(M^+) 402.2034, found 402.2048.

Our carbon-13 chemical shift data differed slightly from the data quoted in the literature.[4] However, a carbon spectrum of the natural product obtained at the same concentration in $CDCl_3$ as our racemic material gave the following data: ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 170.70, 163.93, 154.56, 141.25, 140.72, 138.64, 136.04, 134.26, 131.07, 127.18, 118.54, 107.80, 88.53, 85.68, 84.05, 80.80, 77.00, 56.16, 21.33, 17.20, 13.39, 12.26, 8.85.

Acknowledgment. We thank the Aldred P. Sloan Foundation and the National Institutes of Health (AI17674) for generous support of our research and acknowledge assistance of the National Science Foundation for the purchase of high-field NMR (CHE81-05004) and high-resolution mass spectrometers (CHE81-00957).

Registry No. 1, 110549-63-8; 7, 97514-85-7; 8, 98168-70-8; 9, 98095-59-1; 10, 110510-53-7; 11, 110510-54-8; **12a**, 107613-12-7; **12b**, 110549-54-7; **13a**, 107657-73-8; **13a** (benzoate), 110549-64-9; **13b**, 110549-55-8; **14a**, 107657-74-9; **14a** (3-one deriv), 110510-55-9; **14b**, 110549-56-9; **14b** (3-one deriv), 110549-61-6; **15a**, 107657-75-0; **15a** (3-one deriv), 110510-56-0; **15b**, 110549-57-0; **15b** (3-one deriv), 110549-62-7; **16a**, 107657-76-1; **16b**, 110549-59-2; **17a**, 107657-77-2; **17b**, 110549-58-1; **18**, 98168-77-5; **19**, 110549-60-5; **20**, 107613-13-8; **21**, 98168-73-1; **21** (iodide), 98095-65-9; **22**, 98168-74-2; **23**, 98168-76-4; **24**, 107657-78-3; **25**, 98095-68-2; **26**, 98168-75-3; **27**, 98095-67-1; **27** (benzoate), 98095-66-0; **28**, 110510-57-1; **28** (C-3 epimer), 110510-58-2; **29**, 110510-59-3; **29** (C-3 epimer), 110510-60-6; **30**, 110510-61-7; **30** (C-3 epimer), 110510-62-8; **31**, 102103-89-9; **32**, 110510-67-3; **33**, 110510-63-9; **33** (C-3 epimer), 110510-66-2; **34**, 110510-64-0; **35**, 110610-82-7; **36**, 110510-65-1; **37**, 110510-68-4; **38**, 110510-69-5; **39**, 110510-70-8; **40**, 64361-40-6; **41**, 110510-71-9; **42**, 110510-72-0; **42** (triol deriv), 110510-73-1; **43**, 110510-74-2; **44**, 110510-75-3; vinylmagnesium bromide, 1826-67-1; (*Z*)-2-bromo-2-butene, 3017-68-3; (*E*)-2-bromo-2-butene, 3017-71-8; (carbethoxyethylidene)triphenylphosphorane, 54356-04-6; ethyl 4-(diethylphosphinyl)crotonate, 10236-14-3.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances, and bond angles and stereoscopic views of the X-ray diffraction studies of tetrahydrofuran **15a** (10 pages). Ordering information is given on any current masthead page.

Lipase-Catalyzed Resolution of Chiral 2-Amino 1-Alcohols

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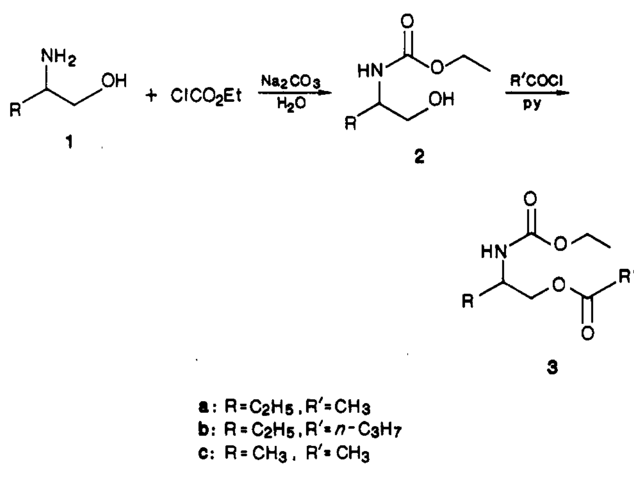
Lipase-catalyzed resolution of 2-amino 1-alcohols was readily accomplished provided that the amino group was protected as an *N*-alkoxycarbonyl derivative. Racemic 2-amino-1-butanol and 2-amino-1-propanol were chosen as model compounds, and the resolution was achieved both by hydrolysis of their ester derivatives and by transesterification in ethyl acetate. In either case the (*R*) enantiomers reacted faster, and at low conversion, the (*R*) form in high optical purity was obtained as alcohol by hydrolysis and as acetate by transesterification. The two procedures can therefore be considered as complementary with respect to the final product composition. By using commercially available lipase preparations both (*R*)-(−) and (*S*)-(+) enantiomers of 2-amino 1-alcohols were isolated in high enantiomeric excesses (≥95%).

