1425, 1375, 1315, 1225 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.70 (s, 3 H, CH_3), 7.07–8.05 (m, 6 H, Ar*H*).

Oxidation of 5,6-Dihydrophenanthridine (8). To a mixture of amine **8** (77 mg, 0.43 mmol) and sodium tungstate (3 mg, 0.01 mmol) in methanol (5 mL) was added dropwise 30% aqueous hydrogen peroxide (149 mg, 1.4 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 48 h. The usual workup and column chromatography (SiO_2, 15 mm × 70 mm, CH_2Cl_2) gave phenanthridine (**9**) (62 mg, 81% yield): mp 106.5–107.5 °C; R_f 0.47 (SiO_2, ether); IR (Nujol) 1970, 1940, 1910, 1625, 1590, 1580, 1490, 1400, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.44–8.30 (m, 6 H, Ar*H* on C-2,3,4,7,8,9), 8.53 (d, J = 7.0 Hz, 2 H, Ar*H* on C-1,10), 9.22 (s, 1 H, Ar*H* on C-6). Anal. Calcd for $C_{13}H_9N$: C, 87.12; H, 5.06; N, 7.82. Found: C, 86.92; H, 5.03; N, 7.68.

Oxidation of 1,2,3,4-Tetrahydroquinoxaline (10). To a mixture of **10** (213 mg, 1.59 mmol) and sodium tungstate (10 mg, 0.03 mmol) in methanol (16 mL) was added dropwise 30% aqueous hydrogen peroxide (368 mg, 3.36 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 24 h. The usual workup and Kugelrohr distillation (155 °C (10 mmHg)) gave quinoxaline (**11**) (76 mg, 37% yield): mp 37–39 °C; R_f 0.15 (SiO_2, ether); IR (Nujol) 1495 (C—C), 1415, 1200 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50–7.85 (m, 2 H, Ar*H* on C-6,7), 7.90–8.20 (m, 2 H, Ar*H* on C-5,8), 8.76 (s, 2 H, Ar*H* on C-2,3).

Oxidation of 5,6,11,12-Tetrahydrodibenz[*b*,*f*]azocine (15). To a mixture of **15** (258 mg, 1.23 mmol) and sodium tungstate (8 mg, 0.02 mmol) in methanol (12 mL) was added dropwise 30% aqueous hydrogen peroxide (426 mg, 3.88 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 28 h. The usual workup and column chromatography (SiO_2, 15 mm × 90 mm, hexane–CH_2Cl_2) gave 2-[2-(2-nitrosophenyl)-ethyl]benzaldehyde (**16**) (91 mg, 31% yield): mp 94.0–94.5 °C; IR (Nujol) 1695 (C=O), 1600 (C—C), 1530 (N=O monomer), 1320, 1310 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.63 (dt, J = 2.0, 8.0 Hz, 2 H, CH_2 ortho to CHO), 4.12 (dt, J = 2.0, 8.0 Hz, 2 H, CH_2 ortho to N=O), 6.17 (d, J = 8.0 Hz, 1 H, Ar*H* meta to N=O), 7.00–7.83 (m, 7 H, Ar*H*), 10.13 (s, 1 H, C*H*O).

Oxidation of 2,3,4,5-Tetrahydro-1*H*-benz[*b*]azepine (20). To a mixture of amine **20** (794 mg, 5.39 mmol) and sodium tungstate (35 mg, 0.11 mmol) in methanol (50 mL) was added dropwise 30% aqueous hydrogen peroxide (1.79 g, 16.3 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 50 h. The usual workup and column chromatography (SiO_2, 20 mm × 130 mm, hexane–dichloromethane) gave 1-hydrozy-3,4-dihydroquinolin-2(1*H*)-one (**2a**) (294 mg, 33% yield): R_f 0.30 (SiO_2, ether); mp 117.5–118.5 °C; IR (Nujol) 3000–2700 (O—H), 1690 (C=O), 1605 (C—C) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.78 (t, J = 6.0 Hz, 2 H, $COCH_2CH_2$), 2.83 (t, J = 6.0 Hz, 2 H, $ArCH_2CH_2$), 6.82–7.58 (m, 4 H, Ar*H*), 8.55 (br s, 1 H, O*H*). Anal. Calcd for $C_8H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.11; H, 5.53; N, 8.30.

Formation of 1-Formyl-1,2,3,4-tetrahydroquinoline (5a). To a mixture of amine **1a** (500 mg, 3.75 mmol) and copper dichloride (10 mg, 0.07 mmol) in methanol (40 mL) was added dropwise 30% aqueous hydrogen peroxide (1.1 mL, 11 mmol) at 0 °C under argon. The reaction mixture was stirred at room temperature for 20 h. The usual workup and column chromatography (SiO_2, 10 g, hexane–dichloromethane, 4:1) gave two products, **5a** and **3a**. **5a** (161 mg, 26% yield), which was further purified by GLC (column temperature 140 °C) to give 50 mg (8% yield) of colorless oil: R_f 0.47 (SiO_2, ether); IR (neat) 2930 (C—H), 1650 (C=O), 1255, 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.95 (tt, J = 6.0, 6.0 Hz, 2 H, $CH_2CH_2CH_2$), 2.81 (t, J = 6.0, 2 H, $ArCH_2CH_2$), 3.79 (t, J = 6.0 Hz, 2 H, CH_2CH_2NH), 6.99–7.30 (m, 4 H, Ar*H*), 8.72 (s, 1 H, C*H*O); mass spectra m/e (rel %) 162 (M^+ + 1, 9), 161 (M^+, 79), 133 (15), 132 (M^+ – CHO, 100), 130 (11), 118 (20), 117 (25), 77 (20). Anal. Calcd for $C_{10}H_{11}NO$: C, 74.50; H, 6.88; N, 8.69. Found: C, 74.23; H, 6.90; N, 8.40. Quinoline (**3a**) (107 mg, 23% yield): R_f 0.47 (SiO_2, ether); ^{1}H NMR ($CDCl_3$) δ 7.26 (dd, J = 4.3, 8.3 Hz, 1 H, Ar*H* on C-3), 7.4–7.7 (m, 3 H, Ar*H* on C-5,6,7), 8.00 (dd, J = 8.3, 1.8 Hz, 1 H, Ar*H* on C-4), 8.81 (dd, J = 4.3, 1.8 Hz, 1 H, Ar*H* on C-2); mass spectra m/e (rel %) 130 (M^+ + 1, 11), 129 (M^+, 100), 128 (M^+ – 1, 19), 102 (M^+ – 27, 26).

