Configuration and Conformation of *cis*- and *trans*-3,5-Dimethylvalerolactones[1]

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The synthesis and resolution of 3-methyl-5-oxohexanoic acid (**5**) are presented. A synthesis of (*S*)-**5** from (4*R*)-4-methyl-6-oxoheptanoic acid is also reported. The different isomers of **5** were used to prepare all four optical isomers, as well as the two racemic pairs of *cis*- and *trans*-3,5-dimethylvalerolactones. The synthetic routes used established the configuration of these lactones at position 3. The configuration at position 5 and the conformational assignment of these lactones were established by an analysis of the ^1H nmr, ^{13}C nmr, and CD spectra.

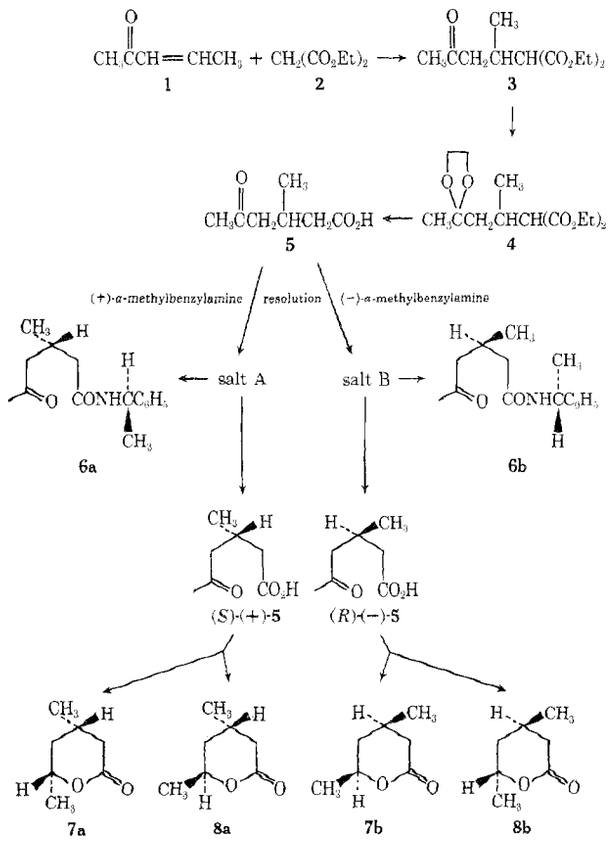
Studies concerning the structure, configuration, and conformation of saturated δ-lactones are a subject of continuing interest. X-Ray analyses of lactones have shown that the carbonyl, the ethereal oxygen, and the two adjacent carbon atoms lie in the same plane.[2] The lactone ring can, therefore, assume either a half-chair or a boat conformation, and both conformations have been found in the crystalline state. In addition, infrared (ir),[2c] ultraviolet (uv),[3] optical rotatory dispersion (ORD), and circular dichroism (CD)[4] and proton nuclear magnetic resonance (^1H nmr)[5] studies have been used to study the structure, configuration, and conformation of saturated lactones in solution. The results have shown that some δ-lactones exist in a half-chair conformation in solution, whereas other δ-lactones possess a boat conformation.

The present paper contains the synthesis and analysis by various ^1H nmr, ^{13}C nmr, and CD techniques of the configuration and conformation of 3,5-dimethylvalerolactones.[6]

Results and Discussion

Synthesis. The synthesis of all four optical isomers of 3,5-dimethylvalerolactone was accomplished as shown in Chart I. Diethyl 1-methyl-3-oxobutylmalonate (**3**) obtained by the Michael addition of diethyl malonate (**2**) to 3-penten-2-one (**1**) was converted to its ethylene ketal derivative (**4**). Alkaline hydrolysis of **4**, followed by acidification and thermal decarboxylation, yielded (*RS*)-3-methyl-5-oxohexanoic acid (**5**).[7] Attempts to prepare **5** directly from **3** without protection of the 3-oxo function gave very low yields of **5**. We found that *d*-(+)- and *l*-(−)-α-methylbenzylamine effected a high yield optical resolution of **5** to give (*S*)-(+)-**5** and (*R*)-(−)-**5**, respectively. When the salts A and B were treated with *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ)[8] in tetrahydrofuran, the diastereomeric amides **6a** and **6b** were obtained in high yield. These products could be used to determine the optical purity of the resolved acids. The nmr spectra of **6a** and **6b** as well as the racemic amide obtained from (*RS*)-**5** and (−)-α-methylbenzylamine showed only one methyl resonance for the CH_3CO and $NCHCH_3$ moieties. However, the nmr spectra of the amide from (*RS*)-**5** obtained in the presence of tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium [Eu(fod)$_3$] showed two singlets for the CH_3CO group and two doublets for the $NCHCH_3$ group. From the integrated intensities of the CH_3CO and $NCHCH_3$ signals(s) of **6a** and **6b** it was possible to assay for their optical purity. These results established that the amides **6a** and **6b** were >95% optically pure, and, thus, the acids (*S*)-(+)-**5** and (R)-(−)-**5** possess similar optical purities (see Experimental Section for details).[9] Reduction of (*S*)-(+)-**5** with sodium borohydride in ethanol or catalytically in the presence of platinum oxide gives a mixture of *cis*-(3*S*,5*R*)- and *trans*-(3*S*,5*S*)-3,5-dimethylvalerolactones **7a** and **8a**, respectively. Reduction of (*R*)-(−)-**5** in a similar manner gives a mixture of the optical isomers **7b** and **8b**, whereas reduction of (*RS*)-**5** gives a mixture of (3*RS*,5*SR*)-*cis*- and (3*RS*,5*RS*)-*trans*-3,5-dimethylvalerolactones **7** and **8**, respectively.

Chart I



It was not possible to separate the cis and trans lactones by distillation or liquid chromatography. However, the amides obtained on treating the mixture of lactones with pyrollidine could be separated by chromatography on aluminum oxide. The lactones could be regenerated by treating the separated pyrollidinamides with ethanolic sodium hydroxide. Regeneration of the lactones from the separated pyrollidinamides under acidic conditions gave a mixture of cis and trans lactones.

