7** to **8** was demonstrated to be first order in **7**. With DBN (0.85 M) as catalyst (−)-**7**-H (0.06 M) was isomerized to **8** at 25 °C in 2:1 (v/v) hexamethylphosphoramide (HMPA)-*tert*-butyl alcohol. Since product **8** racemized very slowly under these conditions (see Experimental Section, run 14), the isomerization could be followed by change in the observed optical rotation, α_{obsd}, at 546 nm.[16] A plot of log $1/\alpha_{obsd}$ vs. time contained a sharp break at ca. 100 h with two essentially straight lines on either side. The break corresponds to the completion of isomerization; thus the curve at times <100 h represents the isomerization of **7** to **8** and at times >100 h the racemization of **8**. The half-life for the isomerization was ca. 22 h, and the correlation coefficient for a least-squares evaluation of the first-order character of the plot after 2 half-lives was 0.9999. The half-life for racemization of **8** was ca. 623 h.

DBN-Catalyzed Racemization and Exchange of Imine 8. Table IV summarizes the DBN-catalyzed racemization and exchange runs with optically active **8**-H in *tert*-butyl alcohol and *tert*-butyl alcohol-*O*-*d* at 50 °C. In run 17, the reaction mixture contained DBN·HI.

With the procedures for runs 1-12 with **7**, each reaction mixture was prepared and sealed in a tube after its rotation was measured. After the reaction period at 50 °C, the tube was opened, and the rotation of the reaction mixture was measured to determine the extent of racemization of **8**. Since K is ≥199 at 50 °C, the amount of **7** present was ≤0.5%, and any optically active **7** present made a negligible contribution to the observed rotation. Furthermore, use of a hydrocarbon internal standard in a control analyzed by GLC demonstrated that under the conditions of run 16, >99% of the starting material **8** was present at the end of the reaction period. On preparative GLC the isolated product in runs 16 and 17 yielded **8**, which was analyzed for deuterium content by ^{1}H NMR.

Other Base-Catalyzed Isomerizations of Imine 7 to 8. Table V summarizes isomerizations of **7** to **8** in pyridine (runs 18-21), dimethyl-d_6 sulfoxide (Me_2SO-d_6, runs 22-24), and HMPA (run 25). In all runs but 20, 21, and 24, 1,4-diazabicyclo[2.2.2]octane (Dabco) was employed as base.

With the procedures used for runs 1-12 each reaction mixture was prepared and sealed in a tube. After the reaction period, the tube was opened, and the extent of isomerization was determined by ^{1}H NMR analysis. For runs 22-25 the analysis procedure was that of runs 1-12, and for runs 18-21 in pyridine, electronic integration of the singlet for the vinyl

Table II. DBN-Catalyzed Isomerizations of **7** to **8**

run	substrate nature	substrate concn, M	solvent[a]	DBN concn, M	t, °C[b]	time, h	% product **8**[c]
3	(−)-**7**-H	0.40	$(CH_3)_3COH$	0.50	25.0	332	32
4	(−)-**7**-H	0.40	$(CH_3)_3COH$	0.50	50.0	67	44
5	(−)-**7**-H	0.40	$(CH_3)_3COH$	0.50	50.0	88	53
6	(−)-**7**-H	0.40	$(CH_3)_3COD$	0.52	50.0	64	48
7	(−)-**7**-H	0.41	$(CH_3)_3COD$	1.08	50.0	36	66
8	(−)-**7**-H	0.42	$(CH_3)_3COD$	0.49[d]	50.0	49	26
9	(−)-**7**-H	0.40	$(CH_3)_3COD$	0.52	25.0	499	43
10	(±)-**7**-D[e]	0.43	$(CH_3)_3COH$	0.38	50.0	238	24
11	(±)-**7**-D[e]	0.39	$(CH_3)_3COH$	0.51	50.0	332	49
12	(±)-**7**-D[e]	0.41	$(CH_3)_3COD$	0.49	50.0	258	25

[a]The $(CH_3)_3COD$ of runs 6–9 and 12 contained 0.98 atom of D per molecule by ^1H NMR analysis. [b]±0.1. [c]Of the **7**–**8** mixture determined by ^1H NMR analysis of the reaction solution, ±3. [d]Solution also contained 0.003 M DBN·HI. [e]0.976 atom of D per molecule at the benzyl position by ^1H NMR analysis.

Table III. Rate Constants and Stereochemical and Isotopic Exchange Data for Isomerizations of **7** to **8**

	run 3	4	5	6	7	8	9	10	11	12
isomerization rate constants										
$k_i \times 10^6$, s^{-1}	0.33 ± 0.06	2.4 ± 0.4	2.4 ± 0.3	2.9 ± 0.4	8.35	1.74	0.35	0.32	0.56	0.31
$k_i' \times 10^6$, L mol^{-1} s^{-1}	0.66 ± 0.12	4.8 ± 0.7	4.8 ± 0.7	5.5 ± 0.8	7.73	3.55	0.67	0.84	1.10	0.64
initial rotation of **7**,[a] deg	−91.2 ± 0.5[b]	−91.2 ± 0.5[b]	−91.2 ± 0.5[b]	−91.2 ± 0.5[b]	−79.5 ± 0.5[c]	−87.0 ± 0.4[d]	−91.2 ± 0.5[b]			
recovered **7**										
rotation,[a] deg	−72.4 ± 1.3[e]	−66.8 ± 1.0[f]	−58.2 ± 1.0[g]	−59.9 ± 3.0[h]	−45.9 ± 1.0[i]	−71.6 ± 1.0[j]	−63.9 ± 1.0			
% racemization	20.7	26.8	36.2	34.3	42.3	17.7	29.9			
% of 1 atom of D[k]				9.9	13.6	5.6	7.4	94.4	93.1	
racemization rate constants for **7**										
$k_\alpha \times 10^6$, s^{-1}	0.20 ± 0.01	1.29 ± 0.06	1.42 ± 0.05	1.84 ± 0.07	4.47	1.06	0.20			
$k'_\alpha \times 10^6$, L mol^{-1} s^{-1}	0.40 ± 0.02	2.58 ± 0.12	2.82 ± 0.10	3.54 ± 0.13	4.13	2.16	0.38			
k_e/k_α for **7**				0.23	0.26	0.28	0.22			
product **8**										
rotation,[a] deg	−5.6 ± 0.3[l]	−5.0 ± 0.4[m]	−5.1 ± 0.3[n]	−6.4 ± 0.4[o]	−4.2 ± 0.3[p]	−6.1 ± 0.3[q]				
% optical purity	10.5	9.4	9.6	12.0	9.1[r]	12.0				
% of 1 atom of D[s]					70	65	73	62	30	

[a]$[\alpha]_{546}^{25}$ ($CHCl_3$). [b]*c* 0.530. [c]*c* 0.820. [d]*c* 1.59, 0.595. [e]*c* 0.525. [f]*c* 0.49. [g]*c* 0.605. [h]*c* 0.580, 0.640, 0.495. [i]*c* 0.78. [j]*c* 0.860. [k]Determined by mass spectrometry, ±1.5. [l]*c* 0.570, 0.450. [m]*c* 0.67, 0.41. [n]*c* 0.850. [o]*c* 0.505, 0.375. [p]*c* 0.955. [q]*c* 1.15. [r]Corrected for lack of optical purity of starting material. [s]Determined by ^1H NMR analysis, ±3.

Table IV. DBN-Catalyzed Racemization and Exchange of **8** at 50.0 ± 0.1 °C

run	substrate nature	substrate concn, M	solvent	DBN concn, M	time, h	recovered **8** % racem	recovered **8** % of 1 atom of D[a]	k_e/k_α
15	(−)-**8**-H	0.037	$(CH_3)_3COH$	0.49	451	12.4 ± 1.6		
16	(−)-**8**-H	0.10	$(CH_3)_3COD$[b]	0.50	235	5.0 ± 0.5	30	6.7 ± 1
17	(+)-**8**-H	0.11	$(CH_3)_3COD$[b]	0.53[c]	236	4 ± 1	35	10 ± 3

[a]Determined by ^1H NMR analysis, ±3. [b]0.98 atom of D per molecule by ^1H NMR analysis. [c]Solution also contained 0.005 M DBN·

methyl group of **8** at δ 1.51 was compared to that of the overlapping patterns between δ 5.2 and 6.2 for the benzyl and ester methylene protons of **7** and the α and ester methylene protons of **8**. The reaction mixture then was hydrolyzed, and resultant **9** was analyzed polarimetrically to determine the percent racemization of **7** in the isomerization of **7** to **8**. The optical purity of **8** was determined by polarimetric analysis of resultant **10** or derived *N*-*p*-toluenesulfonyl-*tert*-leucine.

Base-Catalyzed Racemization and Exchange of 11. Tables VI and VII summarize the results of base-catalyzed racemization and exchange runs with (−)-**11**-H. Runs 26–28 were performed with potassium *tert*-butoxide solutions in *tert*-butyl alcohol and *tert*-butyl alcohol-*O*-*d* at 50–51 °C, and runs 29–32 with DBN solutions in 2:1 (v/v) HMPA–*tert*-butyl alcohol/*tert*-butyl alcohol-*O*-*d* at 175 °C. In run 32 the reaction mixture contained DBN·HI. Run 33 was made with a solution of potassium methoxide in methanol-*O*-*d* at 100 °C.

Each reaction mixture was prepared in a volumetric flask. Then in runs 26–32 the optical rotation of the resultant mixture was measured, and in each run the appropriate number of glass tubes were filled, degassed, and sealed under vacuum. After the appropriate period in the constant-temperature bath, each tube was opened, and in runs 26–32 the optical rotation of the reaction mixture was measured before **11** was isolated. Purified **11** was analyzed polarimetrically in run 33 and for deuterium by mass spectrometry in runs 26–32 and by ^1H NMR in run 33.

Pseudo-first-order (base concentration remained constant) rate constants were calculated as appropriate for racemization and exchange for multipoint runs 26–31 by a least-squares fit of the experimental data. One-point pseudo-first-order rate constants were calculated for runs 32 and 33, and derived second-order rate constants for all runs with **11** are compiled in Table VII.

Controls demonstrated that **11** undergoes neither racemization nor isotopic exchange without added base in *tert*-butyl alcohol at 50 °C or in HMPA–*tert*-butyl alcohol at 175 °C.

Table V. Dabco-Catalyzed Isomerizations of **7** to **8**

run	substrate nature	substrate concn, M	solvent	Dabco concn, M	t, °C[a]	time, h	recovered starting material 7 % racem[b]	product 8 %[c]	product 8 % optical purity[d]
18	(−)-**7**-H	0.51	pyridine	0.51	101.4	112.5	69	72	16
19	(±)-**7**-H	0.40	pyridine	0.38	100	189		80	
20	(±)-**7**-H	0.25	pyridine	no base	98	64.5		0	
21	(±)-**7**-H	0.25	pyridine	no base	150	88.5		70	
22	(−)-**7**-H	0.51	Me_2SO-d_6	0.50	101.4	15	42	33	23
23	(±)-**7**-H	0.49	Me_2SO-d_6	0.57	75.0	87.3		38	
24	(±)-**7**-H	0.47	Me_2SO-d_6	no base	100	121		0	
25	(±)-**7**-H	0.19	HMPA	0.39	99.0	16.5		30	

[a] For runs 18, 20, and 22, ±0.4; runs 19, 21, and 24, ±2; runs 23 and 25, ±0.2. [b] Determined by analysis of derived **9**. [c] Of the **7**–**8** mixture determined by ^{1}H NMR analysis of the reaction solution; ±8 for runs 19 and 21 and ±3 for others. [d] For run 18 determined by analysis of derived *N*-*p*-toluenesulfonyl-*tert*-leucine, and for run 22 by analysis of derived **10**.

Table VI. Base-Catalyzed Racemization and Exchange of (−)-**11**-H

run	(−)-**11** concn, M	solvent	base nature	base concn, M	t, °C[a]	time, h	recovered **11** % racem	recovered **11** % of 1 atom of D[b]
26	0.034	$(CH_3)_3COH$	$(CH_3)_3COK$	0.50	50.7	48.0	87	
27	0.077	$(CH_3)_3COD$[c]	$(CH_3)_3COK$	0.38	50.0	94.5		93
28	0.038	$(CH_3)_3COD$[c]	$(CH_3)_3COK$	0.14	50.7	47.4	74	63
29	0.037	HMPA-$(CH_3)_3COH$[d]	DBN	0.56	175.0	334	61.5	
30	0.045	HMPA-$(CH_3)_3COD$[d,e]	DBN	1.03	175.0	66	62.8	31.4
31	0.100	HMPA-$(CH_3)_3COD$[c,d]	DBN	0.56	175.0	146	82.3	53.4
32	0.117	HMPA-$(CH_3)_3COD$[c,d]	DBN[f]	0.49	175.0	19	23.4	11.5
33	0.33	CH_3OD[g]	CH_3OK	0.15	100.0	14	11	13

[a] ±0.1. [b] For run 33 by ^{1}H NMR analysis and for others by mass spectrometry. [c] 0.98 atom of D per molecule by ^{1}H NMR analysis. [d] 2:1 (v/v) HMPA–*tert*-butyl alcohol. [e] 0.92 atom of D per molecule by ^{1}H NMR analysis. [f] Solution also contained 0.005 M DBN·HI. [g] 0.99 atom of D per molecule by ^{1}H NMR analysis.

Table VII. Rate Constants for Racemization and Exchange of (−)-**11**-H

run	no. of points[a]	rate constants × 10^6, L mol^{-1} s^{-1} k'_α[b]	k'_e[b]	k_e/k_α
26	8	24.8 ± 3.0		
27	7		31.8 ± 1.6	
28	7	57.5 ± 1.3	43.1 ± 0.9	0.75
29	8	1.5 ± 0.1		
30	3	4.00 ± 0.13	1.48 ± 0.12	0.37
31	7	5.89 ± 0.45	2.46 ± 0.18	0.42
32	1	7.98	3.65	0.46
33	1	15.5	18.4	1

[a] Taken during the reaction periods given in Table VI. [b] Second-order rate constants from a least-squares fit of experimental data, ± two standard deviation units; correlation coefficients ranged from a low of 0.9608 to a high of 0.9997.

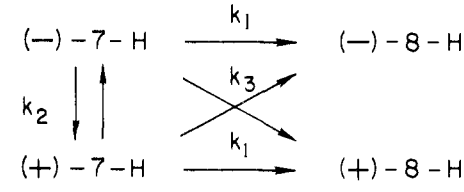
In addition, use of a hydrocarbon internal standard in controls demonstrated that under the conditions of runs 28 and 31, 96 and 93% of **11**, respectively, could be recovered.

Discussion

Stereochemical Course of the Base-Catalyzed Isomerization of 7 to 8. In runs 3–8, recovered **8** was optically active, so asymmetric induction indeed occurred in the DBN-catalyzed isomerization of **7** to **8** in *tert*-butyl alcohol and *tert*-butyl alcohol-*O*-*d*. Likewise, asymmetric induction occurred in the Dabco-catalyzed isomerizations of **7** to **8** in pyridine and Me_2SO-d_6, runs 18 and 22, respectively. In each of the above runs (−)-**7** gave (−)-**8** (eq 3).