Registry No. **1a**, 635-46-1; **1b**, 19343-78-3; **1c**, 91-61-2; **1d**, 120-15-0; **1e**, 114235-55-1; **1f**, 49716-18-9; **1g**, 22190-35-8; **1h**, 113961-88-9; **1i**, 50741-36-1; **1j**, 52601-70-4; **1k**, 1780-19-4; **2a**, 771-19-7; **2b**, 113961-89-0; **2c**, 113961-90-3; **2d**, 113961-91-4; **2e**, 114259-70-0; **2f**, 114259-71-1; **2g**, 125076-71-3; **2h**, 113961-92-5; **2i**, 125076-72-4; **2j**, 114259-72-2; **3a**, 91-22-5; **3f**, 612-57-7; **3h**, 73013-68-0; **3i**, 91-63-4; **5a**, 2739-16-4; **6**, 5223-80-3; **7**, 125108-26-1; **8**, 27799-79-7; **9**, 229-87-8; **10**, 3476-89-9; **11**, 91-19-0; **15**, 5697-88-1; **16**, 114235-54-0; **20**, 1701-57-1; Na_2WO_4, 13472-45-2; 7,8-benzoquinoline, 230-27-3.

Lipase-Catalyzed Resolution of Acyclic Amino Alcohol Precursors[1]

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Lipase-catalyzed resolution of acyclic 2-azido alcohols as precursors for amino alcohols was readily accomplished. Butanoates of racemic acyclic azidoalkanols were hydrolyzed by using commercially available lipases from *Candida cylindracea* and *Pseudomonas fluorescens*, respectively. Some representative examples of acyclic secondary 2-azido alcohols have been obtained with enantiomeric excess ranging from 24 to >98%.

Introduction

Enzymatic hydrolysis has recently been used for the optical resolution of several highly functionalized chiral molecules such as amino acids, lactones, diesters, and hydroxy acids.[2] Surprisingly, there are only few reports on the resolution of chiral amino alcohols, in spite of their importance both as chiral building blocks and as products of pharmaceutical interest.[3,4] They represent important structural features of natural products such as adrenaline, β-adrenergic receptor blockers, and local anesthetics.[5] In

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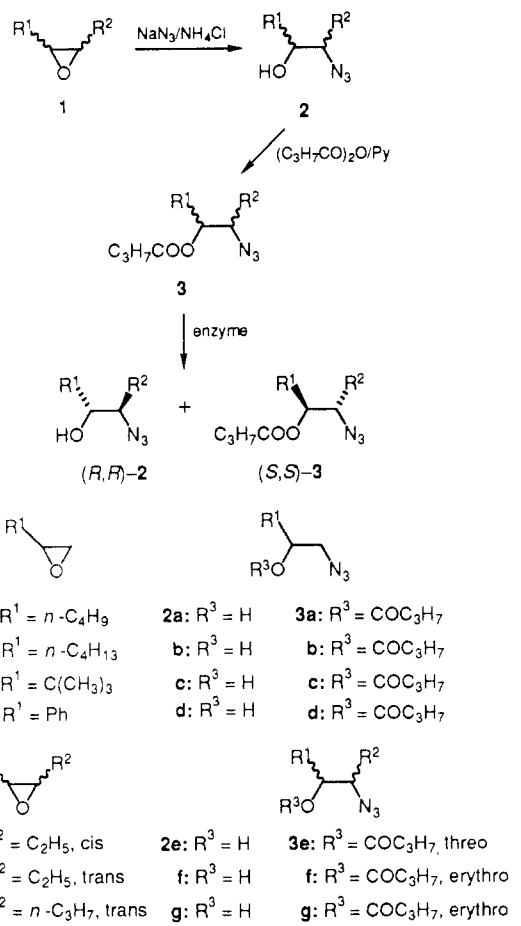
Scheme I



recent years, hydroxy amino acids have gained widespread interest as they are found in such diverse natural and synthetic effectors as tumor growth inhibitors (e.g., bleomycin[6]), immuno stimulants (e.g., bestatin[7]), enzyme inhibitors (including agents that possibly control AIDS, e.g., pepstatin[8]), and substances for the treatment of hypertension (e.g., statin[9]). 1-Amino-2-hexanol has been used as a precursor for antithrombotic amino prostaglandin analogues.[10] In all cases known, the enantiomers differ significantly in their biological activities; therefore, methods for the synthesis of optically pure products seem highly desirable. There are only few reports on enzymatic preparations of synthons for 1-amino-2-alkanols,[3] the majority of the literature dealing with 2-amino-1-alkanols,[4] some of which can also be obtained very easily by reduction of the corresponding, optically active amino acids. There is one report on (5*S*,6*S*)-6-azido-5-decanol obtained via a six-step procedure starting from optically active pinanediol boronic esters.[11]

We recently have developed a very simple procedure for the enzymatic resolution of cyclic azido alcohols[12] as precursors for amino alcohols. We now report on the extension of this method to acyclic compounds.