(3*S*)-3-Methyl-5-oxohexanoic acid (**5**) could also be obtained from (4*R*)-4-methyl-6-oxoheptanoic acid (**9**)[10] by the route shown in Chart II. Esterification of **9** followed by treatment with ethylene glycol in refluxing benzene containing *p*-toluenesulfonic acid gave (4*R*)-methyl 4-methyl-6-ethylenedioxyheptanoate (**10**). Addition of phenylmag-

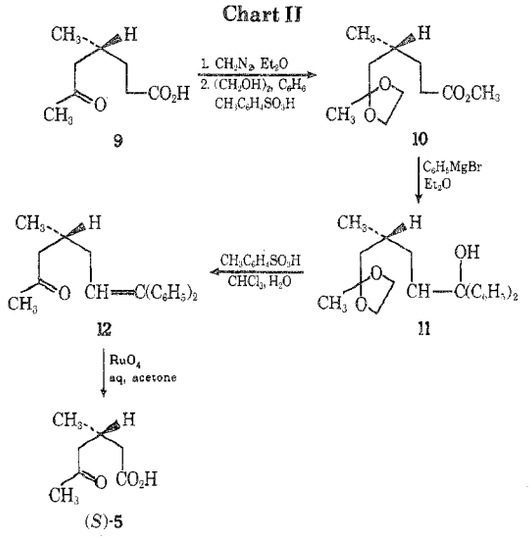
Table I
Proton Chemical Shifts of *cis*- and *trans*-3,5-Dimethylvalerolactones[a]

Compd	Solvent	C-3 CH_3[b]	J_{H,CH_3}[c]	$\Delta_{C_6D_6}^{CDCl_3}$[d]	C-5 CH_3[b]	J_{H,CH_3}[a]	$\Delta_{C_6D_6}^{CDCl_3}$	C-5 H[b]	bw[f]	$\Delta_{C_6D_6}^{CDCl_3}$
7	CCl_4	1.01 (d)	5.7		1.33 (d)	6.0		4.29 (m)	42	
	$CDCl_3$	1.01 (d)	5.5		1.36 (d)	6.2		4.40 (m)	40	
	C_6D_6	0.63 (d)	5.9	+0.38	1.09 (d)	6.2	+0.27	3.86 (m)	36	+0.54
8	CCl_4	1.09 (d)	6.1		1.33 (d)	6.1		4.46 (m)	37	
	$CDCl_3$	1.09 (d)	6.1		1.36 (d)	6.2		4.56 (m)	35	
	C_6D_6	0.66 (d)	6.2	+0.43	1.07 (d)	6.2	+0.29	4.05 (m)	39	+0.51

[a] Spectra obtained on a Varian HA-100 spectrometer. Chemical shifts given in δ values relative to $SiMe_4$. [b] d = doublet, m = multiplet. [c] Coupling constant with C-3 H. [d] $\Delta_{C_6D_6}^{CDCl_3}$ = difference between chemical shift in $CDCl_3$ and C_6D_6. [e] Coupling constant with C-5 H. [f] Band width of H-5.

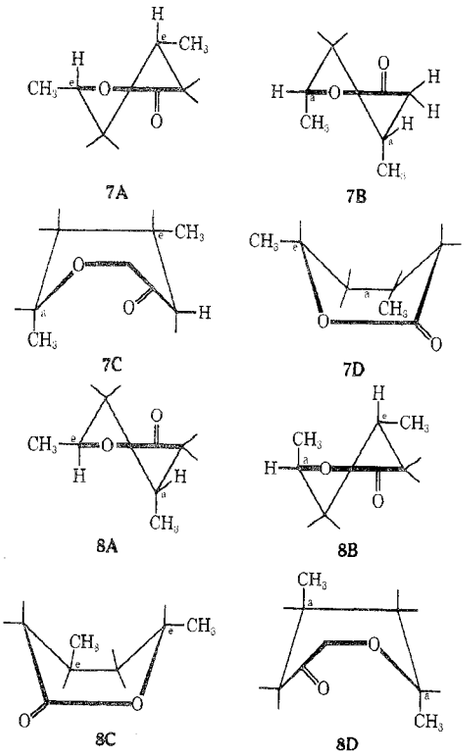
nesium bromide to 10 gave (4*R*)-1,1-diphenyl-4-methyl-6-ethylenedioxyheptanol (11). Treatment of 11 with a refluxing solution of *p*-toluenesulfonic acid in chloroform effected both elimination of water and deketalization to give (4*R*)-7,7-diphenyl-4-methyl-2-oxoheptene (12). Compound 12 was subjected to ruthenium tetroxide oxidation to give (3*S*)-3-methyl-5-oxohexanoic acid (5).

Chart II



Stereochemistry. *cis*- and *trans*-3,5-dimethylvalerolactones 7 and 8, respectively, can each exist in two possible half-chair and two possible boat conformations (A, B, C, and D). Ir studies have demonstrated that δ-lactones that have half-chair conformations show carbonyl stretching frequency in the range 1730–1750 cm^{-1} and δ-lactones that possess boat conformations show absorption in the range 1758–1765 cm^{-1}.[2c] Since both lactones 7 and 8 show infrared carbonyl absorption (CCl_4) at 1736 cm^{-1}, it can be assumed that both 7 and 8 possess half-chair conformations. Inspection of Drieding models shows that the cis isomer has the C-3 CH_3 and C-5 CH_3 groups in a cis 1,3 relationship and would be expected to exist preferentially in conformation 7A which avoids diaxial opposition of these groups.[11] In addition, since the low- and high-temperature nmr analyses of both 7 and 8 show no new signals and show no line broadening of the signals present in the 180 to −80° temperature range, conformational homogeneity is indicated for both lactones. Thus, the problem is to determine which of the two lactones has the cis structure and to choose between the two possible half-chair conformations for the trans isomer. A detailed analysis of the ^1H nmr, ^{13}C nmr, and CD properties of 7 and 8 was used to accomplish these assignments.

Proton Nmr. The proton nmr data for lactones 7 and 8 in three solvents are listed in Table I. Concentrating first on the spectra obtained in CCl_4, the significant aspects are the shifts in the two spectra of the C-3 CH_3 (δ 1.01–1.09) and C-5 H (δ 4.29–4.46) and the appearance of the C-5 CH_3 group at δ 1.33 in both spectra. These results can be explained if the nmr spectrum having the highest field resonance for the C-3 CH_3 is assigned to the cis isomer which for reasons already stated exists preferentially in conformation **7A**. Since the cis and trans isomers have the same



resonance for the C-5 CH_3 group (δ 1.33), the trans isomer seems best represented by conformation **8A** which has this group in an equatorial position. Johnson, *et al.*,[12] have found that equatorial methyl groups on cyclohexanone appear at higher field and have J_{vic} coupling constants smaller than axial methyl groups; thus the shift of δ 1.01–1.09 ppm and the increased J_{vic} for the C-3 CH_3 group in going from **7** and **8** (equatorial to axial CH_3 group) are the results expected. In addition, the 0.17-ppm (δ 4.29–4.46 ppm) downfield shift of the C-5 H in going from **7** to **8** can be explained by the cis 1,3-diaxial interaction of the C-3 CH_3 and C-5 H of **8** which is absent in **7**. Deshielding in the order of 0.18 ppm has been observed in cyclohexanols in going from 1,3-H–H to 1,3-CH_3–H interactions.[13]