For a given run, the stereospecificity of the isomerization of **7** to **8** could not be determined simply by comparison of the rotation of isolated **8** with that of optically pure material because **7** underwent racemization in addition to isomerization

Chart I



at a comparable rate, i.e., $k_\alpha = 1.29 \times 10^{-6}$ s^{-1} and $k_i = 2.4 \times 10^{-6}$ s^{-1} for (−)-**7**-H in run 4. Such a comparison gives a minimal and time-dependent value for the stereospecificity. Therefore, for stereochemical analysis of runs 3, 4, and 5 of Tables II and III and runs 18 and 22 of Table V, the kinetic scheme of Chart I was used, which takes into account the competing racemization of (−)-**7**-H. Equations have been developed[8b] which give the concentrations of (−)-**7**-H, (+)-**7**-H, (−)-**8**-H, and (+)-**8**-H in terms of time (t) and pseudo-first-order rate constants k_1, k_2, and k_3 for the indicated processes; the initial conditions of [(−)-**7**-H] = 1 and [(+)-**7**-H], [(−)-**8**-H], and [(+)-**8**-H] = 0 were incorporated. Subtraction of the equation for (+)-**8**-H from that for (−)-**8**-H gives[8b]

$$k_1 - k_3 = \frac{([(-)\text{-}\mathbf{8}\text{-H}] - [(+)\text{-}\mathbf{8}\text{-H}])(k_1 + 2k_2 + k_3)}{1 - e^{-(k_1+2k_2+k_3)t}} \quad (4)$$

For each of runs 3, 4, 5, 18, and 22 at time t, concentrations [(−)-**8**-H] and [(+)-**8**-H] were calculated using the percent conversion of **7** to **8** and the optical purity of recovered **8**. One-point pseudo-first-order rate constants for isomerization of **7** to **8** and for racemization of **7**, k_i and k_α, respectively, are listed in Table III. Since $k_i = (k_1 + k_3)$ and $k_\alpha = 2k_2$, $k_1 - k_3$ can be calculated directly. Combination of the values of $(k_1 + k_3)$ and $(k_1 - k_3)$ yielded k_1 and k_3. Thus, k_1, k_2, and k_3 were calculated for runs 3, 4, 5, 18, and 22 and are listed in Table VIII. The ratio $(k_1 - k_3)/(k_1 + k_3) \times 100$ represents

Table VIII. One-Point Pseudo-First-Order Rate Constants That Represent the Stereochemical Course of the Base-Catalyzed Isomerization of **7** to **8**

process	schematic designation	$k \times 10^6$, s^{-1} run 3	run 4	run 5	run 18	run 22
(−)-**7** → (−)-**8** (+)-**7** → (+)-**8**	k_1	0.18	1.3	1.3	2.0	4.8
(−)-**7** → (+)-**7** (+)-**7** → (−)-**7**	k_2	0.10	0.64	0.71	1.4	5.0
(−)-**7** → (+)-**8** (+)-**7** → (−)-**8**	k_3	0.14	1.1	1.1	1.2	2.6
net stereospecificity of **7** → **8**	$(k_1 - k_3)/(k_1 + k_3) \times 100$	12	11	12	24	29

the net stereospecificity of the isomerization, and values were calculated and are listed in Table VIII also.

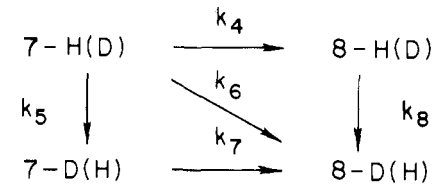
The above analysis of Chart I includes the assumptions that racemization of **8** and return of **8** to **7** are negligible. The latter assumption is justified for runs 4 and 5 since the equilibrium constant, K, is ≥199 at 50 °C, and since K is almost certainly higher valued at 25 °C, the assumption is justified for run 3 at 25 °C also. The value of K at 101 °C was not determined, but it is most likely still large enough (>∼50) to justify the neglect of the return of **8** to **7** in runs 18 and 22. In the similar **3**–**4** system, K = **4**/**3** decreased from ca. 50 at 25 °C to 15 at 100 °C.[8b] Under the conditions of runs 4 and 5, $k_\alpha' = 1.66 \times 10^{-7}$ L mol^{-1} s^{-1} for the racemization of **8** (from run 15) and $k_i' = 4.8 \times 10^{-6}$ L mol^{-1} s^{-1} for the isomerization of **7** to **8**. Therefore, **8** racemizes 29 times slower than **7** isomerizes to **8**, and the assumption that racemization of **8** can be neglected in runs 4 and 5 is reasonable. Data are not available for analogous comparisons of k_α' and k_i' under the conditions of runs 3, 18, and 22, and neglect of the racemization of **8** might not be justified. In this event, the percent stereospecificities listed in Table VIII for these runs would represent minimum values.

Stereochemical Course of the DBN-Catalyzed Isotopic Exchange of 7 and of 8 in *tert*-Butyl Alcohol-*O*-*d*. Runs 6–9 employed (−)-**7**-H in *tert*-butyl alcohol-*O*-*d* with DBN as catalyst. In each run after partial conversion to **8**, **7** was recovered and analyzed polarimetrically and for deuterium content at the benzyl position. One-point pseudo-first-order rate constants for racemization and exchange were calculated, k_α and k_e, respectively, k_e/k_α for each run was determined, and values are summarized in Table III. Runs 6 and 7 at 50 °C yielded k_e/k_α values of 0.23 and 0.26, respectively. In run 8 at 50 °C the reaction mixture contained 0.003 M DBN·HI, and a k_e/k_α value of 0.28 resulted. Run 9 at 25 °C provided a k_e/k_α value of 0.22. The above data indicate that in these runs isoinversion was the dominant stereochemical pathway for isotopic exchange of (−)-**7**-H at the benzyl position.[17] In run 8 the addition of DBN·HI (DBNH$^+$I$^-$) generated a pool of DBND$^+$ by exchange of DBNH$^+$ with *tert*-butyl alcohol-*O*-*d*. The fact that k_e/k_α did not change appreciably on addition of the salt indicates that the low values of k_e/k_α in runs 6 and 7 did not result simply from slow exchange of DBNH$^+$ with *tert*-butyl alcohol-*O*-*d*. The use of DBN·HI in other runs discussed below is based on the same consideration.

Runs 16 and 17 employed optically active **8**-H in *tert*-butyl alcohol-*O*-*d*–DBN at 50 °C, and in each run, after partial exchange of the α protium for deuterium, **8** was recovered and analyzed polarimetrically and for deuterium content. One-point pseudo-first-order rate constants k_α and k_e were calculated, and k_e/k_α values of 6.7 ± 1 and 10 ± 3, respectively, resulted (Table IV). The medium of run 17 but not that of 16 contained 0.005 M DBN·HI. The k_e/k_α values indicate that in these runs retention of configuration was the major stereochemical pathway for isotopic exchange of **8**-H.[17]

Intramolecularity in the DBN-Catalyzed Isomerization of 7 to 8 in *tert*-Butyl Alcohol. In runs 6–11 at 50 °C, the hydrogen isotope at the benzyl position of **7** was opposite that at the hydroxyl position of solvent. In each run recovered **8** contained both deuterium and protium at the α position; therefore, each isomerization of **7** to **8** proceeded with an intramolecular component.

Chart II



In the kinetic scheme of Chart II, 7-H(D) is starting material with either protium or deuterium at the benzyl position; 7-D(H) is starting material that has undergone isotopic exchange with the medium at the benzyl position; **8**-H(D) is product whose α position contains only the isotope present in **7**-H(D); and **8**-D(H) is product whose α position contains only the isotope present in **7**-D(H). The terms k_4, k_5, k_6, k_7, and k_8 are pseudo-first-order rate constants for the indicated processes. Each of the processes associated with k_5 and k_8 is irreversible since the solvent provides a large pool of the opposite isotope in which the exchanged isotope is effectively drowned. The neglect of return of **8** to **7** is justified since $K \geq 199$. Intramolecularity in the isomerization of **7**-H(D) to **8** is defined by the ratio $k_4/(k_4 + k_6)$.

The value of k_7 is equal to k_i for runs in which imine **7** and solvent contained the same isotopic label, and k_8 is equal to k_e for **8**-H(D). The value of the sum, $k_4 + k_5 + k_6$, can be calculated since the disappearance of **7**-H(D) is a first-order process as indicated in the equation

$$[\text{7-H(D)}] = e^{-(k_4+k_5+k_6)t} \quad (5)$$

which includes the initial condition of [7-H(D)] = 1 at time zero. The amounts of **7**-H(D) and **7**-D(H) left after time t can be determined by analysis of the deuterium content of **7** and of the extent of isomerization of **7** to **8**. In an analogous fashion, the amounts of **8**-H(D) and **8**-D(H) left after time t can be determined also.

From the concentration of **7**-D(H) at time t, the values of k_7 and $(k_4 + k_5 + k_6)$, and eq 7 derived from eq 6, the value of k_5 can be determined. Similarly, the value of k_4 can be determined from the concentration of **8**-H(D) at time t, the values of k_8 and $(k_4 + k_5 + k_6)$, and eq 9 derived from eq 8. The value of k_6 is then available by difference.

$$\frac{\text{d[7-D(H)]}}{dt} = k_5[\text{7-H(D)}] - k_7[\text{7-D(H)}] \quad (6)$$

$$[\text{7-D(H)}] = \frac{k_5}{k_7 - (k_4 + k_5 + k_6)} \times [e^{-(k_4+k_5+k_6)t} - e^{-k_7 t}] \quad (7)$$

$$\frac{d[\mathbf{8}\text{-H(D)}]}{dt} = k_4[\mathbf{7}\text{-H(D)}] - k_8[\mathbf{8}\text{-H(D)}] \quad (8)$$

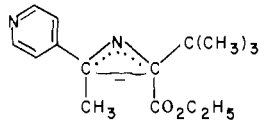
$$[\mathbf{8}\text{-H(D)}] = \frac{k_4}{k_8 - (k_4 + k_5 + k_6)}\left[e^{-(k_4+k_5+k_6)t} - e^{-k_8 t}\right] \quad (9)$$

For **7**-H in *tert*-butyl alcohol-*O*-*d* values of k_4, k_5, k_6, k_7, and k_8 are listed in Table IX. The sum $k_4 + k_5 + k_6$ was obtained from analysis of run 8, k_7 from run 12, and k_8 from run 16.

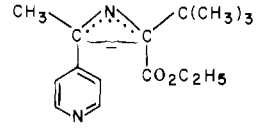
For **7**-D in *tert*-butyl alcohol the rate constant k_8 was not available owing to the lack of isotopically pure **8**-D. However, values of k_e for **8**-D in *tert*-butyl alcohol were estimated using a procedure[15b] based on k_e for **8**-H in *tert*-butyl alcohol-*O*-*d* (run 16). The sum $k_4 + k_5 + k_6$ was obtained from analysis of run 11, and k_7 from run 5. Table IX contains the results of the calculations.

The intramolecularity in the isomerization of **7**-H in *tert*-butyl alcohol-*O*-*d* was 0.37, and the estimated values in that of **7**-D in *tert*-butyl alcohol ranged from 0.46 to 0.95.

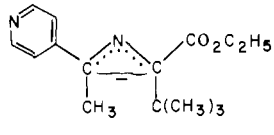
Mechanistic Description of the Isomerization of 7 to 8 in *tert*-Butyl Alcohol. Four aza-allylic carbanions, A, B, C, and D, are envisioned as possible intermediates in the isomerizations. These anions differ only in the relative positions of the 4-pyridyl, methyl, *tert*-butyl, and ethoxycarbonyl substitutents. Each one is intrinsically symmetrical, but one or more of the anions must have intervened at the intermediate stage in the base-catalyzed hydrogen transfer from an asymmetric starting material to an asymmetric product. Asymmetry can be imparted to each of the possible intermediates by ion pairing on only one side with the conjugate acid of DBN. On the basis of steric interactions, carbanion A is the most favorable intermediate because the methyl–ethoxycarbonyl interaction is of lower energy than any of the other 1,3 interactions in carbanions B, C, and D.



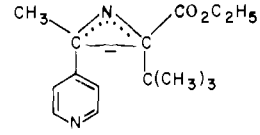
A



B



C



D

The stereospecific component for formation of (−)-**8**-H from (−)-**7**-H can be explained using carbanion A as the sole intermediate, and a mechanism is outlined in Chart III. Abstraction of the benzyl proton of (−)-**7**-H in the conformation formulated (actually N should be above the plane of the page) by DBN yields carbanion (−)-A, ion paired with $DBNH^+$ only on that face from which the proton was abstracted. Collapse to the covalent state then occurs *within* this asymmetrically ion paired carbanion to give (−)-**8**-H, the product of stereospecific isomerization, and (−)-**7**-H, starting material, the product of an invisible reaction. With respect to carbanion A, the isomerization of (−)-**7**-H to (−)-**8**-H is described as having proceeded in a cis or *suprafacial* manner, analogous to the stereochemical pathway of biological transamination.[5]

Chart III

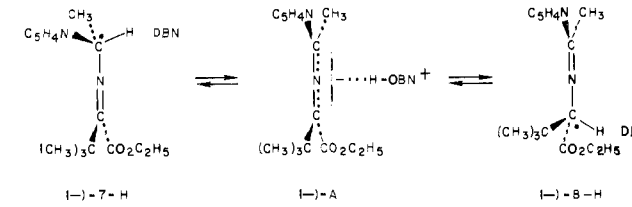
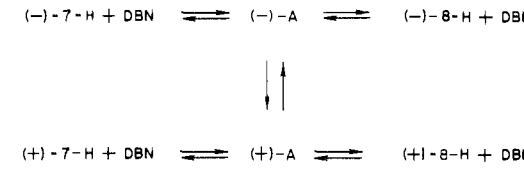


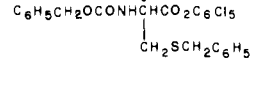
Chart IV



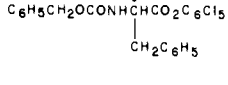
The facts that (−)-**7**-H undergoes concomitant racemization and that the isomerization is not 100% stereospecific complicate the above mechanistic description, and the overall stereochemical results can be explained by the intermediacy of carbanion A alone once again or by that of both A and B. The more likely of the two mechanistic schemes utilizes only carbanion A, and it is outlined in Chart IV. At time zero, only (−)-**7**-H is present, and its interaction with DBN yields (−)-A, which can undergo three processes: (1) collapse to (−)-**8**-H; (2) collapse to (−)-**7**-H; and (3) rearrangement to the enantiomeric ion pair (+)-A. Carbanion (+)-A can undergo three analogous processes, including collapse to (+)-**7**-H, inverted starting material, and collapse to (+)-**8**-H, the product of nonstereospecific isomerization. Collapse by protonation of A occurs only on that side ion paired to $DBNH^+$, i.e., only *within* the ion pair. Protonation by *tert*-butyl alcohol on the opposite face of A would leave $DBNH^+$ in a substrate-separated ion pair with *tert*-butoxide. A consideration of the low dielectric constant of *tert*-butyl alcohol (ϵ = 11 at 19 °C[18]) and the pK_a difference between $DBNH^+$ and *tert*-butyl alcohol (~6.5[19,22]) leads to the conclusion that formation of the substrate-separated ion pair would be a high-energy and therefore unlikely process when compared to those of Chart IV outlined above.

The rearrangement of (−)-A to (+)-A can occur by cation migration and/or carbanion rotation. Above it was noted that (−)-**7**-H undergoes DBN-catalyzed exchange and racemization in *tert*-butyl alcohol-*O*-*d* with $k_e/k_\alpha = 0.25$ (average for runs 6, 7, and 8), a value indicative of isoinversion. Therefore, at least a portion of the (−)-A to (+)-A rearrangement almost certainly proceeds by the migration of $DBNH^+$ in a conducted tour series of stages around the pyridine ring of carbanion A. An analogous conducted tour mechanism is outlined in detail below in Chart VI for the racemization and exchange of **11**.