Enzymatic catalysis has recently been successfully used for the optical resolution of several highly functionalized chiral molecules such as amino acids, diols, diesters, and hydroxy acids.[1] Surprisingly very little attention has been paid to the enzymatic resolution of chiral amino alcohols in spite of their importance both as chiral building blocks and as products of pharmaceutical interest. In particular (*S*)-(+)-2-amino-1-butanol, the chiral precursor in the synthesis of the antitubercular drug Ethambutol,[2] prepared by conventional chemical resolution is the subject of many patents[3] and papers,[4] while in only two cases was the enzymatic approach reported. The first is a Japanese patent,[5] where it is claimed that a culture of *Micrococcus* is able to selectively hydrolyze the (*R*) form of *N*-acetyl-2-amino-1-butanol, leaving the (*S*) form substantially unaffected. More recently, Klibanov and co-workers tried to resolve racemic 2-amino-1-butanol by phosphatase-catalyzed hydrolysis of its phosphate esters.[6] This approach allowed a simple, selective functionalization of the hydroxy group and an easy separation of reaction products, but reaction rate and optical purities were very poor.

Scheme I



In this paper we report two strategies for enzymatic resolution of amino alcohols.

Our experiments showed that when 2-amino 1-alcohols were converted to their *N*-alkoxycarbonyl derivatives, optical resolution was easily achieved by lipase-catalyzed hydrolysis of carboxylic esters and by lipase-catalyzed transesterification in organic solvent. Racemic 2-amino-1-butanol and 2-amino-1-propanol were chosen as model

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

				(S)-(+)-1[b]			(R)-(−)-1[b]		
substr	enzyme	time, h	convn, %	yield, %	$[\alpha]^{20}_D$ [c]	ee,[d] %	yield, %	$[\alpha]^{20}_D$ [c]	ee,[d] %
3a	pancreatin	8	53	36	9.5	94	36	9.2	90
3a	steapsin	11	53	37	9.8	≥95	35	8.8	87
3a	Lipase Amano P	6	58	30	8.1	80	39	5.8	58
3a	pancreatin	3	46	40	8.9	88	30	9.8	≥95
3b	pancreatin	5	65	22	9.3	92	43	5.5	55
3b	steapsin	6	62	23	9.6	≥95	43	7.2	70
3b	Lipase Amano P	1	65	23	8.0	80	44	4.6	46
3c	pancreatin	20	52	29	15.2	≥95	30	14.4	90
3c	steapsin	14	48	30	13.7	87	28	14.8	94
3c	Lipase Amano P	3	60	22	15.2	≥95	33	6.9	44

[a] All reactions performed in 0.1 M phosphate buffer, pH 7.00 (40 mL) at 25 °C; substrate, 15 mmol; enzyme, 100 mg. [b] Recovered after alkaline hydrolysis. [c] Neat. 2-Amino-1-butanol, lit.[8] $[\alpha]^{20}_D$ 10.1°. 2-Amino-1-propanol, lit.[9] $[\alpha]^{20}_D = 15.8°$. [d] Determined by ^{1}H NMR of the corresponding MTPA amide.

Table II. Lipase-Catalyzed Transesterification of 2a,c[a]

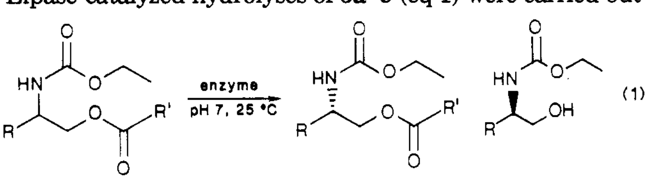
				(S)-(+)-1[b]			(R)-(−)-1[b]		
substr	enzyme	time, h	convn, %	yield, %	$[\alpha]^{20}_D$ [c]	ee,[d] %	yield, %	$[\alpha]^{20}_D$ [c]	ee,[d] %
2a	steapsin/Celite[e]	48	50	32	9.3	92	31	9.6	≥95
2a	steapsin[f]	110	60	26	10.0	≥95	39	7.3	72
2a	steapsin[f]	24	41	38	6.6	65	27	9.8	≥95
2a	pancreatin[f]	60	60	25	9.9	≥95	28	6.4	60
2a	Lipase P/Celite[g]	24	78	14	8.6	85	50	3.4	35
2c	pancreatin[f]	20	55	30	14.4	90	31	14.4	90
2c	steapsin[f]	20	54	31	14.8	94	33	14.5	92
2c	steapsin[f]	15	42	33	9.8	62	22	15.0	≥95
2c	steapsin/Celite[e]	48	51	30	15.0	≥95	31	14.2	90