The correctness of the conformations **7A** and **8A** assigned to the cis and trans lactones, respectively, is further supported by measurements of the solvent effect (Table I). The solvent shifts $\Delta_{C_6D_6}^{CDCl_3}$ measured for the C-5 CH_3 and the C-5 H in lactones 7 and 8 show no significant differences. These results indicate that both lactones 7 and 8

Table II
Nmr Spectral Data of *cis*- and *trans*-3,5-Dimethylvalerolactones 7 and 8 in the Presence of Eu(dpm)$_3$[a]

Compd	Medium	C-3 CH_3[b]	J_{H,CH_3}[c]	C-5 CH_3[b]	J_{H,CH_3}[e]	C-5 H[b]	bw[f]	C-2 H_{ax}	$J_{2ax,2eq}$	$J_{2ax,3ax}$	$J_{2ax,3eq}$	C-2 H_{eq}[g]	$J_{2eq,3ax}$	$J_{2eq,4eq}$	$J_{2eq,3eq}$
7	CCl_4 + 0.23 mol equiv of Eu(dpm)$_3$	1.27 (d)	6.5	1.74 (d)	6.1	5.07	37	3.28 (q)	17.3	10.3		3.98 (o)	5.8	1.9	
	$CDCl_3$ + 0.24 mol equiv of Eu(dpm)$_3$	1.17 (d)	6.3	1.60	6.3	4.83 (m)	40	2.78 (q)	17.3	10.4		3.46 (o)	5.5	1.8	
8	CCl_4 + 0.24 mol equiv of Eu(dpm)$_3$	1.50 (d)	6.5	1.95 (d)	6.3	5.49	38	3.88 (q)	16.1		9.0	4.39 (q)			5.6
	$CDCl_3$ + 0.38 mol equiv of Eu(dpm)$_3$	1.27 (d)	6.3	1.61 (d)	6.1	4.96 (m)	37	2.87 (q)	16.5		9.0	3.33 (q)			5.5

[a-f] See Table I for explanation of footnotes. [g] o = octet.

form collision complexes with approximately the same geometry. Moreover, the $\Delta_{C_6D_6}^{CDCl_3}$ values of +0.27 and +0.29 for the C-5 CH_3 of **7** and **8**, respectively, are close to the +0.22 to +0.28 values found for similarly situated equatorial C-5 CH_3 groups in several δ-lactones and are quite different from the +0.36 to +0.39 values found for similar axial CH_3 groups.[5a] The $\Delta_{C_6D_6}^{CDCl_3}$ values for the C-3 CH_3 in **7** and **8** are +0.38 and +0.43 ppm, respectively. According to the suggested assignments the C-3 CH_3 group is equatorial in **7** and axial in **8**. The axial CH_3 group of **8** shows a larger upfield shift as expected. However, the difference is smaller than might be anticipated. These results suggest that the trans isomer **8** may actually exist as a slightly flattened half-chair form of **8A**.

The application of shift reagents enabled us to obtain additional support for the correctness of the assignments **7A** and **8A** for *cis*- and *trans*-3,5-dimethylvalerolactones. The addition of Eu(dpm)$_3$ to a CCl_4 solution of **7** and **8** shifted the C-2 methylene group into a spectral region where the geminal spin–spin splitting of the C-2 H's and its splitting with the C-3 H becomes amenable to first-order analysis.[14] Both compounds **7** and **8** exhibit a rather large geminal coupling constant $J_{2ax,2eq}$ = 17.3 and 16.1 Hz, respectively.[15] Since the C-2 H protons are attached to an sp^3 carbon, the large J_{gem} values must be due to an enhanced $\sigma^- - \pi$ interaction with the adjacent lactone carbonyl. Such large values for J_{gem} can be accounted for according to Barfield and Grant,[16] if the carbonyl group bisects the methylene group. This stereochemistry in combination with a planar lactone grouping necessitates that the cis and trans lactones exist in the half-chair conformation **7A** and **8A**. In the case of **7** the vicinal coupling $J_{2ax,3ax}$ = 10.3, $J_{2eq,3ax}$ = 5.8, and the long-range coupling of 1.9 Hz observed between C-2 H_{eq} and C-4 H_{eq} in **7A** are also in accord with this assignment. The large long-range coupling between C-2 H_{eq} and C-4 H_{eq} is particularly revealing since the geometry in the half-chair conformation **7A** has these protons in the planar W configuration necessary for maximum effect.[17] The geometry of a boat or half-boat conformation for the cis isomer is not favorable for the observation of such a large long-range $J_{2eq,4eq}$ coupling. In the case of the trans isomer the slightly lower J_{gem} value (16.1 Hz), the slightly larger J_{vic} (9.0 and 5.6 Hz) than expected, and the absence of C-2 H_{eq} and C-4 H_{eq} long-range coupling support the earlier suggestion based on solvent shift studies that the trans lactone **8A** has a slightly flattened half-chair conformation.[18]

Lambert has shown that the geometry about CH_2–CH_2 fragments and certain substituted ethylene fragments in many cyclic six-membered rings can be defined by a ratio of the two coupling constants J_{trans} and J_{cis}.[19] The ratio J_{trans}/J_{cis} which is called an R value will remain constant in similar systems even though J_{trans} and J_{cis} are variable and thus are dependent only on the geometry about the fragment. Since the R-value method has been used to determine the geometry of the X–CH_2CHR–Y segment of several other six-membered rings, we have applied it to the lactones **7** and **8**. The R values calculated from the data in Table II for the CH_2CHCH_3 fragment C-2–C-3 for lactones **7** and **8** are 1.78 and 0.62, respectively. These results show that the C-2–C-3 fragment geometry is different in the two lactones. Thus, if the cis lactone **7** has the conformation **7A** as the steric requirements and ir data indicate, the trans lactone **8** must have the conformation **8A** or **8D** to be consistent with the calculated R values. The latter is inconsistent with the ir data and also seems unlikely for steric reasons. The unusually small R value for the C-2–C-3 fragment of **8** would be compatible with the proposal that **8A** actually exists in a slightly flattened half-chair conformation.