The fact that (−)-**8**-H underwent isotopic exchange with retention of configuration in *tert*-butyl alcohol-*O*-*d*–DBN is contrary to results reported for other esters of α-amino acids in which the α-amino group is blocked. Pentachlorophenyl esters **14** and **15** gave k_e/k_α values of 0.06 and 0.03, respec-



14



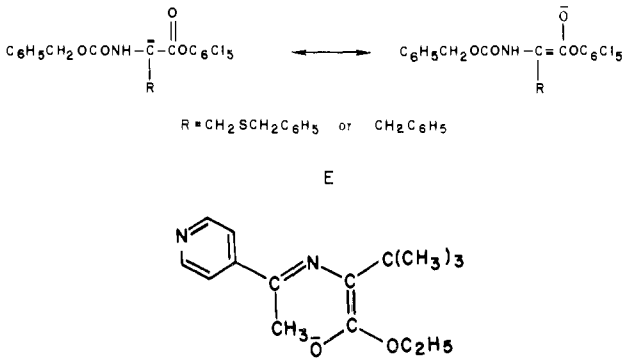
15

tively, in chloroform–methanol-*O*-*d*–triethylamine.[24] A rationalization of the isoinversion stereochemical results was not offered, but a conducted tour mechanism around the carbonyl oxygen in resonance contributor E of the intermediate carbanion is attractive. Resonance structure F of carbanion A

Table IX. One-Point Pseudo-First-Order Rate Constants for DBN-Catalyzed Isomerization of **7** to **8** and Accompanying Isotopic Exchange of **7** and **8** at 50 °C in *tert*-Butyl Alcohol

process	schematic designation	$k \times 10^6$, s^{-1}, for 7-H in $(CH_3)_3COD$[a]	7-D in $(CH_3)_3COH$[b,c] with estimated k_8 values		
isom without exchange	k_4	0.64	0.21	0.23	0.43
exchange of starting material	k_5	0.29	0.14	0.14	0.14
isom with exchange	k_6	1.1	0.25	0.23	0.023
isom of exchanged starting material	k_7	0.31[d]	2.4[e]	2.4[e]	2.4[e]
exchange of product	k_8	0.41[f]	0.27[g]	0.43[g]	1.6[g]
intramolecularity	$k_4/(k_4 + k_6)$	0.37	0.46	0.50	0.95
collapse ratio	k_5/k_6	0.26	0.56	0.61	6

[a] For run 8 (0.49 M DBN). [b] For run 11 (0.51 M DBN). [c] The calculation of the sum $k_4 + k_5 + k_6$ included a correction for the 2.4% 7-H impurity in 7-D. For 7-H in $(CH_3)_3COH$, k_i was known from run 4. [d] From run 12 (0.49 M DBN). [e] From run 5 (0.50 M DBN), corrected to run 11 conditions. [f] From run 16 (0.50 M DBN), corrected to run 7 conditions. [g] Estimations based on k_e for 8-H in run 16, corrected to run 11 conditions.

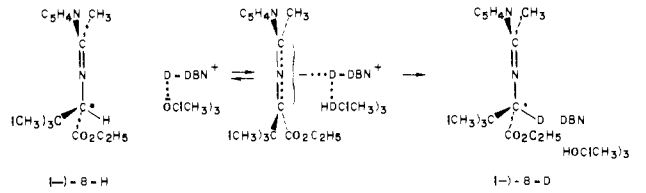


provides a pathway for isoinversion of **8** analogous to that for **14** and **15**. However, examination of a molecular model (CPK) of F indicates that maximum orbital overlap within the extensively conjugated system is prevented by a serious steric interaction of the carbonyl oxygen with the benzyl methyl group. Therefore, it appears that the negative charge of A can be delocalized into either the pyridyl substituted aza-allylic system or into the ethoxycarbonyl group but not simultaneously into both in an efficient fashion. If the extent of delocalization into the former is greater than that into the latter, then $k_e/k_\alpha > 1$ as observed is not unreasonable. The lack of significant charge delocalization into the ethoxycarbonyl group would make a conducted tour mechanism unfavorable for the isotopic exchange of **8** and might ultimately be responsible for the moderate stereospecificity observed in the **7** to **8** isomerization. Protonation at oxygen of F would give a symmetrical enol intermediate which would subsequently yield (±)-**8**.

A mechanism for the isotopic exchange of (−)-**8**-H with retention of configuration in *tert*-butyl alcohol-*O*-*d* is given in Chart V. Initial proton abstraction by a $DBND^+$–*tert*-butoxide ion pair gives carbanion A in which charge is delocalized into the pyridyl substituted aza-allylic system but much less into the ethoxycarbonyl group.[25] Furthermore, the carbanion is ion paired only on that side from which abstraction occurred, and its collapse gives **8**-D of retained configuration. Reaction mechanisms similar to that of Chart V have been proposed to rationalize retention as the dominant stereochemical course of isotopic exchange catalyzed by tertiary amines in *tert*-butyl alcohol.[26] In addition, it should be noted that the contact ion pair used in Chart V may also be the active base in the isomerization of **7** to **8**.

Overall, the DBN-catalyzed isotopic exchange of **8**-H in *tert*-butyl alcohol-*O*-*d* proceeded with retention of configuration in spite of the tendencies of charge-delocalizing amine bases to catalyze[27] and of esters of α-amino acid derivatives to undergo[24] isoinversion processes. The unexpected retention with **8**-H is consistent with a large influence of steric crowding on the course of the reaction. Intramolecularity in the **7** to **8** isomerization results when the hydrogen isotope abstracted from **7** by DBN (Chart III) or $DBNH(D)^+$–*tert*-butoxide ion pair (Chart V) is not lost by exchange with the pool of opposite isotope in the solvent.

Chart V



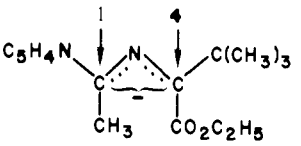
Stereochemical Course of the Base-Catalyzed Isomerization of 7 to 8 in Other Media. In isomerizations of **7** to **8** catalyzed by Dabco in pyridine and Me_2SO-d_6, runs 18 and 22, respectively, moderate asymmetric induction occurred. In each run (−)-**7**-H gave (−)-**8**-H, and since (−)-**7**-H underwent racemization concomitant with isomerization, the net stereospecificity was calculated using Chart I and eq 4, and results are contained in Table VIII. For runs 18 and 22, mechanisms analogous to that of Chart III can be formulated for the stereospecific isomerizations of (−)-**7**-H to (−)-**8**-H.

Runs with Dabco were performed in an attempt to obtain greater stereospecificities than those with DBN in *tert*-butyl alcohol. In the prior discussion of Chart IV it was proposed that reorganization of ion pair (−)-A to (+)-A was largely responsible for the significant nonstereospecific component in the isomerization of **7** to **8**. This reorganization is dependent upon charge separation within the ion pair, which in turn is dependent upon extensive charge delocalization both in carbanion A and in $DBNH^+$. The charge in the conjugate acid of Dabco ($DabcoH^+$) is localized, unlike that in $DBNH^+$, and as a result there would be less charge separation within the ion pair composed of A and $DabcoH^+$, and less reorganization should occur. Unfortunately, Dabco is a much weaker base than DBN and could not catalyze the **7** to **8** isomerization in *tert*-butyl alcohol at a convenient temperature.[28] Therefore, it was necessary to use other solvents. The net stereospecificities of 24 and 29% obtained in pyridine, run 18, and Me_2SO-d_6, run 22, respectively, are both higher by at least a factor of 2 than those obtained with DBN in *tert*-butyl alcohol. Interestingly, a relatively high net stereospecificity was obtained with Dabco in Me_2SO-d_6 even though this high dielectric constant medium (46.68 at 25 °C[29]) promotes ion pair disso-

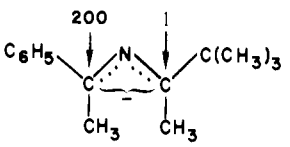
ciation. Therefore, the expected stereospecificity enhancement associated with substitution of Dabco for DBN more than compensated for the expected stereospecificity diminution associated with substitution of Me_2SO-d_6 for *tert*-butyl alcohol.

Intersystem Comparison of Collapse Ratios. For runs with **7**-H in *tert*-butyl alcohol-*O*-*d*, the ratio of the rate constant for isotopic exchange which gives **7**-D to that of isotopic exchange which gives **8**-D is the collapse ratio of the proposed intermediate carbanion A. With respect to Chart II the collapse ratio is k_5/k_6, and data are compiled in Table IX.

A comparison of collapse ratios for several allylic and aza-allylic carbanions including G has been made,[9] and carbanion A can be placed in the context of that comparison (see numbers above formulas). If it is assumed that the effect on a collapse ratio of a 4-pyridyl group is comparable to that of a phenyl group, then the dramatic change in collapse ratio on going from G to A is due primarily to electronic effects associated with the



A



G

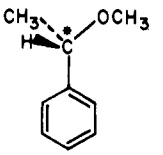
substitution of ethoxycarbonyl for methyl. Steric effects alone would not be expected to be responsible for such a change in the collapse ratio since methyl and ethoxycarbonyl have comparable *A* values, 1.7 and 1.1, respectively.[30]

Summary for the 7–8 System. The structural similarities as outlined above between imines **7** and **8** and their biological analogues provide similar reaction pathways. The biological[5] and **7**–**8** systems both possess a stereospecific and intramolecular pathway for a *suprafacial* base-catalyzed 1,3-proton transfer across an aza-allylic carbanion. Furthermore, both possess a stereospecific route for an isotopic exchange reaction (with retention of configuration) between the α hydrogen of a derivative of an amino acid and the medium. The model differs from the biological system by providing competing stereochemical and isotope exchange reaction pathways.

Stereochemical Course of the Base-Catalyzed Racemization and Exchange of 11. For the potassium *tert*-butoxide catalyzed racemization and exchange of (−)-**11**-H in *tert*-butyl alcohol-*O*-*d* at 50.7 °C, k_e/k_α = 0.75 (run 28). For the same processes catalyzed by DBN in HMPA–*tert*-butyl alcohol-*O*-*d* at 175 °C, k_e/k_α = 0.40 (average of runs 30 and 31), and with added DBN·HI k_e/k_α = 0.46 (run 32). In methanol-*O*-*d* (−)-**11**-H underwent potassium methoxide catalyzed racemization and exchange with k_e/k_α = 1 (run 33).

The k_e/k_α values indicate that in HMPA–*tert*-butyl alcohol-*O*-*d* there is definitely, and in *tert*-butyl alcohol-*O*-*d* there is most likely, an isoinversion mechanistic component in the racemization reactions of (−)-**11**-H. In the isoinversion pathway the proton abstracted by base from (−)-**11**-H is transported within the conjugate acid from one side of the carbanion to the other, and collapse to the covalent state gives (+)-**11**-H. This process must compete with drowning of the proton in the deuterium pool of the surrounding medium. A mechanism for DBN-catalyzed isoinversion of (−)-**11**-H in HMPA–*tert*-butyl alcohol-*O*-*d* is given in Chart VI. The first step of an analogous mechanism for the potassium *tert*-butoxide catalyzed process is given in Chart VII. In each mechanism the ion pair is structured by a series of hydrogen-bonded intermediates, and this hypothesis is consistent with the direct observation by Hogen-Esch[31] of hydrogen-bonded carbanions that are stabilized considerably by charge delocalization.

The effects of a methoxy group and of an *N*,*N*-dimethylamino group on the stereochemical fate of a carbanion have been demonstrated to be identical.[32] In *tert*-butyl alcohol-*O*-*d*–potassium *tert*-butoxide, (−)-**16** underwent isotopic exchange with high retention of configuration ($k_e/k_\alpha \simeq 7$),[33a] and the related system 4-biphenylylmethoxyphenylmethane gave an even higher value of k_e/k_α (~33).[33b] Therefore, the dramatic difference in the behavior of (−)-**11**-H and (−)-**16** in base-catalyzed isotopic exchange reactions can be attributed to the pyridyl group. System **16**, with a phenyl instead of a



(−)-16

pyridyl group, does not contain an electronegative atom such as the pyridyl nitrogen onto which the negative charge of the derived carbanion can be distributed, and therefore its isotopic exchange cannot occur by a conducted-tour pathway. In gen-

Chart VI

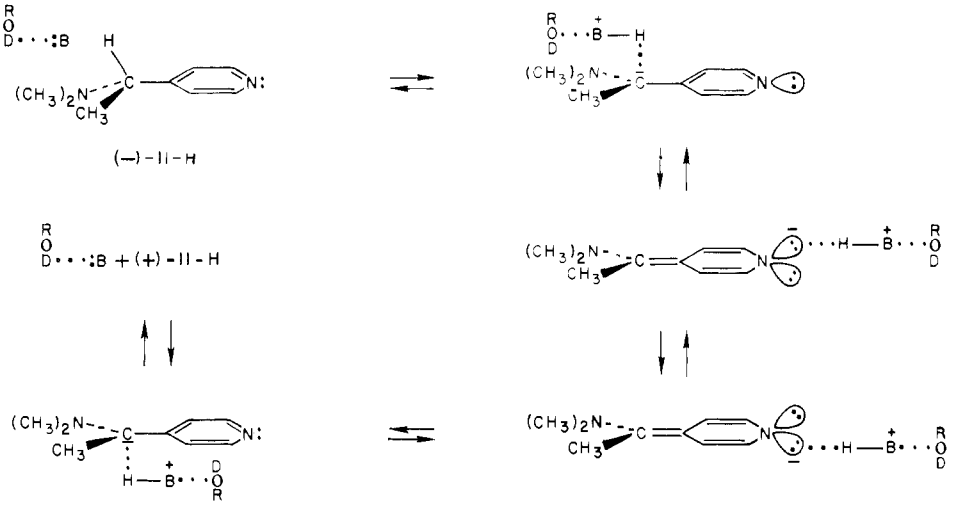
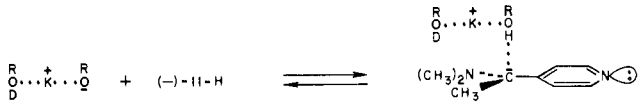


Chart VII



eral, methoxy,[33] alkyl,[27,33a,34a] alkenyl,[34] aryl,[33,34] and haloaryl[27] groups attached to carbanions generated from chiral carbon acids provide no isoinversion reaction pathway for isotopic exchange catalyzed by ordinary alkoxides or tertiary amine bases, and net retention of configuration is observed in nonpolar media such as *tert*-butyl alcohol.

The results of this study with (−)-**11**-H are consistent with past investigations which have demonstrated that functional groups capable of distributing the negative charge of carbanion intermediates onto electronegative atoms normally provide an isoinversion mechanistic pathway for base-catalyzed isotopic exchange.[26,27,35] Substituents such as nitro,[26,27,35a,b] cyano,[26,35a,c] *N,N*-dimethylcarboxamido,[26,27,35a,b,d] sulfonyl (as part of a ring system),[35e] and pentachlorophenoxycarbonyl[24] have all exhibited this property in appropriate systems and reaction media, and a conducted-tour mechanism was used as a hypothesis for most of the isoinversion results.

It should be noted, however, that even with systems that lack charge delocalizing substituents, amine bases such as DBN and pentamethylguanidine catalyze isotopic exchange with isoinversion.[27] These bases apparently derive their unusual stereochemical capabilities in isotopic exchange reactions from the same factor that results in their high base strengths, namely, extensive charge delocalization in the conjugate acids. The conjugate acids seem to form ion pairs with carbanions that undergo internal reorganization faster than intermolecular processes. Thus, it is likely that the isoinversion displayed by (−)-**11**-H in HMPA–*tert*-butyl alcohol-*O*-*d*–DBN (due primarily to the pyridyl group) was enhanced by the special character of DBN.

The k_e/k_α value of one for (−)-**11**-H in methanol-*O*-*d*–potassium methoxide indicates that isotopic exchange proceeded with complete racemization, and this stereochemical result is consistent with others obtained in this medium.[35d,36] Dissociated methoxide ion was most likely the catalytic species, and proton abstraction from (−)-**11**-H gave a carbanion which in the absence of asymmetric ion pairing collapsed to (±)-**11**-D.

A solvent isotope effect (k_D/k_H) of 2.3 was found for the potassium *tert*-butoxide catalyzed racemization of (−)-**11**-H in *tert*-butyl alcohol (runs 26 and 28), and a value of 3.9 was found for DBN catalysis of the same process in HMPA–*tert*-butyl alcohol (runs 29 and 31). The former value is similar to those obtained for other systems in the same medium,[37] and both are consistent with the fact that deuterated alcohols form weaker hydrogen bonds than do their protio counterparts.

Experimental Section

General. All melting and boiling points are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Varian A60D, T-60, and HA-100 instruments in $CDCl_3$ with tetramethylsilane (Me_4Si) as internal standard unless noted otherwise. Infrared (IR) and ultraviolet (UV) spectra were recorded on Beckman IR-5 and Cary 14 spectrophotometers, respectively. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter using a 1-dm cell thermostated at 25 °C.