Results

Starting Materials. The azido alcohols **2a–g** were prepared by nucleophilic ring opening of the respective epoxides **1a–g**[13] (Scheme I). If not available commercially, the latter could easily be obtained by oxidation of the respective alkenes with peracetic[14] or *m*-chloroperbenzoic acid.[15] Of the alkenes, only (*Z*)-3-hexene had to be prepared by hydrogenation of 3-hexyne[16] with the aid of a Lindlar catalyst.[17]

Opening of asymmetric epoxides with azide usually proceeded highly regioselectively, resulting in the racemic azido alcohols with a terminal azido group. Only 5–10% of the respective regioisomers were formed, which could easily be removed by column chromatography on silica gel. In the case of styrene oxide (**1d**), regardless of the reaction conditions employed, the preponderant regioisomer proved to be the one with the hydroxyl group at the terminal position. Even with trimethylsilyl azide, employed together with varying amounts of $ZnCl_2$ or Montmorillonite, respectively, contrary to the literature,[18] at best only 15% of the desired regioisomer could be obtained. **2d** thus was synthesized by reduction of α-azidoacetophenone (obtained from α-bromoacetophenone) in good yield.[19]

Esterifications were carried out according to standard procedures.[20]

Enzymatic Hydrolyses. In our previous studies,[12] butanoates were found to be most suitable for enzymatic hydrolysis of racemic cyclic azido alcohol esters with a series of different lipases. Although several commercially available hydrolytic enzymes have been screened,[21] only two of them, namely, lipases from *Candida cylindracea* (CC) and *Pseudomonas fluorescens* (P), gave satisfactory results. Of these, P showed the better enantiodifferentiation together with acceptable rates and degrees of conversion, especially for substrates *rac*-**3d**, **3e**, **3f**, and **3g**, but gave no conversion at all with *rac*-**3c**. CC acted comparably to P, somewhat less active and with lower enantiodifferentiation except for substrate *rac*-**3c** (see Table I). The hydrolyses were carried out at pH 6.50, which was maintained constant by addition of 1 N NaOH from an autoburet.

By a plot of percent conversion (measured by the consumption of NaOH) versus time, one could easily depict

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(21) In hydrolyses of the substrates used, lipase from porcine pancreas (Sigma) and *Aspergillus niger* (Amano) were not stereospecific; lipase from *Rhizopus* sp. (Amano) and pig liver esterase gave no reaction at all.

Table I. Lipase-Catalyzed Hydrolysis of 3a–g[a]

			hydrolyzed alcohol						remaining ester					
substrate	enzyme	time, h	conv, %	yield,[b] %	$[\alpha]^{20}_D$[c]	isomer[d]	ee,[e] %	E[f]	conv, %	yield,[b] %	$[\alpha]^{20}_D$[c]	isomer[d]	ee,[g] %	E[h]
3a	CC	7	42	38	+0.8	*S*	24	2	60	34	+2.3	*R*	22	2
3a	P	11	35	30	−0.7	*R*	25	2	70	22	−2.9	*S*	28	2
3b	CC	10	39	37	+1.0	*S*	30	2	62	35	+3.1	*R*	29	2
3b	P	15	40	38	−1.0	*R*	30	2	60	36	−2.7	*S*	25	2
3c	CC	8	38	35	−6.8	*R*	>98	180	52	46	+42.2	*S*	>98	90
3d	CC	18	40	36	+78.3	*S*	78	13	58	37	−86.1	*R*	75	4
3d	P	18	42	40	+97.9	*S*	>98	164	53	41	−112.6	*R*	>98	65
3e	CC	18	38	36	−3.3	*R,R*[i]	77	12	62	31	−60.2	*S,S*[i]	75	6
3e	P	28	38	37	−4.2	*R,R*[i]	>98	180	60	38	−78.7	*S,S*[i]	>98	21
3f	CC	45	40	35	−4.0	*R,S*[k]	76	12	62	30	−34.0	*S,R*[k]	73	5
3f	P	55	40	39	−5.1	*R,S*[k]	>98	195	60	35	−45.7	*S,R*[k]	>98	21
3g	CC	17	32	29	−7.7	*R,S*[l]	85	18	68	26	−11.9	*S,R*[l]	87	6
3g	P	30	30	28	−8.9	*R,S*[l]	>98	150	70	28	−13.5	*S,R*[l]	>98	10

[a] All reactions were performed in 0.1 M phosphate buffer (100 mL), pH 6.50 at 25 °C, substrate 25 mmol; enzyme 0.50 g. [b] Isolated yield. [c] c = 2, CH_2Cl_2. [d] Assigned by using lanthanide induced shift (LIS) experiments of the corresponding (*S*)-MTPA esters with $Eu(fod)_3$.[23] [e] Determined by ^1H and ^{19}F NMR spectra of the respective MTPA esters.[22] [f] Enantiomeric ratio.[24] $E = \ln [1 - c(1 + ee_p)]/\ln [1 - c(1 - ee_p)]$, p = product. [g] Obtained from the NMR spectra of the MTPA esters of the respective alcohols, which were formed by methanolysis. [h] $E = \ln [1 - c(1 + ee_s)]/\ln [1 - c(1 - ee_s)]$, s = substrate. [i] 3*R*,4*R* or 3*S*,4*S*, respectively. [k] 3*R*,4*S* or 3*S*,4*R*, respectively. [l] 4*R*,5*S* or 4*S*,5*R*, respectively.