Carbon-13 Nmr. Carbon-13 (^{13}C nmr) chemical shifts are remarkably sensitive to molecular geometry, and consequently ^{13}C nmr studies can be useful for stereochemical and conformational elucidation.[20] From fundamental studies on cyclohexanes[21] and the related investigation of cyclohexanones[22] it was found that, other things being equal, an axial methyl carbon on the ring is more shielded than an equatorial methyl carbon by about 4 ppm. The carbons that are γ to the methyl group (3 and 5 in methylcyclohexane) are also shifted upfield. This effect has been referred to as the γ effect. In addition, equatorial methyl groups impart deshielding α and β effects of about 6 and 9 ppm, respectively, while axial methyl functions exert similar α and β effects of about 1 and 5 ppm, respectively.[23]

The ^{13}C nmr chemical shifts relative to tetramethylsilane for *cis*- and *trans*-3,5-dimethylvalerolactones **7** and **8**, respectively, are listed in Table III. The ^{13}C nmr chemical-shift assignments are based on single frequency off-resonance decoupling (SFORD) experiments and empirical correlations[20,23] including direct comparison to the ^{13}C nmr chemical-shift assignments of *cis*- and *trans*-3,5-dimethylcyclohexanones which are also listed in Table II.[22] The ^{13}C nmr chemical-shift values are in accord with the conformations **7A** and **8A**. The C-5 CH_3 is equatorial in both **7A** and **8A**, and, thus, the ^{13}C nmr chemical shifts of the C-5 CH_3 in both lactones are almost identical. The difference of +2.94 ppm between the equatorial and axial C-3 CH_3 carbon of **7A** and **8A** respectively, results from a steric effect of the C-3 CH_3 of **8A** with C-5 (γ carbon) and its axial hydrogen. The substantial upfield shift (+3.38 ppm) at C-5 (γ

Table III
Carbon-13 Chemical Shifts of *cis*- and *trans*-3,5-Dimethylvalerolactones in C_6D_6[a]

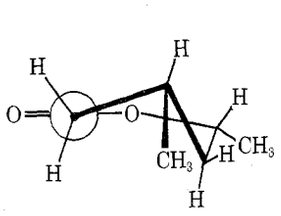
Compound	Solvent	Chemical shifts, ppm[b] C-1	C-2	C-3	C-4	C-5	C-3 CH_3	C-5 CH_3
cis-3,5-Dimethylvalerolactone (**7**)	C_6D_6	169.75 (s)	37.92 (t)	21.80 (d)	38.65 (t)	75.89 (d)	26.75 (q)	21.40 (q)
trans-3,5-Dimethylvalerolactone (**8**)	C_6D_6	170.62 (s)	36.60 (t)	21.31 (d)	37.43 (t)	72.51 (d)	23.81 (q)	21.16 (q)
cis-3,5-Dimethylcyclohexanone[c,d]		208.2	49.4	33.4	43.0	33.4	22.6	
trans-3,5-Dimethylcyclohexanone[c,d]		208.6	48.8	29.8	39.9	29.8	21.1	

[a] Chemical shifts are in parts per million relative to internal tetramethylsilane. [b] Signal multiplicity obtained from single frequency off-resonance experiments is given in parentheses beside the chemical-shift value; s = singlet, d = doublet, t = triplet, q = quartet. [c] Taken from ref 22. [d] Original data converted $\delta(\text{TMS}) = \delta(CS_2) + 192.8$.

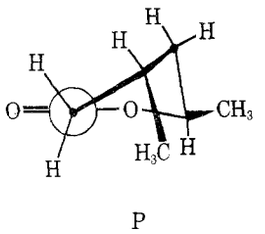
to the C-3 CH_3) of the δ-lactone **8A** with an axial C-3 CH_3 as compared with **7** with an equatorial C-3 CH_3 can be ascribed to the same steric effect (γ effect). In the case of *cis*- and *trans*-3,5-dimethylcyclohexanone shifts of 1.5 and 3.6 ppm were observed for the C-3 CH_3 (C-5 CH_3) and C-5 (C-3) carbon in going from the cis to the trans isomer.[22] The difference in chemical shift between the carbonyl carbons in **7A** and **8A** as well as those in the *cis*- and *trans*-3,5-dimethylcyclohexanones is small. The relative insensitivity of the ^{13}C resonance of this carbon to substituent effects has been attributed to the lack of directly bonded protons which make the normal mechanism of long-range substituted effects inoperative.[22] The ^{13}C nmr resonances of C-2 and C-4 of **7A** appear at lower field relative to the same resonances in **8A.** These results are expected since the equatorial C-3 CH_3 of **7A** would impose a greater deshielding (β effect) than the axial C-3 CH_3 of **8.** Similar results are observed with the 3,5-dimethylcyclohexanones.[22] The ^{13}C nmr chemical shifts of C_3 in both **7A** and **8A** are approximately the same. Everything else being equal, the C-3 of **7A** which has an equatorial CH_3 substituent should be deshielded relative to **8A** which has an axial substituent (α effect). Apparently the deshielding α effect of the equatorial CH_3 group of **7A** is balanced by a larger γ effect from the ethereal oxygen of **7A.** If **8A** actually exists in a flattened half-chair conformation as previously suggested and if the dihedral angle between bonds C-1–O and C-2–C-3 is larger than the same angle in **7A, 7A** would be expected to show a larger γ effect.[24]

CD Spectra. Several empirical rules have been proposed to explain the relation between the sign of the n–π* Cotton effect (CE) of optically active lactones and their absolute configuration. Klyne and coworkers[25] formulated a sector rule, and Snatzke and coworkers[26] used a system with curved nodal surfaces; however, neither of these methods is applicable to lactones that contain a second chiral sphere.[27] Wolf,[28] Beecham,[29] and Legrand and Bucourt[30] have related the sign of the Cotton effects of δ-lactones to the chiral character of the lactone ring. Legrand and Bucourt rules on ring chirality allow the sign of a CE to be predicted for conformations other than half-chair and boat forms.[27] According to the rules of these authors the sign of the n–π* band of nonplanar lactones is opposite to the sign of the torsion angle between bonds C-1–O and C-2–C-3 when a Newman projection is viewed along bond C-2–C-1.[31] The CD spectra of both **7aA** and **8aA** show negative CE for the lactone n–π* transition. Lactone **7aA** shows a negative minimum at 225 nm ($[\theta] = -1760$) and lactone **8aA** shows a negative minimum at lower wavelength (214 nm) but with larger molecular ellipticity ($[\theta] = -5169$).