Solvents and Bases. For kinetic runs *tert*-butyl alcohol was purified by distillation from CaH_2 onto Linde 4Å molecular sieves which had been activated at 350 °C for 24 h. Methanol-*O*-*d*[38a] and *tert*-butyl alcohol-*O*-*d*[38b] (each 0.99 atom of D per molecule by ^{1}H NMR) were prepared by established procedures. The preparation of solutions of potassium *tert*-butoxide in *tert*-butyl alcohol and in *tert*-butyl alcohol-*O*-*d* has been described.[39] Hexamethylphosphoramide (HMPA), tetrahydrofuran (THF), and pyridine were purified by distillation from CaH_2, $LiAlH_4$, and BaO, respectively. Distillation of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, Aldrich) from BaO yielded purified material, bp 107–108 °C (ca. 15 mm), and two sublimations of 1,4-diazabicyclo[2.2.2]octane (**D**abco, Howdry) gave purified material, mp 156.5–158 °C. Other materials were analytical reagent grade and were used without further purification. Uniformly, 4:1 (v/v) $CHCl_3$–C_2H_5OH was used as eluent in TLC analyses.

Gas–Liquid Chromatography (GLC). Analyses and preparative separations were carried out on five columns: column A, 6 ft × 1/4 in. aluminum packed with 10% KOH and 10% Carbowax 4000 on 60–80 mesh Chromosorb W NAW; column B, 6 ft × 1/4 in. aluminum packed with 10% *m*-phenyl ether (five ring) on >40 mesh Fluoropak; column C, 6 ft × 1/4 in. aluminum packed with 20% SE-30 on 80–100 mesh Chromosorb W HMDS; column D, 18 ft × 1/8 in. copper packed with 30% SE-30 on 100–120 mesh Chromosorb W DMCS NAW; and column E, 2 ft × 1/2 in. aluminum packed with 4% SE-30 on >40 mesh Fluoropak 80. The columns were used as indicated in the following gas chromatographs: Perkin-Elmer Model 154, columns A, B, and C; Perkin-Elmer Model 800, column D; and Varian Aerograph A-90-P, column E. Nitrogen was the carrier gas used with the second instrument, and helium was used with the other two.

Ion Exchange Chromatography. Dowex 50W-X8, 100–200 mesh, was prepared for use by the procedure of Wall.[40] It was washed with 6 M HCl three times, with water until the wash was pH 7, with 2 M NaOH three times, and again with water until the wash was pH 7. The resin then was poured into a column as an aqueous slurry and equilibrated with 0.2 M HCl.

Deuterium Analyses. All deuterium analyses by mass spectrometry were performed on an Associated Electronics Industries, Ltd., Model MS-9 mass spectrometer. For **7**, direct insertion was used with an ionizing voltage of 14 eV, a source temperature of 80–105 °C, an accelerating voltage of 8 kV, a trap current of 20 μA, and the ion repeller at 0 V. The calculation of deuterium content was based on relative intensities within the molecular ion (M) group. A ratio of (M + 1)/M = 0.149 was used to correct the intensity of the molecular ion of **7**-D for the M + 1 contribution of **7**-H. At high deuterium contents (>0.9 atom of excess D per molecule) the analysis was subject to error owing to the presence of small M − 1 peaks (1–2% of M). Thus, the M − 1 peak of **7**-D at high deuterium contents significantly increased the intensity of the peak at *m/e* 262 associated with M of **7**-H. This error affected only the analyses of **7** in runs 10 and 11 and not any of the conclusions of this study.

For analyses of **11**, direct insertion was used with an ionizing voltage of 12 eV and a source temperature of 60–90 °C, and other instrumental conditions were the same as those used for **7**. The calculation of deuterium content was based on at least eight scans of the molecular ion group. A ratio of (M + 1)/M = 0.098 was used to correct the intensity of the molecular ion of **11**-D for the M + 1 contribution of **11**-H. The average deviation was <1.5%.

The deuterium content of **8** could not be determined by mass spectrometry because of the complexity of the molecular ion group but was analyzed by ^{1}H NMR. Although the singlet for the α hydrogen (exchangeable) and the quartet for the methylene group overlapped at 60 MHz (Varian A-60D), they did not at 100 MHz (Varian HA-100), and analysis involved these two signals. In 0.1 mL of $CDCl_3$ containing 3 drops of Me_4Si, 15–30 mg of **8** was dissolved, and the sample was analyzed in the field sweep mode at ambient probe temperature with a sweep width of 100 Hz. With a Varian C-1024 time-averaging computer 5–12 scans were accumulated to yield a spectrum which was integrated with a K & E Model 620015 compensating polar planimeter.

Limits of Error. Limits of error for rate constants resulting from computer least-squares analyses are reported as two standard deviations. Otherwise, they were derived by the total differentiation method[41] using the following limits of error for individual experimental data: ±3% for ^{1}H NMR analyses of **7**–**8** mixtures; ±3 and ±1.5% for ^{1}H NMR and mass spectral deuterium analyses, respectively; and ±2% for specific rotations. These limits represent average deviations for multiple analyses.

Methyl 4-Pyridyl Ketone (13).[13] In a dry system under nitrogen 66 g (3.0 mol) of CH_3Li in the form of a 2.0 M ether solution (Alfa) was added with stirring during 3 h to a solution of 312 g (3.00 mol) of recrystallized 4-cyanopyridine (Aldrich) in 2.0 L of anhydrous ether

held at −20 °C. Then 1.5 L of 4.7 M HCl was added carefully, and the resulting mixture was stirred at 25 °C for 2 h. The aqueous layer was adjusted to pH 8 with solid K_2CO_3, separated from the ether layer, and extracted three times with 500-mL portions of ether. The extracts were combined with the original ether layer and dried over Na_2SO_4. Rotary evaporation of ether left impure material which was fractionally distilled through a 3-ft Vigreux column to give 186.9 g (52%) of **13**: bp 109–114 °C (20 mm) (lit.[13] 212–214 °C); ^{1}H NMR δ 2.62 (s, 3 H, CH_3), 7.76 and 8.84 (AA′XX′, $J_{AX} + J_{AX'} = 6.0$ Hz, 4 H, aromatic); IR ($CHCl_3$) 1695 cm^{-1} (C=O).

Anal. Calcd for C_7H_7NO: C, 69.41; H, 5.83. Found: C, 69.52; H, 5.96.

α-(4-Pyridyl)ethylamine (9-H).[42] Hydrogenation of 492 g (3.62 mol) of methyl 4-pyridyl ketoxime, mp 152–154 °C,[43] following an established procedure[44] yielded 310 g (70%) of **9**-H, bp 124–140 °C (30 mm), which was redistilled through a 75-cm gold spinning band column to give a center cut: bp 90–92 °C (20 mm) (lit.[42b] 110–112 °C (21 mm)); ^{1}H NMR δ 1.31 (d, $J = 7.0$ Hz, 3 H, CH_3), 1.57 (s, 2 H, NH_2), 4.03 (q, $J = 7.0$ Hz, 1 H, benzyl), 7.24 and 8.49 (AA′XX′, $J_{AX} + J_{AX'} = 6.0$ Hz, 4 H, aromatic). By GLC analysis (column A, 132 °C) this material contained less than 1% impurities.

Resolution of α-(4-Pyridyl)ethylamine (9-H). The procedure used[15c] was similar to a reported method.[10] From 210 g (1.65 mol) of **9**-H and 495 g (3.30 mol) of *d*-tartaric acid was obtained 167 g of crystalline salt, $[\alpha]^{25}_{546}$ +18.6° (*c* 2.02, H_2O) (lit.[10] $[\alpha]^{25}_{D}$ +17.7° (*c* 8.19, H_2O)). To a hot solution of 11.3 g of this salt in 40 mL of H_2O was added 15 g of $K_2CO_3 \cdot 1.5H_2O$. The resulting solution was extracted five times with CH_2Cl_2 and then continuously for 24 h with the same solvent. The combined extracts were dried over Na_2SO_4, and rotary evaporation left 5.1 g of an oil which was purified by GLC (column A, 135 °C) to give (−)-**9**-H, $[\alpha]^{25}_{578}$ −26.6°, $[\alpha]^{25}_{546}$ −31.5°, $[\alpha]^{25}_{436}$ −53.5°, $[\alpha]^{25}_{365}$ −88.0° (*c* 1.53, absolute C_2H_5OH) (lit.[10] $[\alpha]^{25}_{D}$ −28.0° (*c* 7.89, absolute C_2H_5OH)).

Anal. Calcd for $C_7H_{10}N_2$: C, 68.82; H, 8.25. Found: C, 68.77; H, 8.41.

The resolution of **9**-H was also attempted with *d*-camphoric acid,[15d] but optically pure material was not obtained. The initial crystallization from aqueous ethanol yielded material which was recrystallized six times from the same solvent. Decomposition of the resulting salt using a method similar to that above gave ca. 85% optically pure (+)-**9**-H, $[\alpha]^{25}_{546}$ +26.3° (*c* 0.83, absolute C_2H_5OH).

α-(4-Pyridyl)ethylamine-α-*d* (9-D). Under nitrogen in dry glassware a solution of 7.34 g (60.2 mmol) of α-(4-pyridyl)ethylamine, bp 107–108 °C (ca. 17 mm), and 0.671 g of paraformaldehyde in 150 mL of D_2O (99.4% **D**) was stirred at 25 °C for 5 min. Then 8.3 g (84 mmol) of trifluoroacetic acid-*O*-*d* (98.9% D) was added, and the resulting solution, pH 4–5, was refluxed for 60 h, adjusted to pH 10 with K_2CO_3, and continuously extracted with CH_2Cl_2 for 48 h. The extracts were dried over Na_2SO_4, and rotary evaporation gave 8.7 g of an oil, which was distilled to yield 5.1 g (68%) of **9**-D, bp 112–113 °C (ca. 19 mm). By ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as internal standard this material contained 0.976 atom of D per molecule at the benzyl position, and by GLC analysis (column A, 135 °C) it was homogeneous.

Anal. Calcd for $C_7H_9DN_2$: C, 68.26; H + D, 9.00. Found: C, 68.42; H + D, 8.72.

Ethyl Trimethylpyruvate (12). A modification of an established procedure[45] was used to prepare trimethylpyruvic acid. To a stirred solution of 154.0 g (0.974 mol) of $KMnO_4$ and 50.0 g (1.25 mol) of NaOH in 1.2 L of H_2O at 0 °C was added a slurry of 50.0 g (0.50 mol) of methyl *tert*-butyl ketone (Matheson Coleman and Bell) in 1.0 L of H_2O during 20 min. The initial reaction was very exothermic, and after the addition the mixture was stirred for 1 h at 0 °C and for 2 h at 25 °C. Two additional 50.0-g portions of methyl *tert*-butyl ketone were subjected to the same conditions, the combined reaction mixtures were filtered, and the filtrate was acidified to pH 2 with concentrated HCl and extracted four times with ether. The combined extracts were dried over Na_2SO_4, and rotary evaporation left an oil which was fractionally distilled to give 140 g (72%) of trimethylpyruvic acid: bp 66–69 °C (ca. 7 mm) (lit.[45] 85 °C (ca. 20 mm)); ^{1}H NMR δ 1.31 (s, 9 H, $(CH_3)_3C$), 10.67 (s, 1 H, OH); IR ($CHCl_3$) 1720 and 1785 cm^{-1}.

Anal. Calcd for $C_6H_{10}O_3$: C, 55.37; H, 7.75. Found: C, 55.66; H, 7.89.

A solution of 10.0 g (76.9 mmol) of trimethylpyruvic acid, 4.60 g (0.100 mol) of absolute C_2H_5OH, and 0.57 g of *p*-toluenesulfonic acid in 100 mL of anhydrous benzene was refluxed overnight under a Soxhlet extractor containing a paper thimble filled with 40 g of non-indicating Drierite. The reaction mixture was washed with 50 mL of saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and rotary evaporated to leave 11.0 g of an oil which was fractionally distilled to give 8.6 g (71%) of **12**: bp 74–77 °C (ca. 22 mm); ^{1}H NMR δ 1.26 (s, 9 H, $(CH_3)_3C$), 1.35 (t, $J = 7.1$ Hz, 3 H, CH_3), 4.34 (q, $J = 7.1$ Hz, 2 H, OCH_2). By GLC analysis (column B, 120 °C) this material was homogeneous, and preparative GLC gave an analytical sample.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.85; H, 9.05.

(−)-*N*-(α-Ethoxycarbonylneopentylidene)-α-(4-pyridyl)ethylamine [(−)-7-H]. Under dry conditions in a nitrogen atmosphere a mixture of 2.60 g (21.3 mmol) of (−)-α-(4-pyridyl)ethylamine, $[\alpha]^{25}_{546}$ −31.8° (*c* 0.720, absolute C_2H_5OH), 4.04 g (25.6 mmol) of freshly distilled **12**, 45 g of Linde 4Å molecular sieves activated at 450 °C for 48 h, and 50 mL of THF was refluxed for 40 h. The sieves were removed by filtration and washed with 5% CH_3OH in CH_2Cl_2. Filtrate and washings were combined and rotary evaporation left 6.3 g of material which was distilled (Kugelrohr) to give 2.85 g (51%) of (−)-**7**-H, bp 95–100 °C (0.02 mm), that contained <1.5% of **9** as the only contaminant by GLC analysis (column E, 125 °C). Purification of this material by GLC (column E) gave (−)-**7**-H: $[\alpha]^{25}_{589}$ −77.4°, $[\alpha]^{25}_{546}$ −93.3°, $[\alpha]^{25}_{436}$ −169°, $[\alpha]^{25}_{365}$ −287° (*c* 0.570, absolute C_2H_5OH); ^{1}H NMR δ 1.21 (s, 9 H, $(CH_3)_3C$), 1.30 (t, $J = 7.3$ Hz, 3 H, ester CH_3), 1.41 (d, $J = 6.5$ Hz, 3 H, benzyl CH_3), 4.07 (q, $J = 6.5$ Hz, 1 H, benzyl H), 4.31 (q, $J = 7.3$ Hz, 2 H, CH_2), 7.29 and 8.54 (AA′XX′, $J_{AX} + J_{AX'} = 6.2$ Hz, 4 H, aromatic); IR ($CHCl_3$) 1720 (C=O), 1645 cm^{-1} (C=N); UV (cyclohexane) 256 nm (ϵ 2100), 325 (170).

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45. Found: C, 68.83; H, 8.35.

***N*-(α-Ethoxycarbonylneopentylidene)-α-(4-pyridyl)ethylamine-α-*d* (7-D).** With the above procedure for (−)-**7**-H, 0.523 g (4.30 mmol) of **9**-D (0.976 atom of D per molecule at benzyl position) and 0.946 g (5.98 mmol) of **12** gave 0.462 g (41%) of distilled (Kugelrohr) **7**-D which contained <2% of **9** as the only impurity by GLC analysis (column E, 130 °C). Preparative GLC (column E) gave analytical and mass spectral samples. By mass spectral analysis **7**-D contained >0.95 atom of excess D per molecule, but a more accurate determination was precluded by an intense M − 1 peak (*m/e* 262). The ^{1}H NMR spectrum of **7**-D was identical with that of **7**-H except for the total absence of the benzyl proton quartet and the appearance of the benzyl methyl signal as a broad (D coupling) instead of a clean doublet.

Anal. Calcd for $C_{15}H_{21}DN_2O_2$: C, 68.41; H + D, 8.80. Found: C, 68.61; H + D, 8.45.

***tert*-Leucine.**[46] A mixture of 70.0 g (0.538 mol) of trimethylpyruvic acid, 55.3 g (0.796 mol) of hydroxylamine hydrochloride, 65.7 g (0.475 mol) of K_2CO_3, and 150 mL of H_2O gave[47] 72.0 g (92%) of crude trimethylpyruvic acid oxime, mp 113–115 °C dec, and sublimation at 70 °C (0.04 mm) yielded analytically pure material, mp 118.5–119.5 °C dec (lit.[47] 116–117 °C dec).