substrates with excellent enantiodifferentiation (**3c** and **3g**), where the hydrolysis practically ceased at 50% conversion, whereas other substrates showed only more or less pronounced decreases in conversion rate at this point. Thus, for practical reasons, in these cases the hydrolyses were stopped at a conversion rate of 40%, the mixture of hydrolyzed, optically active azido alcohol and unaffected *ent*-ester separated by column chromatography, and the latter again subjected to a hydrolysis step till about 33% further conversion was reached (which means 60% conversion overall) and worked up as above. The results obtained are reported in Table I. In control experiments under the same conditions, but without enzyme, no hydrolysis was observed.

The optical yields were determined by ^1H and ^{19}F NMR of the respective (*S*)-MTPA esters.[22]

The *ent*-esters obtained were subjected to methanolysis with catalytic amounts of sodium methoxide, to yield *ent*-azido alcohols **2a–g**, and the ee again determined by NMR of the respective (*S*)-MTPA esters. The absolute configurations were determined by comparison of the respective ^{19}F NMR shifts of the CF_3 group of the (*S*)-MTPA ester,[22] including lanthanide induced shift (LIS) experiments with $Eu(fod)_3$.[23] In the case of **2d**, it was confirmed by the sense of optical rotation of the known (+)-(*S*)- or (−)-(*R*)-1-amino-2-phenylethanol[25] obtained via hydrogenation of **2d**. For **2e**, **2f**, and **2g**, comparison with the known (5*S*,6*S*)-6-azido-5-decanol[11] also confirmed our assignment.

Discussion

The enzymatic hydrolysis of acyclic secondary α-azido alcohols—useful precursors for optically active amino alcohols— was efficiently accomplished with the aid of commercially available lipases. Several enzymes were tested, but only two of them (CC and P) proved to be effective catalysts for the substrates employed,[21] CC being more active and less enantioselective than P. We had shown previously[12] that, in the series of cyclic azido esters, the activity of P slowed down significantly with increasing ring size for a constant ee, whereas CC did not show such dependence, while the ee was very low with small rings. In this work, P seems to be the best suited enzyme for effective hydrolysis in the acyclic series, with the exception of the bulky substituted **3c**. This again supports the conjecture that the active site of P exhibits a very narrow cavity.

In the resolution of 1-azido-2-alkanols, the enantioselectivity was very poor with longer chains, being much better with bulky phenyl or *tert*-butyl groups. Substrates **3e**, **3f**, and **3g**, holding the azido alcohol moiety in the center of the molecule, gave nearly the same results as the cyclic equivalents 2-azidocyclohexyl butanoate and 2-azidocyclooctyl butanoate, respectively.

It is remarkable that the two enzymes CC and P, contrary to their normally similar behavior, in the case of **3a** and **3b** hydrolyzed different enantiomers preferentially. Thus, in the reaction with CC as catalyst, the faster reacting ester had the *S* configuration, whereas in the reaction with P it was the *R* form, which was hydrolyzed more quickly. With the exception of **2d**, in all cases the alcohol first isolated had the *R* configuration. The *S* form of this alcohol in structure and sign of optical rotation corresponds to the *R* form of 1-phenylethanol.[26] This demonstrates that there is an ambiguity in the term *R preference or S preference of an enzyme*,[26,27] because this description is only a formal one, depending on the atoms involved in defining the absolute configuration. In conclusion, we found suitable methods for obtaining optically active acyclic azido alcohols in high ee, which can serve as precursors for biologically active amino alcohols. The described method is fast and simple and can easily be scaled up, as shown in the case of *trans*-2-azidocyclohexanol.[28]

Experimental Section

Melting points are uncorrected. Optical rotations were measured on a JASCO DIP-360 polarimeter in CH_2Cl_2 solution. NMR spectra were recorded in $CDCl_3$ on a Bruker MSL 300 instrument at 300 MHz (^1H), 75.47 MHz (^{13}C), and 282.27 MHz (^{19}F).

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Chemical shifts are in parts per million relative to TMS or $CFCl_3$ as internal standard; s = singlet, d = doublet, t = triplet, m = multiplet, and br = broad signal. δ values marked with an asterisk could be reversed. Numbering of carbon atoms in NMR data: prime (′) denotes carbons in the side chain of the alkanol residue, and double prime (″) denotes carbons in the butyric acid part. Reactions were monitored by TLC using silica gel Merck $60F_{254}$ plates; purifications of products and separations of esters and alcohols after the enzymatic conversions were performed on silica gel Merck 60 with mixtures of ethyl acetate and petroleum ether as mobile phase. All esters were purified by bulb-to-bulb distillation prior to enzymatic hydrolysis.

All commercially obtained compounds were used as received. Crude enzyme preparations were employed without further purification. Lipase P (30 units/mg) is a product from Amano Pharmaceutical Co., and *C. cylindracea* lipase (12 units/mg) was purchased from Sigma (1 unit is able to liberate 1 μmol of fatty acid/min at pH 7.0 and 25 °C). All enzymatic hydrolyses were performed with a Schott TR 156 pH-stat.