The Newman projections O and P of **7aA** and **8aA,** respectively, show lactone **7** in the half-chair conformation O and lactone **8A** in a conformation P where the torsion angle is approximately +20°. The conformation P, which is intermediate between a half-chair and boat conformation, predicts a −CE for lactone **8aA.** In addition, this conformation, which has a larger torsion angle than O could account for the larger CE minimum of lactone **8.** The −CE of lactone **8** could also be accounted for by the half-chair conformation (**8B**) or the half-boat conformation (**8C**). However, the chair form **8B** does not account for the 12-nm difference[32] in the CD minimum of **7A** and **8A,** the boat form **8C** does not account for its ir carbonyl absorption at 1736 cm^{-1}, and neither **8B** nor **8C** is consistent with the ^1H and ^{13}C nmr data.



O



P

Conclusions

The synthesis of all four optical isomers of 3,5-dimethylvalerolactone has been achieved. This was accomplished by first resolving (±)-**5-** into (*S*)-(+)- and (*R*)-(−)-3-methyl-5-oxohexanoic acid (**5**), followed by reduction of the 5-keto group of **5,** lactonization of the 5-hydroxy-3-methylhexanoic acids formed, and separation of the resulting cis and trans lactones in each case. Since the optical isomers of the methyl ester of (*R*)-**5** have been related to (*R*)-(+)-3-methylhexanoic acid,[33-35] their configuration, as well as those at the 3 position of the 3,5-dimethylvalerolactones, is established. (*S*)-(+)-**5** was also prepared from (4*R*)-4-methyl-6-oxoheptanoic acid (**9**) whose absolute configuration has been determined.[36,37] The absolute stereochemical assignment at the 5 position of these lactones, and, thus, the complete stereochemical assignment of the four 3,5-dimethylvalerolactone enantiomers was established by a detailed analysis of their ^1H nmr, ^{13}C nmr, and CD spectra. In addition, the cis and trans lactones **7** and **8,** resectively, were shown to possess the half-chair conformations **7A** and **8A,** respectively. In the case of **8** the data indicate **8** to have actually a slightly flattened form of the half-chair **8A.**

Experimental Section

General. Melting points were determined on a Kofler hot stage microscope using a calibrated thermometer. Ir spectra were measured with a Perkin-Elmer Model 467 grating infrared spectrophotometer. Uv absorption spectra were obtained on a Cary Model 14 spectrometer. The purity of the compounds was checked by glc analyses using a Hewlett Packard Model 700 gas chromatograph

equipped with a thermal conductivity detector. Stainless steel columns (6 ft × ⅛ in.) packed with 10% SE-30 (column A) or 10% DEGS (column B) on 40–60 mesh Chromosorb W (AWS) were used. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Ill.

Nmr Spectra. Proton nmr spectra were recorded on a Varian Model HA-100 spectrometer using tetramethylsilane (TMS) as an internal standard. The high- and low-temperature studies were conducted at North Carolina State University at Raleigh, N.C., on a Varian HA-100 spectrometer.[38] Nitrobenzene was used as solvent for the high-temperature studies (up to 180°) and trichlorofluoromethane was used as solvent for the low-temperature studies (−85° to ambient temperature).

The ^{13}C nmr spectra were determined at 24.92 MHz on a modified JEOL JNM-PS-100 FT-NMR interfaced with a Nicolet 1085 Fourier transform computer system. Spectra were obtained in benzene-d_6 (C_6D_6) in a 10-mm tube. The spectra were recorded at ambient temperature by using the deuterium resonance of C_6D_6 as the internal lock signal. All proton lines were decoupled by a broad band (~2500 Hz) irradiation from an incoherent 99.076-MHz source. Interferograms were stored in 8K of computer memory (4K output data points in the transformed phase corrected real spectrum), and chemical shifts were measured on 5000-Hz sweep width spectra. Typical pulse widths were 10.0 μsec, and the delay time between pulses was fixed at 1.0 sec. Normally 1012 (twice as many for single frequence off-resonance experiments) data accumulations were obtained on a 100 mg/2 ml of solvent sample. The chemical shifts reported are believed accurate to within ±0.05 ppm.

CD Spectra and Optical Rotations. CD measurements were made at ambient temperatures (~25°) with a Durrum-Jasco Model-20 ORD–CD spectropolarimeter calibrated with *d*-10-camphorsulfonic acid (0.313° ellipticity for a 1 mg/ml solution in water using a 1.0-cm cell at 290.5 nm). All observed rotations at the sodium D line were determined with a Perkin-Elmer Model 141 polarimeter (1-dm cell).

Diethyl 1-Methyl-3-oxobutylmalonate Ethylene Ketal (4). A mixture of 57.9 g (0.237 mol) of diethyl 1-methyl-3-oxobutylmalonate (**3**),[39] 208 g of ethylene glycol, 2.3 g of *p*-toluenesulfonic acid, and 3500 ml of benzene was refluxed under a Dean-Stark tube for 43 hr. The cooled reaction mixture was washed with 5% potassium hydroxide solution, water, and brine solution and dried (Na_2SO_4). Distillation of the liquid remaining after removal of benzene gave 60.3 g (88%) of **4**: bp 115–117° (0.04 mm); $n^{22}D$ 1.4450; ir (CH_2Cl_2) 1735 cm^{-1} (C=O); the nmr ($CDCl_3$) showed two overlapping triplets and a doublet at δ 0.53–0.68 [CH_3CH_2 and $CH(CH_3)$], a singlet at 0.72 (CH_3CO_2), a doublet at 3.46 [$CH(CO_2Et)_2$], a singlet at 3.92 (OCH_2CH_2O), and a quartet at 4.18 ppm (CH_3CH_2).

Anal Calcd for $C_{14}H_{24}O_6$: C, 58.32; H, 8.39. Found: C, 58.57; H, 8.38.

3-Methyl-5-oxohexanoic Acid (5). To a refluxing solution of 100 g of potassium hydroxide in 100 ml of water was added dropwise 111.4 g (0.386 mol) of ketal diester (**4**). After the addition, the reaction mixture was refluxed an additional 4 hr. Water (100 ml) was added to the reaction and 100 ml of distillate collected (ethanol–water azeotrope). The reaction mixture was cooled in an ice bath and acidified to pH 1 with concentrated hydrochloric acid. The acid solution was refluxed overnight, cooled, and extracted with chloroform. The dried (Na_2SO_4) extracts were concentrated on a rotary evaporator. The resulting liquid was distilled under reduced pressure to give 36.6 g (73%) of **5**: bp 114° (0.5 mm); $n^{25}D$ 1.4442; ir (CH_2Cl_2) 1710 (C=O); the nmr ($CDCl_3$) showed a doublet at δ 1.04 (>$CHCH_3$), a singlet at 2.16 (CH_3CO), and a singlet at 10.0 ppm (acid OH).