Anal. Calcd for $C_6H_{11}NO_3$: C, 49.65; H, 7.64. Found: C, 49.78; H, 7.79.

To a stirred mixture of aluminum amalgam freshly prepared from 67.5 g (2.50 mol) of purified aluminum foil, 400 mL of 95% C_2H_5OH, and 500 mL of H_2O at 0 °C was added a solution of 79.0 g (0.545 mol) of the above oxime in 150 mL of 95% C_2H_5OH during 30 min. The mixture was stirred for 4 h at 0 °C and for 20 h at 25 °C. After the addition of 50 g of Celite, the mixture was filtered, and the solid residue was washed with H_2O. The washings were combined with the filtrate and evaporated in vacuo to leave 47.0 g (66%) of crude *tert*-leucine. Recrystallization of a portion of this material from 95% C_2H_5OH gave analytically pure *tert*-leucine, mp 311–313 °C dec (sealed tube).

Anal. Calcd for $C_6H_{13}NO_2$: C, 54.95; H, 9.99. Found: C, 54.90; H, 9.99.

Ethyl 2-Amino-3,3-dimethylbutanoate (10). Under dry conditions 150 g of anhydrous HCl was dissolved in 600 mL of absolute C_2H_5OH at 0 °C. Then 30.0 g (0.229 mol) of *tert*-leucine was added, and the resulting solution was slowly brought to and held at reflux for 1 h, after which it was concentrated to 100 mL by distillation and added to 500 mL of H_2O. The resulting aqueous solution was adjusted to pH 8 with Na_2CO_3 and extracted five times with 300-mL portions of CH_2Cl_2. The combined extracts were dried over Na_2SO_4, and rotary evapo-

ration left an oil which was fractionally distilled to give 22.8 g (63%) of **10**, bp 74–77 °C (ca. 8 mm), that was homogeneous by GLC analysis (column A, 100 °C): ^{1}H NMR δ 0.97 (s, 9 H, $(CH_3)_3C$), 1.27 (t, J = 7.3 Hz, 3 H, CH_3), 1.46 (s, 2 H, NH_2), 3.13 (s, 1 H, CH), 4.18 (q, J = 7.3 Hz, 2 H, CH_2).

Anal. Calcd for $C_8H_{17}NO_2$: C, 60.35; H, 10.76. Found: C, 60.29; H, 10.52.

Resolution of Ethyl 2-Amino-3,3-dimethylbutanoate (10). A solution of 22.5 g (59.8 mmol) of (−)-dibenzoyl-*d*-tartaric acid monohydrate and 22.8 g (0.143 mol) of (±)-**10** in 240 mL of absolute C_2H_5OH yielded a crop of crystals at 25 °C which was recrystallized from 825 mL of 32:1 (v/v) C_2H_5OH–H_2O to give 2.0 g of hard, white needles, $[\alpha]_{546}^{25}$ −101.7° (*c* 0.68, CH_3OH). To the mother liquors from this recrystallization was added 150 mL of ether, and a crop of 5.0 g of flocculent, white needles, $[\alpha]_{546}^{25}$ −104.0° (*c* 0.89, CH_3OH), resulted which was recrystallized from 163 mL of 11.5:1 (v/v) C_2H_5OH–H_2O to give 3.9 g of white needles, $[\alpha]_{546}^{25}$ −101.6° (*c* 0.55, CH_3OH). Then 1.00 g of this last material was recrystallized from 70 mL of absolute C_2H_5OH to yield 0.811 g of fine, white needles, $[\alpha]_{546}^{25}$ −101.8° (*c* 1.00, CH_3OH), which was recrystallized twice more from absolute C_2H_5OH to give 0.390 g of crystals, $[\alpha]_{546}^{25}$ −101.7° (*c* 1.01, CH_3OH). Treatment of 0.195 g of the original crop of crystals with 20 mL of 30% aqueous $K_2CO_3 \cdot 1.5H_2O$ gave a solution which was extracted with three 20-mL portions of CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and rotary evaporated to give 50 mg of an oil which was purified by preparative GLC (column A, 100 °C) to give (+)-**10**, $[\alpha]_{546}^{25}$ 57.4° (*c* 1.02, $CHCl_3$). A second cutback of salt, $[\alpha]_{546}^{25}$ −101.6° (*c* 0.55, CH_3OH), gave after preparative GLC (+)-**10**: $[\alpha]_{589}^{25}$ +47.8°, $[\alpha]_{578}^{25}$ +50.0°, $[\alpha]_{546}^{25}$ +58.3°, $[\alpha]_{436}^{25}$ +105°, $[\alpha]_{365}^{25}$ +179° (*c* 0.64, $CHCl_3$). A 29.2% yield of **10** was obtained in another cutback, and this corresponds approximately to that expected for a 1:1 salt.

Anal. Calcd for $C_8H_{17}NO_2$: C, 60.35; H, 10.76. Found: C, 60.21; H, 10.76.

(−)-*N*-[α-(4-Pyridyl)ethylidene]-α-ethoxycarbonylneopentylamine [(−)-8-H]. Under dry conditions in a nitrogen atmosphere a mixture of 1.46 g (9.21 mmol) of (+)-**10**, $[\alpha]_{546}^{25}$ +58.3° (*c* 0.640, $CHCl_3$), 1.87 g (15.5 mmol) of **13**, 20 g of Linde 4Å molecular sieves activated at 350 °C for 48 h, and 20 mL of THF was refluxed for 65 h. The sieves were removed by filtration and washed with 100 mL of 5% CH_3OH in CH_2Cl_2. Filtrate and washings were combined and rotary evaporation left 3.1 g of an oil which by GLC analysis (column E, 130 °C) contained ca. 65% **8**. One portion of this material was purified by preparative GLC to give (−)-**8**, $[\alpha]_{578}^{25}$ −43.4°, $[\alpha]_{546}^{25}$ −53.2°, $[\alpha]_{436}^{25}$ −132°, $[\alpha]_{365}^{25}$ −459° (*c* 0.410, $CHCl_3$), and a second was distilled (Kugelrohr) to give (−)-**8**, bp ca. 170 °C (0.03 mm), $[\alpha]_{546}^{25}$ −44.8° (*c* 0.60, $CHCl_3$), which was homogeneous by GLC analysis (column E) although slightly racemized: ^{1}H NMR δ 1.07 (s, 9 H, $(CH_3)_3C$), 8.74, (t, J = 7.2 Hz, 3 H, ester CH_3), 2.22 (s, 3 H, vinyl CH_3), 4.02 (s, 1 H, α-H), 4.19 (q, J = 7.2 Hz, 2 H, CH_2), 7.72 and 8.65 (AA′XX′, $J_{AX} + J_{AX'}$ = 6.0 Hz, 4 H, aromatic); UV (cyclohexane) 235 nm (ε 800), 270 (600), 330 (150).

Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45. Found: C, 68.60; H, 8.22.

***N*-*p*-Toluenesulfonyl-*tert*-leucine.** Under dry conditions, 1.45 g (7.61 mmol) of *p*-toluenesulfonyl chloride was added during 30 min to a stirred solution of 0.65 g (5.0 mmol) of *tert*-leucine, 2.2 mL of triethylamine, 4.0 mL of THF, and 8.0 mL of H_2O at 25 °C. The reaction mixture then was stirred at 25 °C for 1 h and rotary evaporated. The residue was added to 10 mL of H_2O, and the resulting solution was extracted twice with 10-mL portions of ether and acidified with concentrated HCl to precipitate 1.02 g (72%) of crude sulfonamide which was recrystallized from 4:1 (v/v) C_2H_5OH–H_2O to give *N*-*p*-toluenesulfonyl-*tert*-leucine; mp 230–231 °C (lit.[46] 226 °C).

Anal. Calcd for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71. Found: C, 54.63; H, 6.53.

Resolution of *N*-*p*-Toluenesulfonyl-*tert*-leucine. A solution of 5.00 g (1.27 mmol) of brucine alkaloid, mp 176–177 °C, $[\alpha]_D^{25}$ −127° ($CHCl_3$), and 3.62 g (1.27 mmol) of (±)-*N*-*p*-toluenesulfonyl-*tert*-leucine in 375 mL of acetone was concentrated at its boiling point until salt began to precipitate at a volume of ca. 30 mL. Then 20 mL of acetone was added, and the solution was allowed to cool to 25 °C. A crop of 5.1 g of poorly defined but hard crystals, mp 191–198 °C, $[\alpha]_{546}^{25}$ −35.7° (*c* 0.387, acetone), was collected. This material was recrystallized from 75 mL of 4:1 (v/v) acetone–C_2H_5OH to give 2.5 g of very hard crystals, mp 201–203 °C, $[\alpha]_{546}^{25}$ −36.1° (*c* 0.274, acetone), which was further recrystallized from 60 mL of 5:1 (v/v) acetone–C_2H_5OH to give 1.1 g of crystals, mp 202–203 °C, $[\alpha]_{546}^{25}$ −32.7° (*c* 0.416, acetone). A mixture of 420 mg of this last material and 20 mL of 9% aqueous NaOH was heated and then cooled and filtered to remove resultant brucine. The filtrate was extracted twice with 30-mL portions of CH_2Cl_2, acidified with concentrated HCl, and filtered to give crude sulfonamide, mp 241–242 °C, $[\alpha]_{546}^{25}$ +51.8° (*c* 1.00, absolute C_2H_5OH), which gave a single spot by TLC analysis on silica gel. Recrystallization of this material from aqueous C_2H_5OH gave (+)-*N*-*p*-toluenesulfonyl-*tert*-leucine, mp 242–243 °C, $[\alpha]_{546}^{25}$ +52.7° (*c* 1.01, absolute C_2H_5OH).

Anal. Calcd for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71. Found: C, 54.82; H, 6.79.

Conversion of the Dibenzoyl-*d*-tartrate Salt of (+)-Ethyl 2-Amino-3,3-dimethylbutanoate to (+)-*N*-*p*-Toluenesulfonyl-*tert*-leucine. A solution of 498 mg of the dibenzoyl-*d*-tartrate salt of (+)-**10**, $[\alpha]_{546}^{25}$ −101.6° (*c* 0.55, CH_3OH), in 15 mL of 20% aqueous HCl was refluxed for 2 h, cooled, and filtered to remove precipitated dibenzoyl-*d*-tartaric acid. The filtrate was diluted with H_2O to 50 mL and slurried with 50 g of Amberlite IR-4B ion exchange resin until the supernatant liquid was at pH 7. The resin was removed by filtration and washed with H_2O, and washings and filtrate were evaporated in vacuo. To a stirred solution of the residue in a mixture of 0.6 mL of triethylamine, 1.5 mL of THF, and 3 mL of H_2O was added 250 mg of *p*-toluenesulfonyl chloride during 15 min. After 1 h, THF and excess triethylamine were removed by rotary evaporation, and the residue was added to 5 mL of H_2O and extracted twice with ether. The aqueous solution was adjusted to pH 2 with concentrated HCl and filtered to give crude sulfonamide, mp 237–240 °C, $[\alpha]_{546}^{25}$ +49.4° (*c* 0.96, absolute C_2H_5OH), which gave a single spot by TLC analysis on silica gel. The above rotation is 97% of that obtained for sulfonamide from the brucine resolution. Recrystallization of crude sulfonamide from aqueous C_2H_5OH gave (+)-*N*-*p*-toluenesulfonyl-*tert*-leucine, mp 240–242 °C, $[\alpha]_{546}^{25}$ +51.3° (*c* 1.02, absolute C_2H_5OH).

Anal. Calcd for $C_{13}H_{19}NO_4S$: C, 54.72; H, 6.71. Found: C, 54.94; H, 6.80.

Hydrolysis of (+)-Ethyl 2-Amino-3,3-dimethylbutanoate [(+)-10] to (−)-(*S*)-*tert*-Leucine. A solution of 480 mg (3.02 mmol) of (+)-**10**, $[\alpha]_{546}^{25}$ +58.3° (*c* 0.64, $CHCl_3$), in 50 mL of 20% aqueous HCl was refluxed for 15 h and concentrated in vacuo to near dryness. A solution of the residue in 25 mL of H_2O was slurried with 15 g of Amberlite IR-4B and filtered. The resin was washed with 50 mL of H_2O, and filtrate and washings were evaporated to near dryness in vacuo. A solution of the residue in 60 mL of absolute C_2H_5OH was concentrated to 30 mL, and a crop of 150 mg of crystals resulted: $[\alpha]_{589}^{25}$ −7.3°, $[\alpha]_{546}^{25}$ −8.9° (*c* 1.40, H_2O). Concentration of mother liquors gave a second crop of 100 mg: $[\alpha]_{589}^{25}$ −6.5°, $[\alpha]_{546}^{25}$ −7.3° (*c* 1.31, H_2O). Recrystallization of 50 mg of the first crop from 5 mL of absolute C_2H_5OH gave 23 mg of *tert*-leucine: $[\alpha]_{589}^{25}$ −8.2°, $[\alpha]_{546}^{25}$ −9.8° (*c* 1.01, H_2O) (lit.[12] for optically pure material $[\alpha]_{589}^{19}$ −10.4° (*c* 1, H_2O)). Thus it appears that racemization occurred during hydrolysis or that (+)-**10** was not optically pure.

(−)-*N*,*N*-Dimethyl-α-(4-pyridyl)ethylamine (11). With a standard procedure[14] a mixture of 2.80 g (23.0 mmol) of (−)-**9**-H, $[\alpha]_{546}^{25}$ −32.4° (*c* 1.61, absolute C_2H_5OH), 100 mL of aqueous 36–38% formaldehyde solution, 100 mL of H_2O, and 2.0 g of 10% Pd on charcoal was hydrogenated in a Paar shaker under ca. 2 atm of hydrogen for 24 h. The mixture was filtered and the H_2O removed by rotary evaporation. To the residue was added 200 mL of concentrated HCl, and the resulting mixture was heated on a steam bath to dissolve paraformaldehyde. Then the aqueous solution was decanted from undissolved material, extracted three times with 200-mL portions of ether, adjusted to pH 8–9 with K_2CO_3, and extracted three times with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried over Na_2SO_4 and rotary evaporated to leave 3.47 g (100%) of an oil, which was >98% **11** by GLC analysis (column B, 140 °C). This material was purified by preparative GLC to give (−)-**11**: $[\alpha]_{546}^{25}$ −60.6°, $[\alpha]_{436}^{25}$ −111° (*c* 0.80, $CHCl_3$).

Anal. Calcd for $C_9H_{14}N_2$: C, 71.96; H, 9.39. Found: C, 72.05; H, 9.25.

Dry HCl was bubbled through an anhydrous ether solution of 3.65 g of crude (−)-**11** from another preparation[14] starting with optically pure (−)-**9**-H, and 2.62 g of dihydrochloride salt precipitated. This material was recrystallized from 50 mL of absolute C_2H_5OH to give 2.14 g of crystals, $[\alpha]_{546}^{25}$ −7.7 ± 0.2° (*c* 0.867, CH_3OH), and a further

recrystallization from 35 mL of the same solvent gave 1.28 g of salt: mp 225–229 °C dec; $[\alpha]_{546}^{25}$ −7.5 ± 0.2° (*c* 0.906, CH_3OH).

Eschweiler–Clarke methylation[15e,48] of 6.0 g (49 mmol) of optically pure (−)-**9**-H, $[\alpha]_{546}^{25}$ −40.45° (neat, 1 dm), at ≤50 °C gave 6.06 g (82%) of crude (−)-**11**, $[\alpha]_{546}^{25}$ −23.15° (neat 1 dm), which was homogeneous by GLC analysis (column B, 140 °C). This (−)-**11** was converted to 8.52 g (95%) of the dihydrochloride salt, which was recrystallized twice from absolute C_2H_5OH–CH_3OH to give 3.2 g of salt: mp 230–239 °C dec; $[\alpha]_{546}^{25}$ +0.1 ± 0.3° (*c* 1.12, CH_3OH). Dihydrochloride salt recovered from the combined mother liquors on decomposition yielded (−)-**11**, $[\alpha]_{546}^{25}$ −42.8° (*c* 1.44, absolute ethanol).