General Preparation of the Racemic Azido Alcohols. 1-Azido-2-hexanol (2a). A solution of 1,2-epoxyhexane (**1a**) (5.00 g, 50 mmol) in 80% aqueous ethanol (100 mL) was treated with NaN_3 (4.22 g, 65 mmol) and NH_4Cl (3.48 g, 65 mmol). The mixture was refluxed overnight and then poured into ice water (300 mL). The resulting solution was extracted three times with CH_2Cl_2 (50 mL), the combined extracts were dried over anhydrous Na_2SO_4, the solvent was removed in vacuo, and the light brown oil was purified by column chromatography, to give **2a** (5.23 g, 73%) as a colorless oil: n^{20}_D 1.4570 (lit.[10] no data given); ^1H NMR δ 0.87 (3 H, t, 6-H_3), 1.20–1.50 (6 H, m, 3-H_2, 4-H_2, 5-H_2), 2.64 (1 H, br s, OH), 3.15–3.30 (2 H, m, 1-H_2), 3.70 (1 H, m, 2-H); ^{13}C NMR δ 14.0 (C-6), 22.7 (C-5), 27.7 (C-4), 34.2 (C-3), 57.3 (C-1), 71.0 (C-2). Anal. found: C, 50.0; H, 9.2. Calcd for $C_6H_{13}N_3O$: C, 50.3; H, 9.2. A byproduct isolated was identified as **2-azido-1-hexanol**: ^1H NMR δ 0.85 (3 H, t, 6-H_3), 1.10–1.50 (6 H, m, 3-H_2, 4-H_2, 5-H_2), 3.05 (1 H, br s, OH), 3.30–3.40 (1 H, m, 2-H), 3.45–3.65 (2 H, m, 1-H_2); ^{13}C NMR δ 13.9 (C-6), 22.6 (C-5), 28.3 (C-4), 30.4 (C-3), 64.6 (C-2), 65.2 (C-1). Anal. Found: C, 50.2; H, 9.4. Calcd for $C_6H_{13}N_3O$: C, 50.3; H, 9.2.

Other azido alcohols were prepared in an analogous manner.

1-Azido-2-octanol (2b): 7.02 g, 82%; bp 117–120 °C/14 mmHg; n^{20}_D 1.4572; ^1H NMR δ 0.85 (3 H, t, 8-H_3), 1.25–1.55 (10 H, m), 2.54 (1 H, br s, OH), 3.15–3.35 (2 H, m, 1-H_2), 3.65–3.75 (1 H, m, 2-H); ^{13}C NMR δ 13.9 (C-8), 22.5 (C-7), 25.4 (C-4), 29.2 (C-5), 30.5 (C-6), 34.2 (C-3), 56.9 (C-1), 70.7 (C-2). Anal. Found: C, 55.9; H, 10.4. Calcd for $C_8H_{17}N_3O$: C,56.1; H, 10.0. A byproduct isolated was identified as **2-azido-1-octanol**: ^1H NMR δ 0.82 (3 H, t, 8-H_3), 1.20–1.60 (10 H, m), 2.20 (1 H, br s, OH), 3.30–3.40 (1 H, m, 2-H), 3.40–3.70 (2 H, m, 1-H_2); ^{13}C NMR δ 14.1 (C-8), 22.7 (C-7), 26.2 (C-4), 29.3 (C-3)*, 30.8 (C-5)*, 31.8 (C-6), 64.7 (C-2), 65.4 (C-1). Anal. Found: C, 56.0; H, 10.3. Calcd for $C_8H_{17}N_3O$: C, 56.1; H, 10.0.

1-Azido-3,3-dimethyl-2-butanol (2c): 3.36 g, 47%; n^{20}_D 1.4572; ^1H NMR δ 0.90 (9 H, s, 3*Me), 2.50 (1 H, br s, OH), 3.20–3.30 (2 H, m, 1-H_2), 3.40–3.45 (1 H, m, 2-H); ^{13}C NMR δ 25.8 (3*Me), 34.2 (C-3), 53.9 (C-1), 78.5 (C-2). Anal. Found: C, 50.0; H, 9.2. Calcd for $C_6H_{13}N_3O$: C, 50.3; H, 9.1.

2-Azido-1-phenylethanol (2d): 0.98 g, 82%; n^{20}_D 1.5503 (lit.[19] bp 112 °C/1 mmHg, n^{20}_D 1.5518); ^1H NMR δ 3.30–3.50 (2 H, m, 2-H_2), 3.53 (1 H, br s, OH), 4.70–4.85 (1 H, m, 1-H), 7.30–7.50 (5 H, m, aryl H); ^{13}C NMR δ 57.9 (C-2), 73.3 (C-1), 126.0 (Ar, o), 128.2 (Ar, p), 128.8 (Ar, m), 140.9 (Ar, i). A byproduct isolated was identified as **2-azido-2-phenylethanol**: 5.47 g, 67%; n^{20}_D 1.5462; ^1H NMR δ 3.50 (1 H, br s, OH), 3.84 (2 H, d, 1-H_2), 4.74 (1 H, t, 2-H), 7.40–7.65 (5 H, m, aryl H); ^{13}C NMR δ 66.2 (C-1), 67.6 (C-2), 126.7 (Ar, o), 128.5 (Ar, p), 128.8 (Ar, m), 136.4 (Ar, i).