Anal Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.40; H, 8.23.

Resolution of 3-Methyl-5-oxohexanoic Acid (5). To a solution of 100 g (0.83 mol) of *l*-(−)-α-methylbenzylamine in 4700 ml of ethyl ether was added 118.5 g (0.82 mol) of **5** in 200 ml of ethyl ether. The solid which separated after standing at 10° for 3 days was isolated by filtration, and the filtrate was retained for further examination. The salt obtained was recrystallized five more times from ethyl ether to give 21.1 g of *l*-(−)-α-methylbenzylamine (−)-3-methyl-5-oxohexanoate as a hygroscopic salt.[40]

Anal Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.28. Found: C, 68.03; H, 8.70; N, 5.35.

To a solution of the salt in 200 ml of water was added 10 ml of concentrated hydrochloric acid, and the solution was extracted with chloroform. The chloroform extracts were dried (Na_2SO_4) and concentrated on a rotatory evaporator. The resulting liquid was distilled to give 7.6 g of (−)-**5**: bp 110° (0.05 mm); $[\alpha]^{29.5}D$ −2.3°; $[\alpha]_{365}^{29.5}$ −33.2° (*c* 0.519, C_2H_5OH). The ir and nmr spectral properties were identical with those of (±)-**5**.

The filtrates retained from the preparation of (−)-**5** were concentrated *in vacuo* and the free acid regenerated. The liquid obtained was distilled to give 75.4 g (0.52 mol) of partially resolved **5**. A solution of the acid in 200 ml of ethyl ether was added to 63.3 g (0.52 mol) of *d*-(+)-α-methylbenzylamine in 2000 ml of ethyl ether. The solid which separated on standing at 10° for 3 days was recrystallized three more times from ethyl ether to give 18.5 g of *d*-(+)-α-methylbenzylamine (+)-3-methyl-5-oxohexanoate as a hygroscopic salt.[40]

Anal. Calcd for $C_{15}H_{23}NO_3$: C, 67.89; H, 8.74; N, 5.28. Found: C, 68.11; H, 8.92; N, 5.45.

Using the same procedure described for the preparation of (−)-**5**, the salt above gave 8.2 g of (+)-**5**: bp 110° (0.05 mm); $[\alpha]^{26}D$ +2.8°; $[\alpha]_{365}^{26}$ +35° (*c* 0.50, C_2H_5OH).

In a separate experiment conducted in the same manner as above, (+)-**5** having $[\alpha]^{23}D$ +2.64°, $[\alpha]_{365}^{23}$ +33.6° (*c* 0.568, C_2H_5OH), was obtained.

Determination of the Optical Purity of (+)- and (−)-5. The salt (0.200 g) obtained from (±)- or (+)-**5** with *l*-(+)-2-methylbenzylamine was dissolved in 10 ml of tetrahydrofuran containing 0.202 g of 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), and the mixture was heated at 50° for 16 hr. The reaction mixture was concentrated on a rotary evaporator, and the remaining residue was dissolved in benzene. The benzene extracts were washed with 5% hydrochloric acid solution and water, and dried (Na_2SO_4). The benzene solution was concentrated to a small volume and chromatographed on alumina using benzene–chloroform (3:1) as the eluent. The product fractions were combined to give 0.150–0.175 g of the amides from (±)- and (+)-**5**. The 100-MHz nmr spectrum ($CDCl_3$) of 0.026 g of the mixture of diastereomers obtained from (±)-**5** in the presence of 0.120 g of Eu(fod)$_3$ exhibited two doublets at δ 4.82 and 5.08 and two singlets at 5.85 and 6.02 ppm for the NCHCH_3 and CH_3CO resonances, respectively. The 100-MHz nmr spectrum ($CDCl_3$) of the amide (**6b**) from (+)-**5** ($[\alpha]_{365}$ +35°) showed one doublet at 5.08 and one singlet at 6.02 ppm for the NCHCH_3 and CH_3CO resonances indicating that this compound is optically pure. The calculated optical purities of (−)-**5** ($[\alpha]_{365}$ −33.2°) and (+)-**5** ($[\alpha]_{365}$ +33.6°) are 95 and 96%, respectively. These values were substantiated by nmr analyses of their respective α-methylbenzylamine amides as described for the analysis of the racemic amide of (+)-**5**.

***cis*- and *trans*-3,5-Dimethylvalerolactones (7 and 8). (A) Sodium Borohydride Method.** To a cooled (ice bath) solution of 5.5 g (0.038 mol) of (−)-, (+)-, or (±)-**5** in 50 ml of 95% ethanol was added 1.45 g of sodium hydroxide in 8 ml of water. To this solution was added portionwise 2.93 g of sodium borohydride, and the reaction mixture was stirred an additional 2–4 hr after the addition. The reaction mixture was acidified with hydrochloric acid and 19 g of tartaric acid was added. The resulting clear solution was extracted with ether. The extracts were washed with water, dried (Na_2SO_4), and concentrated on a rotary evaporator to give a mixture of *cis*- and *trans*-3,5-dimethylvalerolactones, which was distilled under reduced pressure to give 4.2–4.3 g (86–88%) of a mixture of **7** and **8**; bp 65–67° (0.08 mm).

(B) Catalytic Reduction. A solution of 2.17 g (0.015 mol) of (−)-**5** in 40 ml of absolute ethanol containing 1 g of platinum oxide was shaken on a Parr hydrogenator under 50 lb of hydrogen pressure for 3 days. The catalyst was separated by filtration and the filtrate concentrated on a rotary evaporator. The remaining liquid was distilled under reduced pressure to give 1.66 g (76%) of a mixture of *cis*- and *trans*-3,5-dimethylvalerolactones; bp 50–55° (0.05 mm). Reduction of 10 g (0.069 mol) of (±)-**5** under similar conditions gave 6.5 g (72%) of racemic *cis*- and *trans*-3,5-dimethylvalerolactones; bp 75–77° (2 mm).

