5 can certainly proceed according to a mechanism involving the regiospecific 1,4-cycloaddition.

Experimental Section

Melting points are uncorrected. The ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer R-24 B spectrometer and a Varian EM 390 spectrometer. Me_4Si was used as internal standard (δ 0). IR spectra were recorded on a Hitachi EPI-G3 spectrophotometer.

Mass spectra were determined on a AEI MS 902 mass spectrometer equipped with VG ZAB console and GC-MS analysis was performed on a VG micromass 7070F apparatus.

Preparation of Starting Materials. 5-Nitropyrimidine (1) was prepared by the method described in the literature.[8] Amidines were prepared according to known synthetic procedures.[9,10] The amidines were isolated and used as hydrochlorides. ^{15}N-labeled amidines were prepared according to the method described for the preparation of ^{15}N-labeled benzamidine.[11]

Reactions of 5-Nitropyrimidine (1) with Amidines. The reactions of 1 with benzamidine, pivalamidine, and acetamidine were carried out according to known procedures.[4] The reactions of 1 with ^{15}N-labeled amidines were carried out in the same manner to yield **5a***-**5c***.

Reaction of 1 with Benzamidine Hydrochloride in the Absence of Triethylamine. 1 (125 mg, 1 mmol) and 1 mmol of benzamidine hydrochloride were dissolved in 2 mL of Me_2SO. The mixture was heated at 100 °C for 12 h. After cooling, the precipitate was collected, washed with water and ethanol, and recrystallized from ethanol. Yield of **5a** was 46 mg (23%). The same procedure was used for the reaction of 1 with ^{15}N-labeled benzamidine hydrochloride.

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Registry No. 1, 14080-32-1; **5a**, 68906-00-3; benzamidine, 618-39-3; pivalamidine, 59950-56-0; acetamidine, 143-37-3; benzamidine hydrochloride, 1670-14-0.

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Chiral 3-Substituted Aldehydes: Determination of Absolute Configurations and Enantiomeric Excesses by NMR Analysis of Derived Oxazolidines

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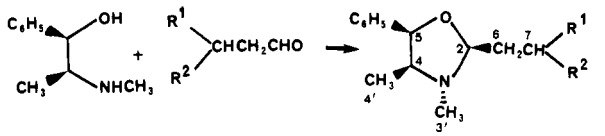
The absolute configurations and the enantiomeric excesses of chiral 3-alkyl- and 3-aryl-substituted aldehydes are determined by ^{13}C NMR and ^1H NMR analysis of the corresponding oxazolidines derived from (-)-ephedrine.

NMR spectroscopy is a well-documented method of determining optical purities and absolute configurations of partially resolved enantiomers;[1] chiral shift reagents, chiral solvating agents, and diastereomeric derivatives have been the subject of countless articles.

In this paper, we will report the use of oxazolidines derived from the condensation of (-)-ephedrine with chiral 3-substituted aldehydes providing both a measure of the enantiomeric ratios of the aldehydes and the assignments of their absolute configurations. Related determinations of the enantiomeric excesses of 2-substituted (and a few 3-substituted) aldehydes and ketones via their diastereomeric imines or acetals have already been reported.[2]

This method makes use of the stereoselective condensation of naturally occuring (1*R*,2*S*)-(-)-ephedrine with aldehydes (eq 1), leading to oxazolidines which exhibit the



2*S* configuration (2*S*/2*R* ~ 93/7) when the reaction is performed under the usual conditions, i.e., under thermodynamic control.[3]

Very mild conditions (methylene chloride solution, molecular sieves, room temperature) are required for reaction 1 to proceed quantitatively; therefore, ephedrine is perfectly suited as a chiral derivatizing agent for aldehydes. As the main ^1H NMR and ^{13}C NMR features of oxazolidines are well established,[4,5] analysis of the diastereomeric