***threo*-4-Azido-3-hexanol (2e)**: 5.80 g, 81%; n^{20}_D 1.4550; ^1H NMR δ 0.92 (3 H, t, 6-H_3), 1.00 (3 H, t, 1-H_3), 1.45–1.70 (4 H, m, 2-H_2, 5-H_2), 2.17 (1 H, br s, OH), 3.10–3.20 (1 H, m, 4-H), 3.45–3.55 (1 H, m, 3-H); ^{13}C NMR δ 10.1 (C-1)*, 10.8 (C-6)*, 24.2 (C-5), 27.3 (C-2), 68.6 (C-4), 74.8 (C-3). Anal. Found: C, 50.3; H, 9.3. Calcd for $C_6H_{13}N_3O$: C, 50.3; H, 9.1.

***erythro*-4-Azido-3-hexanol (2f)**: 3.22 g, 45% n^{20}_D 1.4572; ^1H NMR δ 0.92 (3 H, t, 6-H_3), 0.98 (3 H, t, 1-H_3), 1.30–1.70 (4 H, m, 2-H_2, 5-H_2), 2.75 (1 H, br s, OH), 3.10–3.20 (1 H, m, 4-H), 3.45–3.55 (1 H, m, 3-H); ^{13}C NMR δ 10.2 (C-1)*, 11.0 (C-6)*, 22.8 (C-5), 25.5 (C-2), 69.0 (C-4), 75.2 (C-3). Anal. Found: C, 50.2; H, 9.1. Calcd for $C_6H_{13}N_3O$: C, 50.3; H, 9.1.

***erythro*-5-Azido-4-octanol (2g)**: 6.25 g, 73%; n^{20}_D 1.4580; ^1H NMR δ 0.92 (6 H, m, 8-H_3, 1-H_3), 1.20–1.60 (8 H, m), 2.30 (1 H, br s, OH), 3.30–3.40 (1 H, m, 5-H), 3.60–3.70 (1 H, m, 4-H); ^{13}C NMR δ 14.0 (C-1)*, 14.1 (C-8)*, 19.2 (C-2)*, 19.7 (C-7)*, 31.8 (C-6), 34.8 (C-3), 67.6 (C-5), 73.9 (C-4). Anal. Found: C, 56.0; H, 10.3. Calcd for $C_8H_{17}N_3O$: C, 56.1 H, 10.0.

Preparation of Butanoates. The esters were prepared by standard methods[20] and purified by distillation or by column chromatography.

1-(Azidomethyl)pentyl Butanoate (3a). To a solution of **2a** (7.00 g, 50 mmol) in absolute CH_2Cl_2 (100 mL) were added butyric anhydride (10.28 g, 65 mmol), pyridine (3.95 g, 65 mmol), and 4-(dimethylamino)pyridine (0.05 g), and the mixture was left at room temperature till the conversion was complete (TLC, 16 h). Excess anhydride was quenched by addition of methanol (2 mL). After 2 h, the solution was washed with saturated $NaHCO_3$ (2 × 20 mL), 5% HCl (2 × 20 mL), and water (2 × 20 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography, to give **3a** (9.38 g, 88%): n^{20}_D 1.4411; ^1H NMR δ 0.84 (3 H, t, 5-H_3)*, 0.92 (3 H, t, 4″-H_3)*, 1.20–1.35 (4 H, m, 3-H_2, 4-H_2), 1.50–1.70 (4 H, m, 2-H_2, 3″-H_2), 2.25 (2 H, t, 2″-H_2), 3.25–3.40 (2 H, m, 1′-H_2), 4.90–5.00 (1 H, m, 1-H); ^{13}C NMR δ 13.7 (C-4″)*, 13.9 (C-5)*, 18.6 (C-3″), 22.6 (C-4), 27.4 (C-3), 31.4 (C-2), 36.5 (C-2″), 53.8 (C-1′), 72.6 (C-1), 173.1 (C-1″). Anal. Found: C, 56.1; H, 9.1. Calcd for $C_{10}H_{19}N_3O_2$: C, 56.3; H, 9.0.

The other esters were prepared in an analogous manner.

1-(Azidomethyl)heptyl butanoate (3b): 9.89 g, 82%; n^{20}_D 1.4455; ^1H NMR δ 0.78 (3 H, t, 7-H_3)*, 0.85 (3 H, t, 4″-H_3)*, 1.10–1.30 (8 H, m), 1.45–1.65 (4 H, m, 2-H_2, 3″-H_2), 2.25 (2 H, t, 2″-H_2), 3.15–3.35 (2 H, m, 1′-H_2), 4.90–5.00 (1 H, m, 1-H); ^{13}C NMR δ 13.5 (C-4″)*, 13.9 (C-7)*, 19.3 (C-3″), 22.5 (C-6), 25.1 (C-3), 29.0 (C-4), 31.5 (C-2)*, 31.6 (C-5)*, 36.2 (C-2″), 53.5 (C-1′), 72.4 (C-1), 172.8 (C-1″). Anal. Found: C, 59.5; H, 9.7. Calcd for $C_{12}H_{23}N_3O_2$: C, 59.7; H, 9.6.

1-(Azidomethyl)-2,2-dimethylpropyl butanoate (3c): 9.60 g, 90%; n^{20}_D 1.4382; ^1H NMR δ 0.90 (9 H, s, 3*Me), 1.00 (3 H, t, 4″-H_3), 1.60–1.80 (2 H, m, 3″-H_2), 2.30 (2 H, t, 2″-H_2), 3.25–3.45 (2 H, m, 1′-H_2), 4.80–4.90 (1 H, m, 1-H); ^{13}C NMR δ 13.7 (C-4″), 18.5 (C-3″), 26.1 (3*Me), 34.1 (C-2), 36.4 (C-2″), 51.4 (C-1′), 78.4 (C-1), 173.1 (C-1″). Anal. Found: C, 56.2; H, 9.0. Calcd for $C_{10}H_{19}N_3O_2$: C, 56.3; H, 9.0.