Separation of *cis*- and *trans*-3,5-Dimethylvalerolactones. Method A. A solution of 5.7 g (0.045 mol) of a mixture of *cis*- and *trans*-3,5-dimethylvalerolactones obtained from (−)-, (+)-, or (±)-**5** in 25 ml of benzene containing 25 ml of freshly distilled pyrollidine was refluxed under a Dean-Stark tube for 24 hr. The benzene and excess pyrollidine were removed on a rotary evaporator. An ir spectra of the remaining liquid showed the absence of lactone carbonyl. The mixture of hydroxyamides was chromatographed on 1800 g of Woelm neutral alumina (II) eluting first with benzene and then with the following solvents: benzene and chloroform mixture, chloroforms, and finally 3% methanol in chloroform. One amide (I) was eluted with benzene and chloroform eluents and

Table IV
Optical Rotations of *cis*- and *trans*-3,5-Dimethylvalerolactone Samples[a]

Compd (no.)	Optical rotations (deg), $[\alpha]_D$; $[\alpha]_{365}$, *c* (CH_3OH)
(3*RS*,5*SR*)-*cis* (7)	0
(3*RS*,5*RS*)-*trans* (8)	0
(3*S*,5*R*)-*cis* (7a)[b]	+6.15; +14.99, 0.521
(3*S*,5*S*)-*trans* (8a)[b]	−62.7; −224, 0.498
(3*R*,5*S*)-*cis* (7b)	−6.18; −15.0, 0.534
(3*R*,5*R*)-*trans* (8b)	+63.2; +222, 0.498

[a] The optically active lactones reported in this table were prepared from (+)- and (−)-**5** having $[\alpha]_{365}$ +33.6 and −33.2°, respectively. [b] The values for (3*S*,5*R*)-*cis* (**7a**) and (3*S*,5*S*)-*trans* (**8a**) previously reported (ref 6d) were −7.33 and −68.17°, respectively. The rotation of the (3*S*,5*R*)-*cis* (**7a**) previously reported (ref 6b) actually possessed a positive rotation.

the other amide (II) with 3% methanol in chloroform eluent. The progress of the chromatography and the purity of the amides were determined by tlc analysis on alumina plates using chloroform as the eluent. The plates were developed in an iodine chamber. The tubes containing pure amide I and amide II were combined and concentrated to give 2.11–2.24 and 2.39–2.68 g of amides I and II, respectively. The ir spectra (CH_2Cl_2) of both amides showed broad absorption at 3400 (OH) and 1675 cm^{-1} (amide carbonyl), and only slight differences were apparent in the fingerprint region of the spectra; the nmr ($CDCl_3$) of amides I and II were also very similar. Amide I showed doublets at δ 1.00 and 1.17 ppm for the 3- and 5-methyl groups whereas amide II showed doublets at δ 1.00 and 1.15 ppm for the same groups. The mass spectra of amides I and II were essentially identical: (70 eV) *m/e* (rel intensity) 199 (8, molecular ion), 181 (43), 166 (93), 140 (14), 124 (21), 113 (100), 98 (71), and 85 (36).

Amide I was refluxed in 10% sodium hydroxide solution for 4 hr. The cooled reaction mixture was acidified with concentrated hydrochloric acid and extracted with ether. Concentration of the dried (Na_2SO_4) ether extracts followed by evaporative distillation of the liquid obtained gave 82–85% of *cis*- 3,5-dimethylvalerolactone (**7**): $n^{25}D$ 1.4445; ir (CCl_4) 1735 cm^{-1} (C=).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.59; H, 9.19.

Amide II was converted to *trans*-3,5-dimethylvalerolactone (**8**) in exactly the same manner as described for the conversion of amide I to **7**: $n^{25}D$ 1.4476; ir (CCl_4) 1736 cm^{-1} (C=O).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.54; H, 9.54.

Glc of all the isomers of **7** and **8** showed only one peak on both columns A and B. The ^1H nmr and ^{13}C nmr properties of **7** and **8** are listed in Tables I and III, respectively. The optical properties of **7** and **8** are listed in Table IV.

Method B. The lactones **7** and **8** could also be separated by preparative gas–liquid chromatography on a Model 700 Autoprep GC using a 15 ft × ⅜ in. copper column packed with 20% DEGS on 60–80 Chromosorb W AW-DMCS (165°, flow rate 150 ml/min of helium). For isolation 30-μl samples were processed on this column. The cis isomer (**7**) had a retention time of 48 min, and the trans isomer (**8**) had a retention time of 59 min 30 sec. The collection efficiency was 75–80%. The $n^{25}D$, ir, and ^1H nmr of the lactones **7** and **8** separated by this procedure were identical with those separated by method A.

(*R*)-(+)-Methyl 4-Methyl-6-oxoheptanoate Ethylene Ketal (10). To a solution of 19.6 g of (+)-4-methyl-6-oxoheptanoic acid[36] in 100 ml of ether was added an ethereal diazomethane solution until all reaction ceased. The solution was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Reduced pressure distillation of the crude product yielded 18.6 g (88%) of methyl 4-methyl-6-oxoheptanoate: bp 92° (3 mm); ir (CH_2Cl_2) 1712 (ketone C=O) and 1735 cm^{-1} (ester C=O).

A mixture of 18.1 g (0.105 mol) of methyl 4-methyl-6-oxoheptanoate, 65 g of ethylene glycol, and 0.7 g of *p*-toluenesulfonic acid was refluxed 4 hr under a Dean-Stark tube. The cooled solution was washed with 5% KOH (2 × 250 ml), water (1 × 250 ml), and saturated brine (1 × 250 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude product was fractionated at reduced pressure to yield 17.02 g (75%) of the title compound: bp 71° (0.06 mm); $n^{25}D$ 1.4414; d^{22} 1.033; $[\alpha]^{24}D$ +2.68° (neat).

Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.08; H, 9.32. Found: C, 60.90; H, 9.20.

(*R*)-(+)-7,7-Diphenyl-7-hydroxy-4-methyl-2-oxoheptane Ethylene Ketal (11). To a solution of 15.8 g (0.073 mol) of **10** in 75 ml of dry ethyl ether was added 58.5 ml (an excess) of a 3 *M* phenylmagnesium bromide solution in ethyl ether, and the mixture was refluxed for 5 hr. The cooled reaction mixture was poured onto ice, and glacial acetic acid was added until the solids dissolved. The ether phase was separated and combined with the ether extract (7 × 100 ml) of the aqueous phase, washed with 0.4% $NaHCO_3$ (5 × 100 ml) and saturated brine (1 × 100 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude solid obtained was purified by a combination of chromatography on Woelm aluminum oxide (III) (benzene eluent) and recrystallization from a cyclohexane and hexane mixture. A total of 17.64 g (71%) of **11** was obtained, mp 75–80°. The analytical sample prepared by recrystallization from a cyclohexane and hexane mixture had mp 80–81°; $[\alpha]^{22.5}D$ +5.19° (*c* 1.54, C_2H_5OH); ir (CH_2Cl_2) 3595 and 3380 (OH) and 1595 cm^{-1} (aromatic); nmr ($CDCl_3$) showed a doublet at δ 0.93 (>CHCH_3, *J* = 5.7 Hz), a singlet at 1.23 (CH_3CO_2), a singlet at 3.80 (OCH_2CH_2O), and a multiplet at 7.10–7.61 ppm (aromatic); mass spectrum (70 eV) *m/e* 340 for molecular ion.