Anal. Calcd for $C_9H_{16}Cl_2N_2$: C, 48.44; H, 7.23. Found: C, 48.60; H, 7.18.

Eschweiler–Clarke methylation[48] of (+)-**9**-H, $[\alpha]_{546}^{25}$ +3.60° (neat, 1 dm), at ≤100 °C gave (35%) (±)-**11**, $[\alpha]_{546}^{25}$ 0.000 ± 0.003° (neat, 1 dm).

(±)-*N,N*-Dimethyl-α-(4-pyridyl)ethylamine (11) by Eschweiler–Clarke Methylation.[48] A reaction mixture of 80.0 g (0.656 mol) of (±)-**9**-H, 238 mL of 36–38% aqueous formaldehyde, and 238 mL of 98–100% formic acid was stirred at 25 °C for 17 h and at 100 °C for 12 h, and yielded 42.3 g (43%) of crude (±)-**11**, which was distilled to give a center cut: bp 97–100 °C (ca. 20 mm); ^{1}H NMR δ 1.32 (d, J = 6.5 Hz, 3 H, CCH_3), 2.16 (s, 6 H, $(CH_3)_2N$), 3.21 (q, J = 6.5 Hz, 1 H, benzyl), 7.13 and 8.36 (AA′XX′, $J_{AX} + J_{AX'}$ = 5.8 Hz, 4 H, aromatic).

Numerous combinations of resolving agents and solvents were used in an attempt to find a crystalline salt of (±)-**11** or of partially resolved (−)- or (+)-**11** suitable for resolution purposes. Of *d*-tartaric, dibenzoyl-*d*-tartaric, *d*-10-camphorsulfonic, *d*-camphoric, and L-malic acids, only the first in 95% C_2H_5OH–$CHCl_3$ gave a crystalline salt, which unfortunately did not fractionate appreciably after five recrystallizations from aqueous C_2H_5OH.

1,5-Diazabicyclo[4.3.0]non-5-ene Hydriodide. To 1.30 g of 1,5-diazabicyclo[4.3.0]non-5-ene, bp 107–108 °C (ca. 15 mm), was added 47% hydriodic acid (Merck, with 1.5% H_3PO_2) until the solution was acidic. Water was removed in vacuo (1 mm); the resulting salt was dissolved in CH_3CN, which then was evaporated. This procedure with CH_3CN was repeated several times, and the hydriodide was dried at 25 °C (0.1 mm) for 40 h and recrystallized from absolute C_2H_5OH at −20 °C. The resulting material was dried at 25 °C (1 mm) for 5 h and at 80 °C (0.03 mm) for 12 h to give analytically pure hydriodide, mp 154–156 °C, which was stored and dispensed only in a drybox.

Anal. Calcd for $C_7H_{13}IN_2$: C, 33.35; H, 5.20. Found: C, 33.48; H, 5.17.

General Procedures for Runs 1–12 and 15–17 with 7 and 8 in *tert*-Butyl Alcohol. When (−)-**7**-H was used it was purified by two molecular distillations (Kugelrohr) and was optically pure, $[\alpha]_{546}^{25}$ −91.2° (*c* 0.53, $CHCl_3$), unless noted otherwise, and contained 0.5–1.4% of **9** as the only impurity by GLC analysis (column C, 160 °C or E, 125 °C). Controls demonstrated that contaminant **9** had no effect on the results of these runs.

All glassware was cleaned with $Na_2Cr_2O_7$–H_2SO_4 cleaning solution, rinsed sequentially with H_2O, 5% aqueous ammonia, and H_2O, and dried at 120 °C for 24 h. Each reaction mixture was prepared in a volumetric flask and transferred to a thick-walled tube which was fitted with a rubber serum cap. Then the tube was degassed through a syringe needle inserted into the cap by three freeze (liquid N_2)–pump (0.2 mm)–fill (N_2)–thaw cycles, sealed at 0.2 mm, and placed in the appropriate constant-temperature bath. After the reaction period, the tube was cooled in a dry ice–acetone bath, allowed to warm to room temperature, and opened. For most runs, ^{1}H NMR spectra of the reaction mixture were recorded on a Varian A-60D instrument. The extent of isomerization, ±3%, was determined by electronic integration of the well-separated AA′XX′ patterns for the aromatic protons of **7** and **8**. In some runs, the reaction mixture was analyzed by GLC.

For product isolation, the reaction mixture was immediately added to 50 mL of ether and extracted with three 25-mL portions of aqueous buffer, 0.5 M each in $NaHCO_3$ and Na_2CO_3. The aqueous extracts were back-extracted with 50 mL of ether, and the combined ether extracts were dried over Na_2SO_4 and concentrated in vacuo. Isomers **7** and **8** were preparatively separated by GLC (column E, 130 °C), and each isomer then was resubmitted to preparative GLC to remove traces of the other isomer. Resultant **7** contained <0.1% **8**, and **8**, <1% **7** by GLC analysis (column D, 125 °C). Optical rotations were measured as $CHCl_3$ solutions which then were evaporated to recover **7** and **8** for deuterium analyses as needed.

Run 1. To a 1-mL volumetric flask were added 103.7 mg (0.396 mmol) of (±)-**7**-H and ca. 0.5 mL of *tert*-butyl alcohol, followed by 62.3 mg (0.502 mmol) of DBN. The flask was shaken and filled to the mark with *tert*-butyl alcohol, and the resulting solution was sealed in a tube which was placed in a rate bath at 50.0 ± 0.1 °C for 810.5 h. After the tube was opened, ^{1}H NMR analysis of the solution indicated the presence of **8** to the exclusion of **7**, and the spectrum contained no extraneous signals. By GLC analysis (column D) ca. 0.5% **7** was detected. The results are summarized in Table I. The reaction time used for this run corresponds to ca. 10 half-lives based on the data of run 5.

Run 2. With the procedure of run 1, a solution was prepared in a 1-mL volumetric flask from 70.7 mg (0.571 mmol) of DBN, 22.2 mg (0.0848 mmol) of (±)-**8** purified by preparative GLC (column E, 125 °C), and *tert*-butyl alcohol. After 231 h at 50.0 ± 0.1 °C in a sealed tube, the solution was analyzed by GLC (column D, 125 °C). No **7** was detected (<0.1%); the results are summarized in Table I.

Run 4. With the procedure of run 1, a solution was prepared in a 1-mL volumetric flask from 104.9 mg (0.400 mmol) of optically pure (−)-**7**-H, 63.7 mg (0.505 mmol) of DBN, and *tert*-butyl alcohol. After 67.42 h at 50.0 ± 0.1 °C in a sealed tube, the solution was analyzed by ^{1}H NMR; the extent of isomerization of **7** to **8** was 44.5%. Standard isolation procedures given above yielded a mixture of **7** and **8** which was separated by preparative GLC. The (−)-**7**-H obtained, $[\alpha]_{546}^{25}$ −66.7° (*c* 0.70, $CHCl_3$), contained ca. 0.3% **8** by GLC analysis (column D, 125 °C) and was resubmitted to preparative GLC to give (−)-**7**-H, $[\alpha]_{546}^{25}$ −66.8° (*c* 0.49, $CHCl_3$), which was homogeneous by GLC analysis. The **8** obtained, $[\alpha]_{546}^{25}$ −6.4° (*c* 1.27, $CHCl_3$), contained ca. 4% **7** by GLC analysis (column D, 125 °C) and was resubmitted to preparative GLC to yield (−)-**8**, $[\alpha]_{546}^{25}$ −5.0° (*c* 0.35, $CHCl_3$), which contained 0.5% **7** by GLC analysis. The results are summarized in Tables II and III.

Run 6. With the procedure of run 1, a solution was prepared in a 1-mL volumetric flask from 104.6 mg (0.400 mmol) of optically pure (−)-**7**-H, 67.9 mg (0.523 mmol) of DBN, and *tert*-butyl alcohol-*O*-*d* (0.98 atom of D per molecule). The solution was sealed in a tube, which was placed in a rate bath at 50.0 ± 0.1 °C for 63.5 h. After the tube was opened, ^{1}H NMR analysis of the solution indicated a 47.9% isomerization of **7** to **8**. Standard isolation procedures gave a mixture of **7** and **8** which was separated by preparative GLC to give (−)-**7**, $[\alpha]_{546}^{25}$ −60.4° (*c* 0.495, $CHCl_3$), and (−)-**8**, $[\alpha]_{546}^{25}$ −6.4° (*c* 0.375, $CHCl_3$). By mass spectral analysis **7** contained 0.099 atom of excess D per molecule. The results are summarized in Tables II and III.

Run 8. With the procedure of run 1, a solution was prepared in a 1-mL volumetric flask from 109.6 mg (0.418 mmol) of (−)-**7**-H, $[\alpha]_{546}^{25}$ −87.0° (*c* 1.59, $CHCl_3$), 61.0 mg (0.492 mmol) of DBN, 0.8 mg (0.003 mmol) of DBN hydriodide, mp 154–156 °C, and *tert*-butyl alcohol-*O*-*d* (0.98 atom of D per molecule). The solution was sealed in a tube, which was placed in a rate bath at 50.0 ± 0.1 °C for 48.5 h. After the tube was opened, ^{1}H NMR analysis of the solution indicated a 26.1% isomerization of **7** to **8**. Standard isolation procedures gave a mixture of **7** and **8** which was separated by preparative GLC. Each isomer was resubmitted to preparative GLC to give (−)-**7**, $[\alpha]_{546}^{25}$ −71.6° (*c* 0.860, $CHCl_3$), and (−)-**8**, $[\alpha]_{546}^{25}$ −6.1° (*c* 1.15, $CHCl_3$). By mass spectral analysis (−)-**7** contained 0.056 atom of excess D per molecule and by ^{1}H NMR analysis (−)-**8** contained 0.653 atom of D at the α position. The results are summarized in Tables II and III.

Run 11. With the procedure of run 1, a solution was prepared in a 1-mL volumetric flask from 103.5 mg (0.394 mmol) of (±)-**7**-D (0.98 atom of D at the benzyl position), 63.4 mg (0.511 mmol) of DBN, and *tert*-butyl alcohol. After 332.25 h at 50.0 ± 0.1 °C in a sealed tube, the solution was analyzed by ^{1}H NMR; the extent of isomerization of **7** to **8** was 48.7%. Standard isolation procedures gave a mixture of **7** and **8**, which were isolated by double preparative GLC. By mass spectral analysis **7** contained 0.931 atom of excess D per molecule and by ^{1}H NMR analysis **8** contained 0.295 atom of D per molecule at the α position. The results are summarized in Tables II and III.

Run 12. With the procedure of run 1, a solution was prepared in a 1-mL volumetric flask from 107.8 mg of (±)-**7**-D contaminated with ca. 5% (±)-**9**-D (each 0.98 atom of D at the benzyl position), 60.2 mg (0.486 mmol) of DBN, and *tert*-butyl alcohol-*O*-*d* (0.98 atom of D per molecule). After 258 h at 50.0 ± 0.1 °C in a sealed tube, the solution was analyzed by ^{1}H NMR; the extent of isomerization of **7** to **8** was 25.1%. The results are summarized in Table III.

Run 15. With the procedure of run 1, a solution was prepared in a 1-mL volumetric flask from 9.6 mg (0.037 mmol) of (−)-**8**-H,

$[\alpha]_{546}^{25}$ −44.8° (*c* 0.60, $CHCl_3$), purified by preparative GLC (column E, 130 °C), 61.1 mg (0.492 mmol) of DBN, and *tert*-butyl alcohol. The resulting solution, α_{578}^{25} −0.365°, α_{546}^{25} −0.438° (neat, 1 dm), was held at 50.1 ± 0.1 °C for 451 h in a sealed tube and then gave rotations α_{578}^{25} −0.314°, α_{546}^{25} −0.391° (neat, 1 dm). These values correspond to 12.4 ± 1.6% racemization of (−)-**8** during the run. The results are summarized in Table IV. It can then be calculated that under the conditions of run 5, **8** would undergo 2.2% racemization per half-life of isomerization of **7** to **8**.

Run 16. With the procedure of run 1, a solution was prepared in a 1-mL volumetric flask from 25.9 mg (0.0988 mmol) of optically pure (−)-**8**-H, $[\alpha]_{546}^{25}$ −53.2° (*c* 0.41, $CHCl_3$), purified by preparative GLC (column E, 130 °C), 61.5 mg (0.495 mmol) of DBN, and *tert*-butyl alcohol-*O*-*d* (0.98 atom of D per molecule). The resulting solution, α_{578}^{25} −1.151°, α_{546}^{25} −1.385° (neat, 1 dm), was held at 50.1 ± 0.1 °C for 234.6 h in a sealed tube and then gave rotations α_{578}^{25} −1.098°, α_{546}^{25} −1.309° (neat, 1 dm). These values correspond to 5.0 ± 0.5% racemization of (−)-**8** during the run. Then standard isolation procedures gave **8**, which was purified by preparative GLC (column E, 130 °C), and by ^{1}H NMR analysis purified material contained 0.299 atom of D at the α position. The results are summarized in Table IV.

Run 17. With the procedure of run 1, a solution was prepared in a drybox in a 2-mL volumetric flask from 2.8 mg (0.011 mmol) of DBN·HI, 59.7 mg (0.228 mmol) of (+)-**8**-H, $[\alpha]_{546}^{25}$ +10.4° (*c* 1.31, $CHCl_3$), 130.3 mg (1.05 mmol) of purified DBN,[49] and *tert*-butyl alcohol-*O*-*d* (0.98 atom of D per molecule). The resulting solution, α_{578}^{25} +0.264°, α_{546}^{25} +0.317° (neat, 1 dm), was held at 50.0 ± 0.1 °C for 236 h in a sealed tube and then gave rotations α_{578}^{25} +0.250°, α_{546}^{25} +0.298° (neat, 1 dm). These values correspond to 5.6% racemization of (+)-**8** during the run. Then standard isolation procedures gave **8**, which was purified by preparative GLC (column E, 130 °C), and by ^{1}H NMR analysis purified material contained 0.348 atom of D at the α position. The results are summarized in Table IV.

Run 13. DBN-Catalyzed Isomerization of (−)-7-H to 8 in 2:1 (v/v) Hexamethylphosphoramide-*tert*-Butyl Alcohol. In a drybox 47.0 mg (0.179 mmol) of (−)-**7**-H, $[\alpha]_{546}^{25}$ −89.5° (*c* 0.37, $CHCl_3$), was weighed into a 3-mL volumetric flask and diluted to the mark with a 2:1 (v/v) mixture of HMPA–*tert*-butyl alcohol. Most of this thoroughly mixed solution was used to dilute 316.9 mg (2.555 mmol) of DBN in a second 3-mL volumetric flask to the mark to give a solution ca. 0.06 M in (−)-**7**-H and ca. 0.85 M in DBN. Time was recorded from the initial mixing of the second solution which was added to a water-jacketed polarimeter cell thermostated at 25 °C. The initial rotation of the solution, α_{546}^{25} −1.245° (neat, 1 dm), was measured 24 min after solution preparation. The isomerization of **7** to **8** and ultimately the racemization of **8** were then followed polarimetrically at 546 nm through 23 points; a final rotation of α_{546}^{25} −0.089° (neat, 1 dm) was recorded after 215.1 h.

Run 14. DBN-Catalyzed Racemization of (−)-8-H in 2:1 (v/v) Hexamethylphosphoramide-*tert*-Butyl Alcohol. In a 2-mL volumetric flask 13.6 mg of (−)-**8**-H, $[\alpha]_{546}^{25}$ −52.6° (*c* 0.41, $CHCl_3$), was diluted with ca. 1.5 mL of 2:1 (v/v) HMPA-*tert*-butyl alcohol. Then 302.7 mg of DBN was added, and after dilution to the mark with additional HMPA–*tert*-butyl alcohol, time zero was recorded. The solution was 0.026 M in (−)-**8** and 1.22 M in DBN, and a portion of it was used to fill a water-jacketed polarimeter cell thermostated at 25.0 °C. The first rotation of the solution, α_{546}^{25} −0.583° (neat, 1 dm), was measured after 17 min, and the racemization of **8** was followed polarimetrically through 20 points. A final rotation of α_{546}^{25} −0.229° (neat, 1 dm) was recorded after 575.78 h.