2-Azido-1-phenylethyl butanoate (3d): 11.08 g, 95%; n^{20}_D 1.4880; ^1H NMR δ 0.95 (3 H, t, 4″-H_3), 1.60–1.80 (2 H, m, 3″-H_2), 2.40–2.50 (2 H, t, 2″-H_2), 3.45–3.65 (2 H, m, 2-H_2), 5.90–6.00 (1 H, m, 1-H), 7.30–7.40 (aryl H); ^{13}C NMR δ 13.6 (C-4″), 18.4 (C-3″), 36.3 (C-2″), 53.4 (C-2), 74.4 (C-1), 126.5 (Ar, o), 128.7 (Ar, p), 128.9 (Ar, m), 137.5 (Ar, i), 172.5 (C-1″). Anal. Found: C, 61.8; H, 6.6. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.8; H, 6.5.

***threo*-1-Ethyl-2-azidobutyl butanoate (3e)**: 9.81 g, 92%; n^{20}_D 1.4418; ^1H NMR δ 0.80–1.00 (9 H, m, 4-H_3, 2′-H_3, 4″-H_3), 1.45–1.70 (6 H, m, 3-H_2, 1′-H_2, 3″-H_2), 2.25 (2 H, t, 2″-H_2), 3.05–3.15 (1 H, m, 2-H), 4.80–4.90 (1 H, m, 1-H); ^{13}C NMR δ 9.9 (C-4)*, 10.8 (C-2′)*, 13.7 (C-4″), 18.6 (C-3″), 23.9 (C-3), 24.8 (C-1′), 36.2 (C-2″), 65.2 (C-2), 76.0 (C-1), 173.2 (C-1″). Anal. Found: C, 56.0; H, 9.0. Calcd for $C_{10}H_{19}N_3O_2$: C, 56.3; H, 9.0.

***erythro*-1-Ethyl-2-azidobutyl butanoate (3f)**: 8.85 g, 83%; n^{20}_D 1.4415; ^1H NMR δ 0.88 (3 H, t, 4-H_3)*, 0.94 (3 H, t, 2′-H_3)*, 1.00 (3 H, t, 4″-H_3)*, 1.35–1.70 (6 H, m, 3-H_2, 1′-H_2, 3″-H_2), 2.30 (2 H, t, 2″-H_2), 3.30–3.40 (1 H, m, 2-H), 4.80–4.90 (1 H, m, 1-H); ^{13}C NMR δ 10.0 (C-4)*, 11.1 (C-2′), 13.8 (C-4″), 18.6 (C-3″), 22.6 (C-3), 23.7 (C-1′), 36.4 (C-2″), 66.7 (C-2), 76.7 (C-1), 173.3 (C-1″). Anal. Found: C, 56.3; H, 9.2. Calcd for $C_{10}H_{19}N_3O_2$: C, 56.3; H, 9.0.

***erythro*-1-Propyl-2-azidopentyl butanoate (3g)**: 10.26 g, 85%; n^{20}_D 1.4411; ^1H NMR δ 0.80–1.00 (9 H, m, 5-H_3, 3′-H_3, 4″-H_3), 1.10–1.70 (10 H, m), 2.25 (2 H, t, 2″-H_2), 3.40–3.50 (1 H, m, 2-H), 4.90–5.00 (1 H, m, 1-H); ^{13}C NMR δ 13.7 (C-5)*, 13.8 (C-3′)*, 13.9 (C-4″)*, 18.5 (C-3″), 18.8 (C-4)*, 19.8 (C-2′)*, 31.4 (C-3), 32.6 (C-1′), 38.4 (C-2″), 65.1 (C-2), 75.4 (C-1), 173.1 (C-1″). Anal. Found: C, 59.6; H, 9.9. Calcd for $C_{12}H_{23}N_3O_2$: C, 59.7; H, 9.6.

Enzymatic Resolution of Racemic 3a–g with Lipases. The following procedure is representative. To a solution of lipase P

(0.5 g) in phosphate buffer (0.1 N, pH 6.50, 100 mL) was added **3e** (5.00 g, 24 mmol). While vigorous stirring was maintained, the pH was kept constant at pH 6.50 by addition of 1 N NaOH from an autoburet. When the appropriate degree of conversion was accomplished [40% for (*R,R*)-**2e**, 28 h], the product was extracted with CH_2Cl_2 (3 × 100 mL). Evaporation of organic solvents and subsequent column chromatography gave 1.24 g (37%) of (*R,R*)-**2e** ($[\alpha]^{20}_D$ −4.2° [c = 2, CH_2Cl_2]) and 2.40 g (48%) of optically enriched (*S,S*)-**3e** ($[\alpha]^{20}_D$ −54.8° [c = 2, CH_2Cl_2]). The latter was submitted to a further 33% conversion as described above. Subsequent workup yielded 1.90 g (38%) of (*S,S*)-**3e** ($[\alpha]^{20}_D$ −78.7° [c = 2, CH_2Cl_2]). From that, 1.17 g (35%) of (*S,S*)-**2e** ($[\alpha]^{20}_D$ +4.2° [c = 2, CH_2Cl_2]) was obtained by methanolysis with catalytic amounts of NaOMe, in 30% yield.