Anal. Calcd for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.90; H, 8.30.

(*R*)-(+)-7,7-Diphenyl-4-methyl-6-hepten-2-one (12). A solution of 14.88 g (0.0437 mol) of **11** in 450 ml of chloroform containing 3 ml of water and 0.45 g of *p*-toluenesulfonic acid was refluxed for 1 hr. The cooled reaction mixture was washed with water, 0.4% sodium bicarbonate solution, and water. The organic layer was dried (Na_2SO_4) and concentrated on a rotary evaporator. The liquid obtained was distilled under reduced pressure to give 10.76 g (89%) of **12**: bp 178° (0.02 mm); $n^{25}D$ 1.5705; $[\alpha]^{23.5}D$ +15.54° (*c* 2.02, C_2H_5OH); ir (CH_2Cl_2) 1705 cm^{-1} (C=O); nmr ($CDCl_3$) showed a singlet at δ 2.01 (CH_3CO), a triplet at 6.11 (CHCH$_2$), and a multiplet centered at 7.23 ppm (aromatic protons).

Anal. Calcd for $C_{20}H_{22}O$: C, 86.28; H, 7.97. Found: C, 86.24; H, 7.98.

(*S*)-(+)-Methyl-5-oxohexanoic Acid (5) Prepared from 12. A solution of ruthenium tetroxide was prepared by adding 4.0 g of sodium metaperiodate in 40 ml of water to a suspension of 1.0 g of ruthenium dioxide in 300 ml of acetone (distilled from potassium permanganate) and 120 ml of water. To this solution was added dropwise a solution of 8.5 g (0.003 mol) of **12** in 400 ml of acetone over a 2-hr period. The solution turned dark as **12** was added, and the ruthenium tetroxide was regenerated by adding a solution of 60 g of sodium metaperiodate in 600 ml of acetone–water (1:1) as needed. After the addition, more of the solution was added as the mixture darkened in color. Two hours after the addition was completed, 400 ml of isopropyl alcohol was added. The reaction mixture was filtered through a Celite pad and the precipitate washed well with acetone. The filtrate was concentrated on a rotary evaporator until an oil began to separate. This mixture was extracted with chloroform (5 × 200 ml). The extracts were combined and extracted with 400 ml of 5% sodium hydroxide solution in three portions. These extracts were cooled in an ice bath, acidified with concentrated hydrochloric acid, and extracted with chloroform. The chloroform fraction was dried (Na_2SO_4) and concentrated on a rotary evaporator to give a yellow liquid. Distillation under reduced pressure gave 2.74 g (62%) of (+)-**5**:[41] bp 105° (0.08 mm); $n^{25}D$ 1.4451; $[\alpha]^{25}D$ +1.96° (*c* 0.46, C_2H_5OH); $[\alpha]^{23}D$ +4.52 (neat). The ir and nmr spectra of this sample of (+)-**5** were identical with the sample prepared by resolution of (±)-**5**.

Anal. Calcd for $C_7H_{12}O_3$: C, 58.31; H, 8.39. Found: C, 58.13; H, 8.23.

Registry No.—**3,** 52920-95-3; **4,** 52920-96-4; (±)-**5,** 52920-97-5; (−)-**5,** 52949-94-7; (−)-**5** (−)-α-methylbenzylamine salt, 52949-95-8; (+)-**5,** 52949-96-9; (+)-**5** (+)-α-methylbenzylamine salt, 52949-97-0; **6a,** 52920-98-6; **6b,** 52920-99-7; **7,** 52949-98-1; **7a,** 32747-16-3; **7b,** 52949-99-2; **8,** 52950-00-2; **8a,** 32747-17-4; **8b,** 52950-01-3; **9,** 52921-00-3; **9** methyl ester, 52921-01-4; **10,** 52921-02-5; **11,** 52921-03-6; **12,** 52921-04-7; amide I, 52921-05-8; amide II, 52921-06-9; (−)-α-methylbenzylamine, 2627-86-3; (+)-α-methylbenzylamine, 3886-69-9; pyrrolidine, 123-75-1.

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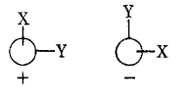

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(33) (−)- and (+)-3-methylhexanoic acid have been related to (−)- and (+)-methylsuccinic acid which has been related with (*S*)- and (*R*)-glyceraldehyde.[33,34]
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(40) The progress of the resolution was followed by converting small samples of salt to the free acid and obtaining its optical rotation at 365 nm. The progrss of the resolution could also be followed by a procedure similar to that used to determine its optical purity which is described in the next experiment.
(41) The acid (+)-**5** was also prepared by ozonolysis of **12** using a formic acid 30% hydrogen peroxide work-up. However, the yield of acid (+)-**5** obtained by this method was low (14%), and the sample was not as pure as the sample obtained by ruthenium tetroxide oxidation.

The pH Independent Equilibrium Constants and Rate Constants for Formation of the Bisulfite Addition Compound of Isobutyraldehyde in Water[1]

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The magnitudes of the apparent equilibrium constants for the formation of adduct in aqueous solutions of isobutyraldehyde and sodium bisulfite were determined spectrophotometrically and titrimetrically from pH 2.3 to 12.8 at 25°. The equilibrium constant for the addition of sulfite ion to isobutyraldehyde is 3.70 M^{-1} (at zero ionic strength) and the pK_a of the sodium bisulfite addition compound of isobutyraldehyde is 11.32 (at zero ionic strength). Rate constants were determined spectrophotometrically using potassium triiodide as a scavenger. General acids and general bases appear to have no effect on the rate of dissociation over the pH range of 4.4–7.8 and the rate-determining step is clearly a unimolecular decomposition of the doubly charged anion. The pH independent rate constants k_d and k_f, for decomposition and formation of this dianion, respectively, are 3800 sec^{-1} and 14,000 M^{-1} sec^{-1}, respectively.

Among the types of reactions used to characterize certain reactive ketones and aldehydes is the formation of sodium bisulfite addition compounds, which may at a later time be decomposed to yield the aldehyde or ketone. The fact that the carbonyl compound is recoverable is responsible for the role this reaction has as a means of separating aldehydes and reactive ketones from mixtures that contain other organic substrates. It is surprising that so little information is available with regard to the equilibria, kinetics, and mechanism of adduct formation and decomposition.