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Table I. Carbon-13 NMR Chemical Shifts of Oxazolidines[a,b]

compd	R^1	R^2	C-2	C-4	C-5	others
1	CH_3	C_2H_5	96.1/96.7	64.0	81.8	31.1/31.4 (C-7)
						19.2/20.2 (R^1)
2	CH_3	n-C_3H_7	96.0/96.7	64.0/64.1	81.8	36.3/36.4 (C-3′)
						29.2/29.7 (C-7)
						19.6/20.7 (R^1)
3	CH_3	n-C_4H_9	96.0/96.7	64.1/64.2	81.8	36.3/36.4 (C-3′)
						29.4/29.9 (C-7)
						19.7/20.8 (R^1)
4	CH_3	i-C_3H_7	96.1/97.3	63.9/64.1	81.7	36.3/36.5 (C-3′)
5	CH_3	t-C_4H_9	96.6/99.4	64.1/64.6	81.9	36.1/36.8 (C-3′)
						27.8/29.6 (C-7)
6	n-C_3H_7	t-C_4H_9	97.0/98.7	64.2	80.2/81.5	36.3/36.8 (C-3′)
7	CH_2=CH	n-C_3H_7	95.8/96.1	64.2	81.8/81.9	113.7/115.0 (CH_2=CH)
						142.6/143.2 (CH_2=CH)
8	CH_3	C_6H_{11}[c]	95.7/95.9	64.0/64.2	81.8	36.2/36.4 (C-3′)
9	CH_3	C_6H_{11}[d]	96.1/96.8	64.1/64.2	81.8	36.4/36.9 (C-3′)
						29.3/29.8 (C-7)
10	n-C_3H_7	C_6H_{11}[c]	96.8/97.3	64.3	81.8	39.3/39.8 (C-3′)
11	CH_3	C_6H_5	95.7/96.0	64.0/64.3	81.8	36.2/36.6 (C-3′)
						21.5/23.8 (R^1)
12	CH_3	$C_{10}H_7$[e]	95.6/96.2	63.8/64.1	81.6/81.9	36.1/36.6 (C-3′)
13	CH_2=CH	C_6H_5	95.4/95.5	64.1	81.7	36.2/36.4 (C-3′)
						14.9/15.4 (C-4′)
14	C_2H_5	C_6H_5	95.7/95.9	64.0/64.2	81.6/81.8	36.0/36.7 (C-3′)
						14.8/15.0 (C-4′)
15	C_4H_9	C_6H_5	95.6/95.9	64.0/64.2	81.6/81.8	36.0/36.7 (C-3′)
						14.8/15.0 (C-4′)
16	t-C_4H_9	C_6H_5	92.4/97.8	62.4/64.3	80.0/80.7	34.3/38.2 (C-3′)

[a] For the carbon atoms numbering, see eq 1. [b] Underlined values are connected to diasteromeric oxazolidines derived from aldehydes showing the A configuration. [c] Cyclohexyl. [d] $(CH_3)_2C$=$CHCH_2CH_2$. [e] α-Naphthyl.

mixtures were carried out in this way.

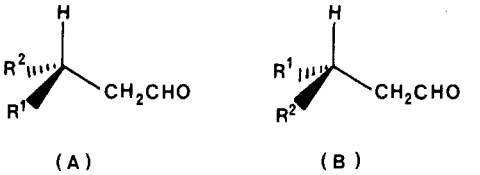
Optically active 3-substituted aldehydes have been prepared by addition of organocuprates to oxazolidines derived from α,β-unsaturated aldehydes and (−)-ephedrine according to a published method.[6] The absolute configurations and the optical purities of the resulting 3-substituted aldehydes were determined: (i) by comparison of their optical rotations with those of the reported literature values (R^1 = CH_3; R^2 = C_2H_5, C_6H_5, $(CH_3)_2C$=$CHCH_2CH_2$) or (ii) by chemical correlations with the known corresponding carboxylic acids.