The rate constant for the pseudo-first-order racemization of (−)-**8** was 4.6×10^{-7} s^{-1}, and it yields a half-life of 603 h when corrected to the conditions of run 13 (ca. 0.85 M DBN). This value is remarkably close to the 623-h value calculated from the data of run 13.

General Procedure for Runs 18–25 with 7. For these runs, procedures through the sealing of reaction mixtures in thick-walled tubes were identical with those used in runs 1–12 and 15–17. Also, for runs other than those in pyridine, the extent of isomerization of **7** to **8**, ±3%, was determined using the same ^{1}H NMR analysis procedure. For pyridine runs, the singlet at δ 1.51 for the vinyl methyl group of **8** was compared by electronic integration to the set of signals between δ 5.2 and 6.2 for the benzyl hydrogen of **7**, the α hydrogen of **8**, and the ester methylene groups of **7** and **8**. Product isolation involved initial hydrolysis followed by ion exchange chromatography on Dowex 50W-X8.

Run 18. Into a 3-mL volumetric flask was weighed 402.6 mg (1.54 mmol) of optically pure (−)-**7**-H, $[\alpha]_{546}^{25}$ −93.5° (*c* 0.465, $CHCl_3$), which was diluted with ca. 2 mL of pyridine. Then 170.9 mg (1.52 mmol) of Dabco was added, and the reagents were thoroughly mixed and diluted to the mark with pyridine. The resulting solution was held at 101.4 ± 0.4 °C for 112.5 h in a sealed tube and then analyzed by ^{1}H NMR. The extent of isomerization of **7** to **8** was 72%. Then the solution was added to 100 mL of ether and extracted three times with 50-mL portions of H_2O. The ether was dried over Na_2SO_4 and concentrated to leave 500 mg of a brown oil. A solution of this residue in 100 mL of 1 M HCl was held at 25 °C for 5 h, diluted with 100 mL of concentrated HCl, heated on a steam bath for 17 h, and concentrated to 1 mL by rotary evaporation. With 10 mL of H_2O the residue was transferred onto a 2 × 8 cm Dowex 50W-X8 column. With 0.2 M HCl as eluent an initial 100-mL fraction, which presumably contained any residual ethyl trimethylpyruvate (**12**), was collected and discarded. Then fractions 2–5, 200 mL each, were collected with 0.2 M HCl, followed by subsequent fractions, 500 mL each, with 1.0 M HCl as eluent. Fraction 3 contained *tert*-leucine, fraction 7 methyl 4-pyridyl ketone (**13**), fraction 8 α-(4-pyridyl)ethylamine (**9**) and **13**, and fraction 9 amine **9**. Amine **9** and *tert*-leucine were detected by ninhydrin, and positive identifications of these two plus **13** were made by ^{1}H NMR.

Fraction 3 was concentrated to ca. 1 mL by rotary evaporation, basified with K_2CO_3, and diluted to 6 mL with H_2O. Then 3 mL of THF and 1.5 mL of triethylamine were added, and the resulting solution was stirred for 5 min before 300 mg of *p*-toluenesulfonyl chloride was added during 10 min. After the mixture was stirred at 25 °C for 1 h, the THF and excess triethylamine were removed by rotary evaporation, and the basic residue was extracted twice with 10-mL portions of ether and adjusted to pH 1 with concentrated HCl. With ether, *N*-*p*-toluenesulfonyl-*tert*-leucine was extracted, and the extracts were dried over Na_2SO_4 and rotary evaporated to leave 63 mg (20% from **7**) of crude sulfonamide, mp 150–180 °C, $[\alpha]_{546}^{25}$ +8.0° (*c* 0.51, absolute C_2H_5OH), which gave only one spot on TLC analysis on silica gel. The above rotation represents 16% optical purity, and recrystallization of this crude material from absolute C_2H_5OH gave sulfonamide of 19% optical purity. However, the increase in optical purity was most likely due in part to fractionation of optically pure material away from racemate. It is important to note that (−)-(*S*)-**7**-H gave (+)-sulfonamide above and that the latter also resulted from (+)-**10**. Previously it was shown that (+)-**10** gave (−)-*tert*-leucine, which has the *S* configuration.[12] Therefore, since the asymmetric center was not affected in any of these interconversions, (+)-sulfonamide also has the *S* configuration, and, consequently, as was the case in *tert*-butyl alcohol, (−)-**7**-H gave (−)-**8** in this run.

To recover **9**, fraction 9 was concentrated to near dryness by rotary evaporation, diluted to 100 mL with H_2O, and adjusted to pH 10 with K_2CO_3. The resulting solution was continuously extracted with CH_2Cl_2 for 24 h, and the extract was dried over Na_2SO_4 and rotary evaporated to give 35 mg of a yellow oil. Preparative GLC (column A, 135 °C) of this material gave (−)-**9**-H, $[\alpha]_{546}^{25}$ −10.0° (*c* 1.65, absolute C_2H_5OH). The results of this run are summarized in Table V.

Run 22. With the procedure of run 18, a solution was prepared in a 3-mL volumetric flask from 399 mg (1.52 mmol) of optically pure (−)-**7**-H, $[\alpha]_{546}^{25}$ −93.5° (*c* 0.465, $CHCl_3$), 169 mg (1.51 mmol) of Dabco, and Me_2SO-d_6 (99.5% D). After 15.0 h at 101.4 ± 0.4 °C in a sealed tube, the solution was analyzed by ^{1}H NMR; the extent of isomerization of **7** to **8** was 32.9%. Then the reaction mixture was added to 100 mL of 1 M HCl, and the resulting solution was stirred at 25 °C for 1 h, extracted four times with CH_2Cl_2, stirred for an additional 6 h at 25 °C, and heated on a steam bath for 3 h. After the reaction mixture was concentrated to ca. 5 mL in vacuo it was transferred with water onto a 2 × 8 cm Dowex 50W-X8 column. With 0.2 M HCl as eluent an initial 100-mL fraction, which presumably contained **12** and Me_2SO-d_6, was collected and discarded. Then fractions 2–6, 200 mL each, were collected with 0.2 M HCl, followed by subsequent fractions with 1.0 M HCl as eluent. Fractions 2–4 contained *tert*-leucine and α-amino ester **10** and fractions 7–10 amine **9** and ketone **13**. Detection and identification were the same as in run 18. The resolution of this chromatogram was poorer than that of run 18, probably owing to Me_2SO-d_6.

Since there was more **10** than *tert*-leucine in fractions 2–4, the former was isolated. Fractions 2–4 were combined and rotary evaporated to near dryness. The acidic residue was diluted to 10 mL with H_2O, adjusted to pH 10 with K_2CO_3, and extracted twice with 20-mL portions of ether. The combined extracts were dried over Na_2SO_4, and rotary evaporation left 15 mg (20%) of crude ester which was purified

by preparative GLC (column A, 100 °C) to give (+)-**10**, $[\alpha]_{546}^{25}$ +13.1° (*c* 0.29, $CHCl_3$), 23% optically pure.

Fractions 7–9 were combined, concentrated to 5 mL by rotary evaporation, diluted to 100 mL with H_2O, and basified with K_2CO_3. The basic solution was continuously extracted with CH_2Cl_2 for 24 h, and the extracts were dried over Na_2SO_4 and rotary evaporated to leave 230 mg of a yellow oil which contained ca. 60% amine **9**, 20% ketone **13**, and 20% of an unidentified material by GLC analysis (column A, 135 °C). Preparative GLC under the same conditions gave (−)-**9**-H, $[\alpha]_{546}^{25}$ −18.4° (*c* 0.59, absolute C_2H_5OH), 58% optically pure. The results of this run are summarized in Table V.

General Procedure for Runs 26–32 with (−)-11-H. Amine **11**, $[\alpha]_{546}^{25}$ −60.6 ± 0.2° (*c* 0.90, 1.05, $CHCl_3$), purified by preparative GLC (column B, 190 °C), was used. All glassware was cleaned with the procedure of runs 1–12 and 15–17, and solutions were prepared and thick-walled glass tubes filled and fitted with rubber serum caps in a drybox in a nitrogen atmosphere. Then tubes were degassed and sealed with the procedure of runs 1–12 and 15–17. Optical rotations were taken directly on the reaction mixture before sealing and shortly after opening a tube.

Run 28. A 10-mL volumetric flask was filled to the mark with *tert*-butyl alcohol-*O*-*d* (0.98 atom of D per molecule) 0.14 M in potassium *tert*-butoxide after the addition of 57.2 mg of (−)-**11**-H, and the resulting solution gave rotation α_{589}^{25} −0.199° (neat, 1 dm). Seven tubes were filled, sealed, and placed in a rate bath at 50.7 ± 0.1 °C. Upon removal from the bath each tube was immediately placed in dry ice–acetone. It was allowed to warm to room temperature and opened, and the optical rotation of the solution was measured. Immediately, the solution was added to 20 mL of saturated aqueous NaCl and extracted with three 15-mL portions of CH_2Cl_2. The combined extracts were washed with 10 mL of saturated aqueous NaCl, dried over Na_2SO_4, and rotary evaporated. The residue yielded **11** on preparative GLC (column B, 190 °C) which was analyzed for deuterium content by mass spectrometry. Table VI summarizes the results.

Run 31. A 10-mL volumetric flask was filled to ca. 8 mL with a freshly prepared solution of 2:1 (v/v) HMPA-*tert*-butyl alcohol-*O*-*d* (0.98 atom of D per molecule) after the addition of 149.4 mg of (−)-**11**-H. After thorough mixing, 690.8 mg of DBN was added and the flask was filled to the mark with more of the same HMPA-*tert*-butyl alcohol-*O*-*d*, and the resulting solution gave rotation α_{546}^{25} −0.812° (neat, 1 dm). Six tubes were filled, sealed, and placed in a rate bath at 175.0 ± 0.1 °C. Upon removal from the bath each tube was cooled rapidly to 25 °C and opened, and the optical rotation of the solution was measured. Then the solution was added to 50 mL of 0.2 M HCl and extracted four times with CH_2Cl_2. The aqueous solution then was adjusted to pH 8–9 with K_2CO_3 and extracted three times with CH_2Cl_2, and the combined extracts were dried over Na_2SO_4 and rotary evaporated. The residue yielded **11** on preparative GLC (column B, 190 °C), which was analyzed for deuterium content by mass spectrometry. Table VI summarizes the results.

Run 32. To a 2-mL volumetric flask was added 2.8 mg of DBN·HI, mp 154–156 °C, followed by 35.1 mg of (−)-**11**-H and ca. 1.5 mL of 2:1 (v/v) HMPA-*tert*-butyl alcohol-*O*-*d* (0.98 atom of D per molecule). Then 119.9 mg (0.968 mmol) of DBN was added, and the solution was diluted to the mark with additional HMPA-*tert*-butyl alcohol-*O*-*d* and gave rotation α_{546}^{25} −0.672° (neat, 1 dm). A tube containing ca. 1.2 mL of solution was sealed and placed in a rate bath at 175.0 ± 0.1 °C for 19.0 h. Upon removal from the bath the tube was cooled rapidly to 25 °C and opened, and the optical rotation of the solution was measured, α_{546}^{25} −0.514° (neat, 1 dm). The remainder of the procedure through deuterium analysis was identical with that of run 31. Table VI summarizes the results.

Run 33. In a 2-mL volumetric flask 98.8 mg of (−)-**11**-H, $[\alpha]_{546}^{25}$ −5.2°, $[\alpha]_{436}^{25}$ −9.4°, $[\alpha]_{365}^{25}$ −16.0° (*c* 1.48, absolute C_2H_5OH), was diluted to the mark with methanol-*O*-*d* (0.995 atom of D per molecule) 0.15 M in potassium methoxide. The resulting solution was held at 100 °C for 14 h in a sealed tube and added to 10 mL of H_2O. The aqueous layer was extracted four times with 10-mL portions of ether, and the combined extracts were dried over Na_2SO_4. Rotary evaporation left crude material, which was purified by GLC (column B, 135 °C) to give (−)-**11**, $[\alpha]_{546}^{25}$ −4.6°, $[\alpha]_{436}^{25}$ −8.4°, $[\alpha]_{365}^{25}$ −14.3° (*c* 0.963, absolute C_2H_5OH), that by ^1H NMR analysis contained 0.13 ± 0.01 atom of D at the benzyl position.

Racemization Control for 7 during Its Formation. According to the procedure for preparation of (−)-**7**-H given above, a mixture of 0.636 g (5.44 mmol) of (−)-**9**-H, $[\alpha]_{546}^{25}$ −31.5° (*c* 0.65, absolute C_2H_5OH), and 1.1 g (6.6 mmol) of **12** in THF containing activated 4Å molecular sieves was refluxed for 20 h, and analysis by GLC (column C, 160 °C) indicated ca. 50% conversion of **9** to **7**. After product isolation, 290 mg of resultant (−)-**7**-H, $[\alpha]_{546}^{25}$ −91.2° (*c* 0.53, $CHCl_3$), was added to 75 mL of 1 M HCl at 0 °C. The reaction mixture was allowed to warm to 25 °C and was stirred for 20 h. Then it was adjusted to pH 9 with K_2CO_3 and continuously extracted for 24 h with CH_2Cl_2. The extract was dried over Na_2SO_4 and rotary evaporated to leave 180 mg of an oil which gave (−)-**9**-H, $[\alpha]_{546}^{25}$ −30.9° (*c* 0.59, absolute C_2H_5OH), after preparative GLC (column A, 135 °C).

Racemization Control for 8 during Its Formation. According to the procedure for preparation of (−)-**8** given above, a mixture of 255 mg (1.60 mmol) of (+)-**10**, $[\alpha]_{546}^{25}$ 58.3° (*c* 0.64, $CHCl_3$), and 532 mg (4.4 mmol) of **13** in THF containing activated 4Å molecular sieves was refluxed for 17 h, and analysis by GLC (column C, 160 °C) indicated ca. 60% conversion of **10** to **8**. After product isolation, crude material was held at 90 °C (ca. 0.01 mm), and resultant **8** contained **13** as the only impurity. A mixture of 410 mg of this material in 50 mL of 1 M HCl was stirred at 0 °C for 2 h and then at 25 °C for 18 h and was basified with K_2CO_3 and extracted twice with 50 mL portions of ether. The combined extracts were dried over Na_2SO_4 and rotary evaporated to leave 190 mg of a 2.3:1 mixture of **10** and **13**, respectively, by GLC analysis (column A, 135 °C). By preparative GLC (column A, 100 °C) pure (+)-**10**, $[\alpha]_{546}^{25}$ 58.4 ± 0.4° (*c* 0.81, 0.74, $CHCl_3$), was obtained.

Racemization Control for 7 and 8 during Isolation in Isomerization Runs. A solution of 7.0 mg of (−)-**7**-H, $[\alpha]_{546}^{25}$ −79.5° (*c* 0.350, $CHCl_3$), 13.6 mg of (−)-**8**-H, $[\alpha]_{546}^{25}$ −43.7° (*c* 0.453, $CHCl_3$), and 50.1 mg (0.405 mmol) of DBN in 1 mL of *tert*-butyl alcohol was added to 50 mL of ether. The isolation procedure used in isomerization runs gave a product mixture which was separated by preparative GLC (column E, 130 °C); 5.2 mg of (−)-**7**-H, $[\alpha]_{546}^{25}$ −76.9° (*c* 0.26, $CHCl_3$), and 9.2 mg of (−)-**8**, $[\alpha]_{546}^{25}$ −45.3° (*c* 0.46, $CHCl_3$), resulted. Each imine was resubmitted to preparative GLC to give (−)-**7**-H, $[\alpha]_{546}^{25}$ −78.8° (*c* 0.41, $CHCl_3$), and (−)-**8**, $[\alpha]_{546}^{25}$ −44.1° (*c* 0.59, $CHCl_3$).