The other enzymatic resolutions were carried out in the same way. Results including ee's are shown in Table I.

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Registry No. **1a**, 122922-40-1; **1b**, 77549-73-6; **1c**, 62137-90-0; **1d**, 67253-49-0; **1e**, 36611-94-6; **1f**, 124718-82-7; **1g**, 124718-83-8; **2a**, 124718-84-9; (*R*)-**2a**, 124817-02-3; (*S*)-**2a**, 124817-01-2; **2b**, 124718-85-0; (*R*)-**2b**, 124817-04-5; (*S*)-**2b**, 124817-03-4; **2c**, 124718-86-1; (*R*)-**2c**, 124817-05-6; **2d**, 124718-87-2; (*S*)-**2d**, 124817-06-7; **2e**, 124718-88-3; (*R,R*)-**2e**, 124817-07-8; **2f**, 124718-89-4; (3*R*,4*S*)-**2f**, 124817-08-9; **2g**, 124718-90-7; (3*R*,4*S*)-**2g**, 124817-09-0; **3a**, 124718-94-1; (*R*)-**3a**, 124817-11-4; **3b**, 124718-95-2; (*R*)-**3b**, 124817-12-5; (*S*)-**3b**, 124817-13-6; **3c**, 124718-96-3; (*S*)-**3c**, 124817-14-7; **3d**, 124718-97-4; (*R*)-**3d**, 124817-15-8; **3e**, 124718-98-5; (*S,S*)-**3e**, 124817-16-9; **3f**, 124718-99-6; (3*S*,4*R*)-**3f**, 124817-17-0; **3g**, 124719-00-2; (3*S*,4*R*)-**3g**, 124817-18-1; lipase, 9001-62-1; butyric anhydride, 106-31-0; (±)-2-azido-2-phenylethanol, 124718-93-0; (±)-2-azido-1-octanol, 124718-92-9; (±)-2-1-hexanol, 124718-91-8.

Oxidative Cyclization of Acyclic Aryl-Substituted *N*-Vinylurethanes

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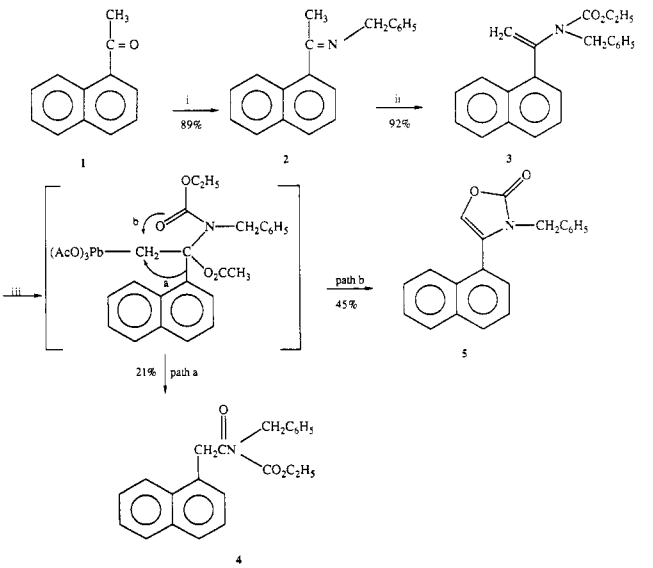
Oxidation of the acyclic *N*-(1-(1-naphthyl)vinyl)urethane (**3**) with lead tetraacetate (LTA) forms a naphthyloxazolone as the major product, accompanied by the product of rearrangement, *N*-(ethoxycarbonyl)-1-naphthylacetamide. When the naphthyl group is replaced by alkoxy-substituted aromatic rings, the *N*-vinylurethane undergoes three successive oxidations by LTA leading to novel substituted nitrogen containing cyclic anhydrides, oxazolidine-2,5-diones. The structure of this unusual oxidation product was proven by X-ray analysis. The mechanism of the oxidation is discussed in terms of known enamide oxidations, and the intermediacy of an oxazolone is demonstrated.

The photochemistry of enamides, *N*-vinylamides and urethanes, leads to a variety of interesting and useful reactions,[1,2] which have been extensively used in natural product synthesis.[3] We have been interested in extending the uses of these types of compounds and have investigated their reactivity toward various oxidizing agents,[4] particularly lead tetraacetate (LTA).[5] Simple enamides readily undergo bis-acetoxylation across the double bond, and the resultant bis-acetates can then undergo subsequent reactions.[6] In the isoquinoline enamides, where the enamide double bond is contained in a 1-benzylidene group, LTA introduces a β-acetoxy group onto the double bond in the *N*-aroyl series, while oxazolone formation is observed with the urethanes.[4] However, with the isoquinoline 1-methylene enamides, LTA causes an oxidative ring expansion, in which the aromatic ring migrates from the α position of enamide double bond to the β position, forming benzazepinones.[7] When the isoquinoline enamide double bond is dialkyl substituted, LTA oxidation causes an oxidative cyclization to form hydroxyoxazolidinones.[8] Since the isoquinoline enamides may be considered as rigid systems, we have extended the LTA oxidation studies to the acyclic case to determine the effects of conformational flexibility on the reaction pathways. The results reported here for the urethane series led to a surprising example of a triple oxidation but did, however, indicate the primary pathway that acyclic *N*-vinylurethanes prefer to take

Scheme I[a]



[a] Reagents: (i) benzylamine, 5-Å molecular sieves; (ii) diethyl pyrocarbonate, toluene, Δ; (iii) lead tetraacetate, acetic acid.

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