The diastereomeric oxazolidines (2*S*,7*S* and 2*S*,7*R*) obtained from the 3-substituted chiral aldehydes are clearly identified by ^{13}C and ^1H NMR spectroscopy: selected data are reported in Tables I and II. The minor mixture of 2*R*,7*S* and 2*R*,7*R* epimeric oxazolidines (vide supra) does not exceed 7% and can be neglected in calculating the 7*S*/7*R* ratio.

^{13}C NMR Spectroscopy. In the ^{13}C NMR spectra of oxazolidines, the peaks pertaining to the heterocyclic ring carbon atoms stand out very clearly (Table I). Among these three signals, the carbon-2 chemical shift is specially convenient for measuring the diastereomeric ratios as each diastereoisomer gives rise to a distinct peak. Assuming that differences in relaxation times are negligible for these diastereotopic carbon atoms, signal intensities allow the determination of the diastereomeric ratios of oxazolidines and consequently the enantiomeric excesses of the chiral 3-substituted aldehydes.

The uncertainty of this method was estimated by analyzing the C-2 chemical shift intensities of oxazolidines **9** derived from (*R*)-citronellal showing various enantiomeric purities. A 3% relative error was thus determined.

As regards the absolute configurations, the assignments can be drawn on the following basis: the more shielded C-2 chemical shift is connected with configuration A of the corresponding aldehyde. In configurations A and B, R^2



(A) (B)

stands for either the aryl group (3-aryl aldehydes) or the bulkiest alkyl group (3-alkyl aldehydes).

^1H NMR Spectroscopy. Unlike the ^{13}C NMR method, ^1H NMR spectroscopy is not equally applicable to 3-aryl and 3-alkyl aldehydes: only the diastereomeric oxazolidines derived from chiral 3-aryl aldehydes exhibit pronounced hydrogen chemical shift differences (Table II).[7] In each diastereomeric mixture, the chemical shifts of 2-H, 3′-H, and 5-H appear deshielded in oxazolidines derived from chiral aldehydes showing the configuration A where R^2 is the aryl group.

The enantiomeric excesses of the starting aldehydes can be calculated easily from signal intensities. Relative error depends on the applied field: 2% or 3% using a 250-MHz or a 60-MHz spectrometer, respectively.

Table II. Hydrogen NMR Chemical Shifts of Oxazolidines[a]

compd	2-H[b]	3′-H[c]	5-H[d]
11	3.44/3.86	2.00/2.12	4.80/4.86
12	3.73/4.10	2.20/2.26	4.91/5.23
13	3.56/4.00	2.14/2.27	4.96/5.04
14	3.52/3.97	2.09/2.24	4.94/5.00
15	3.57/3.92	2.06/2.23	4.90/4.97
16	3.73/4.02	2.06/2.30	4.80/5.10

[a] Underlined values are connected to diastereomeric oxazolidines derived from aldehydes showing the A configuration. [b] Doublet × doublet, J = 2–2.5 and 5–8 Hz. [c] Singlet. [d] Doublet, J = 8–8.5 Hz.

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(7) ^1H NMR data of compounds **11** and **15** have already been published and connected to the absolute configurations of the aldehydes.[6a]

In the case of oxazolidines derived from 3-alkyl aldehydes, small chemical shifts differences can be observed only with high-field NMR; for instance, the 2-H peaks ($\delta \sim 3.90$) here again appear at lower field in configuration A where R^2 is the bulkiest alkyl group. However, partial overlap of signals prevents accurate determinations of the diastereomeric ratio. Therefore ^{13}C NMR spectroscopy is by far the most convenient method as regards 3-alkyl-substituted aldehydes.