Controls on the Optical Stability of 9 and 10. A sample of crude (+)-**10** from the cutback of its dibenzoyl-*d*-tartrate salt was purified by GLC (column A, 100 °C) to give (+)-**10**, $[\alpha]_{546}^{25}$ +57.4° (*c* 1.02, $CHCl_3$), which was subjected to the same GLC conditions to give (+)-**10**, $[\alpha]_{546}^{25}$ +57.5° (*c* 0.58, $CHCl_3$).

Amine (−)-**9**-H, $[\alpha]_{546}^{25}$ −30.7° (*c* 0.86, absolute C_2H_5OH), was subjected to preparative GLC (column A, 135 °C) to yield (−)-**9**-H, $[\alpha]_{546}^{25}$ −30.8° (*c* 0.72, absolute C_2H_5OH).

A solution of 5.16 g of (+)-**9**-H, α_{546}^{25} +1.593° (neat, 1 dm), in 90 mL of aqueous 10% $K_2CO_3 \cdot 1.5H_2O$, pH 9–10, was stirred for 17 h at 25 °C and extracted five times with 50-mL portions of CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and rotary evaporated to leave 4.7 g of an oil which was fractionally distilled to give (+)-**9**-H: bp 100–102 °C (ca. 20 mm); α_{546}^{25} +1.581° (neat, 1 dm). Therefore, **9**-H is optically stable to the cutback procedure used in its resolution and to distillation.

Controls on the Variation of Rotation of 7 and 8 with Concentration. From a sample of (−)-**7**-H several solutions in $CHCl_3$ were prepared and their rotations measured: $[\alpha]_{578}^{25}$ −75.8°, $[\alpha]_{546}^{25}$ −87.3°, $[\alpha]_{436}^{25}$ −159° (*c* 1.59); $[\alpha]_{578}^{25}$ −75.2°, $[\alpha]_{546}^{25}$ −86.6°, $[\alpha]_{436}^{25}$ −158° (*c* 0.595); $[\alpha]_{578}^{25}$ −74.4°, $[\alpha]_{546}^{25}$ −85.7°, $[\alpha]_{436}^{25}$ −156° (*c* 0.300); $[\alpha]_{578}^{25}$ −72.7°, $[\alpha]_{546}^{25}$ −83.5°, $[\alpha]_{436}^{25}$ −153° (*c* 0.128).

Similarly, from a sample of (−)-**8**-H purified by preparative GLC (column E, 130 °C) several solutions in $CHCl_3$ were prepared and their rotations measured: $[\alpha]_{578}^{25}$ −40.7°, $[\alpha]_{546}^{25}$ −49.8°, $[\alpha]_{436}^{25}$ −126° (*c* 0.650); $[\alpha]_{578}^{25}$ −41.6°, $[\alpha]_{546}^{25}$ −52.0°, $[\alpha]_{436}^{25}$ −130° (*c* 0.325); $[\alpha]_{578}^{25}$ −41.2°, $[\alpha]_{546}^{25}$ −53.4°, $[\alpha]_{436}^{25}$ −128° (*c* 0.163).

Thermal Isomerization and Racemization Control for (−)-7-H in *tert*-Butyl Alcohol. In a 1-mL volumetric flask 101.7 mg (0.389 mmol) of (−)-**7**-H, $[\alpha]_{546}^{25}$ −87.7° (*c* 0.66, $CHCl_3$), was diluted to the mark with *tert*-butyl alcohol. The solution, α_{578}^{25} −8.153°, α_{546}^{25} −9.381°, α_{436}^{25} −16.864° (neat, 1 dm), was held at 50.0 ± 0.1 °C for 282.5 h in a sealed tube. By ^1H NMR analysis the resulting solution, α_{578}^{25} −8.259°, α_{546}^{25} −9.502°, α_{436}^{25} −17.085° (neat, 1 dm), contained no **8**.

Control on Mass Spectral Deuterium Analysis for 7. Samples of **7**-D (0.98 atom of excess D per molecule) and **7**-H were purified by preparative GLC (column E, 130 °C). A solution of 10.6 mg of **7**-D and 9.7 mg of **7**-H in $CHCl_3$ was evaporated under a steam of nitrogen to leave an imine residue which was purified by GLC. By mass spectral analysis resultant **7** contained 0.46 and by calculation 0.49 atom of excess D per molecule.

Yield Control for Run 5. To a mixture of 22.8 mg (0.0870 mmol)

of (±)-**7**-H and ca. 0.5 mL of *tert*-butyl alcohol in a 1-mL volumetric flask were added 20.6 mg (0.166 mmol) of DBN and 3.9 mg (0.018 mmol) of *n*-pentadecane as internal standard. The mixture was diluted to the mark with *tert*-butyl alcohol, and the resulting solution was analyzed by GLC (column D, 125 °C). Of the **7** and *n*-pentadecane, 53.7 ± 0.4% was **7**. The solution was held at 50.0 ± 0.1 °C for 141 h in a sealed tube and analyzed by ^{1}H NMR; the extent of isomerization of **7** to **8** was ca. 20%. Of the total **7**, **8**, and *n*-pentadecane in the solution, 53.2% was **7** and **8** by GLC analysis (column D, 125 °C). This represents >99% recovery of imines. Routine product isolation gave a mixture of **7**, **8**, and *n*-pentadecane which contained 51.0% **7** and **8**. This represents a 95% recovery of imines.

Yield Control for Run 16. With the procedure for the control for run 5 a solution was prepared in a 1-mL volumetric flask from 18.0 mg of (+)-**8**, $[\alpha]_{546}^{25}$ +10.4° (*c* 1.31, $CHCl_3$), 22.9 mg of *n*-hexadecane, 59.9 mg of DBN, and *tert*-butyl alcohol-*O*-*d* (0.98 atom of D per molecule). The resulting solution, α_{546}^{25} +0.195° (neat, 1 dm), was analyzed by GLC (column D, 125 °C); of the **8** and *n*-hexadecane, 33.1 ± 0.1% was **8**. After 236.0 h at 50.0 ± 0.1 °C in a sealed tube, the solution exhibited α_{546}^{25} +0.183° (neat, 1 dm) and was analyzed by GLC using the above conditions; of the **8** and *n*-hexadecane, 32.9 ± 1.4% was **8**. Therefore, >99% recovery of **8** was obtained after 6% racemization. Routine product isolation gave a mixture of **8** and *n*-hexadecane which contained 20.9 ± 2.0% **8**; this represents a 63% recovery.

Racemization and Exchange Control for 11 in *tert*-Butyl Alcohol-*O*-*d* without Added Base. In a drybox a 3-mL volumetric flask containing 18.0 mg of (−)-**11**-H was filled to the mark with *tert*-butyl alcohol-*O*-*d* (0.92 atom of D per molecule). The resulting solution, 0.04 M in **11**, α_{546}^{25} −0.362° (neat, 1 dm), was sealed in a tube, which was placed in a rate bath at 50.7 ± 0.1 °C for 141.5 h and opened. The solution then gave rotation α_{546}^{25} −0.360° (neat, 1 dm), and on workup with the procedure of run 28, **11** resulted which contained 0.007 ± 0.015 atom of excess D per molecule by mass spectrometry.

Racemization Control for 11 in HMPA–*tert*-Butyl Alcohol without Added Base. In a drybox a 2-mL volumetric flask containing 22.0 mg of (−)-**11**-H was filled to the mark with 2:1 (v/v) HMPA–*tert*-butyl alcohol. The resulting solution, 0.074 M in **11**, α_{546}^{25} −0.596°, α_{578}^{25} −0.518° (neat, 1 dm), was sealed in a tube, which was placed in a rate bath at 175.0 ± 0.1 °C for 80.0 h and opened. The solution then gave rotation α_{546}^{25} −0.591°, α_{578}^{25} −0.519° (neat, 1 dm).

Yield Control for Run 28. A mixture of **11** and *n*-hexadecane was prepared and contained 20.4 ± 0.4% of **11** by GLC analysis (column B, 190 °C). A 1-mL volumetric flask containing 31.2 mg of this mixture was filled to the mark with *tert*-butyl alcohol-*O*-*d* (0.98 atom of D per molecule) 0.34 M in potassium *tert*-butoxide. A sealed tube containing the resulting solution, 0.035 M in **11**, was placed in a rate bath at 50.0 ± 0.1 °C for 45.5 h (ca. 4.5 half-lives for racemization) and opened. With the procedure of run 31 the solution yielded a mixture of **11** and *n*-hexadecane which contained 19.5 ± 0.3% **11** by GLC analysis.

Yield Control for Run 31. To a 1-mL volumetric flask was added 19.0 mg of a mixture of **11** and *n*-hexadecane containing 20.4 ± 0.4% **11** by GLC analysis (column B, 190 °C) followed by ca. 0.5 mL of 2:1 (v/v) HMPA–*tert*-butyl alcohol-*O*-*d* (0.98 atom of D per molecule) and 62.1 mg of DBN. The mixture was diluted to the mark with the same HMPA–*tert*-butyl alcohol-*O*-*d* to give a solution 0.01 M in **11** and 0.50 M in DBN. A sealed tube containing the solution was placed in a rate bath at 175.0 ± 0.1 °C for 80.0 h (ca. 1 half-life for racemization) and opened. The workup procedure used for run 31 would separate *n*-hexadecane from **11**, so the solution was added to 50 mL of H_2O and extracted with two 25-mL portions of ether. The combined extracts were dried over Na_2SO_4 and concentrated in vacuo to give a mixture of **11** and *n*-hexadecane that contained 19.4 ± 0.3% **11** by GLC analysis.

References and Notes

(1) This research was supported in part by U.S. Public Health Service Research Grant GM 12640-09 from the Department of Health, Education and Welfare.

(2) Some of these results have been published in preliminary form: (a) D. A. Jaeger, M. D. Broadhurst, and D. J. Cram, *J. Am. Chem. Soc.*, **95**, 7525 (1973); (b) M. D. Broadhurst and D. J. Cram, *ibid.*, **96**, 581 (1974). Some of the rate constants and values reported therein were only approximate, and more correct values are reported here.

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Size and Asymmetry of Spatial Distributions for Unperturbed Triglycerides

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Abstract: A triglyceride in the interior of a chylomicron or very low density lipoprotein is essentially unperturbed by long-range interactions. Configuration-dependent properties for unperturbed triglycerides are obtained from a representative sample generated by Monte Carlo methods. Necessary a priori and conditional probabilities were obtained from a rotational isomeric state treatment which incorporates first- and second-order interaction. Triglycerides studied have 1–22 carbon atoms in each acyl group. Unperturbed radii of gyration, $\langle s^2\rangle_0^{1/2}$, are in the range 8–10 Å for those triglycerides which occur most frequently in human chylomicrons and very low density lipoproteins. Asymmetry of the spatial distribution was assessed by examination of averaged principal moments ($\langle L_1^2\rangle_0 \geq \langle L_2^2\rangle_0 \geq \langle L_3^2\rangle$) of the moment of inertia tensor. An increase in asymmetry occurs upon progressing from triformin to tricaprylin, due almost entirely to a decrease in $\langle L_2^2\rangle_0/\langle L_1^2\rangle_0$. The higher triglycerides examined all have essentially identical asymmetries, $\langle L_2^2\rangle_0/\langle L_1^2\rangle_0 \approx 1/3$ and $\langle L_3^2\rangle_0/\langle L_1^2\rangle_0 \approx 1/12$. Thus the increase in average dimensions as the acyl group goes from C8 to C22 is achieved with no alteration in the asymmetry of the spatial distribution. Introduction of unsaturation, as it occurs in oleic and linoleic acids, brings about a reduction in $\langle s^2\rangle_0^{1/2}$, but does not significantly alter the asymmetry.

Triglycerides are transported in blood primarily by chylomicrons and very low density lipoproteins. These large lipid–protein complexes have molecular weights of about 0.5×10^9 and $8\text{–}31 \times 10^6$, respectively.[1] Triglycerides account for 5/6 of the dry weight of chylomicrons[2] and half the dry weight of very low density lipoproteins.[3] According to these results, each chylomicron contains about 500 000 molecules of triglyceride, while roughly 10 000 triglyceride molecules occur in each very low density lipoprotein molecule.[1] Neutron[4] and X-ray[5–13] scattering from dilute aqueous solutions of high- and low-density lipoproteins reveals that neutral lipid occurs preferentially at the core. This arrangement apparently also occurs in chylomicrons and in very low density lipoproteins.[1] Mobility of fatty acid chain nuclei in very low density lipoproteins is that of lipids in a liquid-like state, although segmental and rotational motion is not as free as for lipids in organic solvents.[14]

The foregoing considerations of composition, segregation, and mobility suggest that triglyceride at the core of a chylomicron or very low density lipoprotein approaches the bulk amorphous state, in which it would be unperturbed by long-range interactions. Size and asymmetry (more precisely, mean square radius of gyration and average principal moments of the moment of inertia tensor) for unperturbed triglycerides can be obtained from a successful rotational isomeric state treatment.[15–19] These terms assume importance in determining transport properties for triglycerides within a chylomicron or very low density lipoprotein.

The present work has as its foundation a recent rotational isomeric state treatment of triacetin which successfully accounts for experimentally determined dipole moments, optical anisotropies, and molar Kerr constants.[20] Confidence can therefore be placed in the accuracy of the representation of conformational preferences within the glycerol moiety. Most additional bonds in saturated carboxylic acid moieties will experience the well-characterized short-range interactions which occur in polymethylene.[21] The few remaining bonds are readily treated by customary methods.

Computational Methods

Structure. Carbon and oxygen atoms in a representative triglyceride are depicted in Figure 1. The molecule is comprised of three branches. Each atom is indexed by a presubscript which denotes the branch and by a postsubscript which denotes sequential position within a branch. Branch j contains n_j bonds in its main chain. Atoms in the carbonyl group are denoted by primes, and a single subscript j is used for each carbonyl oxygen atom. Ester groups are maintained in the planar trans configuration.

Bond lengths and bond angles are collected in Table I. Geometry for triacetin, as well as ∠CCC′, corresponds to the average of the relevant parameter in crystalline β-tricaprin.[22] Structural parameters required for longer saturated carboxylic acid chains are those appropriate for polymethylene.[21] Geometry for the cis carbon–carbon double bond is that used for poly(*cis*-1,4-butadiene).[23]

Statistical Weight Matrices and Rotational States. The statistical weight matrix for bond i in branch j is denoted by ${}_j\mathbf{U}_i$. Matrices for bonds in the glycerol moiety have been described by Mattice and Saiz.[20] They may be written as shown in eq 1–5.

$$ {}_1\mathbf{U}_{n_1} = \begin{array}{c} \\ \end{array} \begin{array}{c} \begin{array}{cc} \text{t (20°)} & \text{g}^+\text{ (102.7°)} \end{array} \\ \begin{bmatrix} 1 & 1 \end{bmatrix} \end{array} \tag{1} $$

$$ {}_2\mathbf{U}_1 = \begin{array}{c} \\ \text{t} \\ \text{g}^+ \end{array} \begin{array}{c} \begin{array}{ccc} \text{t (−5°)} & \text{g}^+\text{ (126.4°)} & \text{g}^-\text{ (−117.3°)} \end{array} \\ \begin{bmatrix} \sigma_1 & \sigma_2 & 1 \\ \sigma_1 & \sigma_2 & \omega_1 \end{bmatrix} \end{array} \tag{2} $$

$$ {}_2\mathbf{U}_2 = \begin{array}{c} \\ \text{t} \\ \text{g}^+ \\ \text{g}^- \end{array} \begin{array}{c} \begin{array}{ccc} \text{t (0°)} & \text{g}^+\text{ (102.7°)} & \text{g}^-\text{ (−102.7°)} \end{array} \\ \begin{bmatrix} 1 & \sigma_3 & \sigma_3\omega_4 \\ 1 & \sigma_3\omega_4 & \sigma_3\omega_4 \\ 1 & \sigma_3\omega_4 & \sigma_3 \end{bmatrix} \end{array} \tag{3} $$

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