The reliability of NMR techniques applied to the determination of enantiomeric compositions, compared to the polarimetric method, is widely attested.[1] The empirical rule we suggest is based on 14 compounds: **1–5** and **8–16** whose absolute configurations were already assigned (see Experimental Section). The absolute configuration of 3-*tert*-butylhexanal was deduced from the above general relationship via oxazolidine **6**: the levorotatory enantiomer of this aldehyde shows the *R* configuration and its ee value (66%) was measured from the NMR data. Therefore, the maximum optical rotation $[\alpha]^{20}_D$ may be calculated, −30.7 ± 1.2° (*c* 3, EtOH). Likewise, the calculated maximum optical rotation $[\alpha]^{20}_D$ of (*S*)-3-propylpent-4-enal (corresponding to oxazolidine **7**) is +8.6 ± 0.3° (*c* 1.5, EtOH).

In view of the active current interest[8] on chiral β-substituted aldehydes (and the parent primary alcohols and carboxylic acids), the above examples show that this NMR method may be a useful tool for structural determinations.

Experimental Section

The ^{13}C NMR spectra were recorded on a JEOL FX 90 Q spectrometer as solutions in $CDCl_3$. The ^1H NMR spectra were obtained on Varian T 60, on Brucker 270, and on Cameca 250 spectrometers ($CDCl_3$ solutions). Chemical shifts (δ) are given in ppm, downfield from tetramethylsilane as internal standard. The optical rotations were measured with a Perkin-Elmer 141 polarimeter.

3-Substituted Aldehydes. The optically active 3-substituted aldehydes were prepared by addition of organocuprates[6] to α,β-ethylenic oxazolidines derived from ephedrine and the following commercially available aldehydes: (*E*)-cinnamaldehyde, (*E*)-crotonaldehyde, (*E*)-hexenal, and (*E*)-3-naphthylpropenal.[9] Optical purities are in the range 10–50%. Both partially resolved enantiomers were obtained by using (+)- or (−)-ephedrine. The corresponding racemic aldehydes were prepared from a published procedure[10] and the preceding optically active aldehydes exhibited identical NMR, IR, and MS spectra.

3-Substituted Carboxylic Acids. Oxidations of the aldehydes to their parent carboxylic acids were performed by potassium permanganate under acidic conditions.[11] Optical rotations of the acids and/or the corresponding aldehydes were compared, under identical experimental conditions, to literature data (the following numbers refer to the oxazolidine derivatives): **1** (aldehyde),[12] **1** (acid),[13] **2** (acid),[14a] **3** (acid),[15] **4** (acid),[16] **5** (acid),[16] **8** (acid),[14b] **9** (aldehyde),[17] **10** (acid),[14b] **11** (aldehyde),[18] **12** (acid),[19] **14** (acid),[20] **15** (acid),[21] and **16** (acid).[22] Absolute configuration of **13** (acid) was deduced by chemical correlation (catalytic reduction over Raney nickel[23]) with the corresponding saturated compound **14** (acid).[20]

Oxazolidines were prepared by mixing the aldehyde (2 mmol), (−)-ephedrine (2 mmol)[24] in dichloromethane (4 mL) over molecular sieves (3 Å). The mixture was allowed to stand overnight at room temperature and was then filtered (Celite). The oxazolidines were obtained as colorless or pale yellow oils which were used without any further purification.

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Conversion of Shikimic Acid to 5-Enolpyruvylshikimate 3-Phosphate

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The synthesis of (−)-5-enolpyruvylshikimate 3-phosphate (**3**), a principle metabolite in the shikimic acid pathway, has been accomplished in 22% overall yield from the known acetonide **6**. A key intermediate in the synthesis is diester **9**. Direct cyclization of this material affords lactone **10** and distinguishes the three hydroxyl groups of the shikimate nucleus. The phosphate moiety is introduced efficiently with tetrabenzyl pyrophosphate, followed by deprotection with trimethylsilyl bromide. (−)-5-Enolpyruvylshikimic acid (**4**), a secondary metabolite in the shikimate/chorismate pathway, is formed on hydrolysis of **9**.

The shikimate/chorismate biosynthetic pathway is present in plants and a number of microorganisms, converting D-glucose to a variety of metabolites including the aromatic amino acids, folate coenzymes, and quinones of

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