[a] All reactions performed in ethyl acetate (120 mL) at 25 °C with 20 mmol of 2a,c. [b] Recovered after alkaline hydrolysis. [c] Neat. 2-Amino-1-butanol, lit.[8] $[\alpha]^{20}_D = 10.1°$. 2-Amino-1-propanol, lit.[9] $[\alpha]^{20}_D = 15.8°$. [d] Determined by ^{1}H NMR of the corresponding MTPA amide. [e] 0.2 g of steapsin adsorbed on 1 g of Celite 577. [f] 1 g of powdered enzyme. [g] 0.1 g of Lipase Amano P adsorbed on 0.5 g of Celite 577.

compounds, and resolution was carried out to high optical purity with commercial lipases.

Results

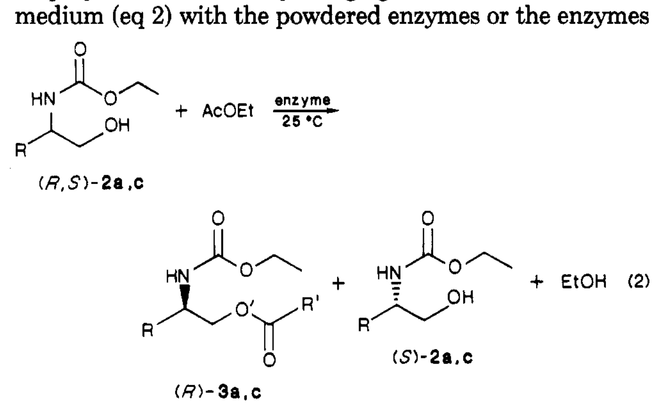
Lipase-Catalyzed Hydrolysis of 2-[*N*-(Alkoxycarbonyl)amino] 1-Alcohols. Title compounds have been synthesized as shown in Scheme I. Although several commercially available hydrolytic enzymes have been tested, only three lipase preparations, namely pancreatin, steapsin, and Lipase Amano P, gave satisfactory results. Lipase-catalyzed hydrolyses of **3a–c** (eq 1) were carried out



(*R,S*)-**3a-c** (*S*)-**3a-c** (*R*)-**2a-c**

at pH 7.0. The pH was maintained constant by the addition of 1 N aqueous NaOH. The reactions were stopped at different degrees of conversion. After separation of the products, the protective groups were removed by alkaline hydrolysis, and the free optically enriched 2-amino 1-alcohols were recovered. The enantiomeric excesses (ee's) were determined by 300-MHz ^{1}H NMR of the MTPA (Moshers' acid)[7] amides and the absolute configurations by comparison of the measured optical rotations with literature values.[8,9] Some experimental results are reported in Table I.

Lipase-Catalyzed Transesterification of 2-[*N*-(Alkoxycarbonyl)amino] 1-Alcohols. According to the well-documented capability of enzymes to work in nonaqueous environments.[10] optical resolutions of *N*-alkoxycarbonyl derivatives of 2-amino alcohols were achieved by using lipase-catalyzed transesterification in organic solvents. The reactions were carried out in ethyl acetate employed both as an acylating agent and as the reaction medium (eq 2) with the powdered enzymes or the enzymes



supported on Celite. The same enzymes employed in the hydrolytic approach were used as catalysts. Powdered or supported lipases were added to a solution of **2a,c** in ethyl acetate at 25 °C, and the suspension was shaken on an orbital shaker at 200 rpm. Periodically, 1-μL aliquots were withdrawn and analyzed by gas chromatography. The reactions were stopped at different degrees of conversion, and the crude reaction mixes were worked up as described above. Experimental results are reported in Table II.

Discussion

Racemic 2-amino 1-alcohol esters are not convenient substrates for lipolysis, since they are not easily prepared. On the other hand, resolution of 2-amino 1-alcohols by

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enzymatic transesterification in ethyl acetate resulted only in the nonstereospecific acylation of the more nucleophilic amino group (see the Experimental Section).

We have found that protection of the amino group is necessary to achieve the optical resolution of these molecules. The alkoxycarbonyl group was chosen for N-protection because it was selectively introduced, did not affect enzymatic activity, and was easily removed at the end of the reaction.

Several commercially available hydrolytic enzymes were tested, but only two of animal origin (steapsin and pancreatin) and one of bacterial origin (Lipase Amano P from *Pseudomonas fluorescens*) proved to be effective catalysts.[11]

In the hydrolytic reaction, the two mammalian lipases were more stereoselective than the bacterial one, and using acetates as substrates, we obtained both (*R*) and (*S*) enantiomers of 2-amino 1-alcohols in high ee at about 50% conversion (see Table I). When butyrates were used as substrates, the stereoselectivity was lower, and according to the general theory of enzyme-catalyzed kinetic resolution,[12] it was necessary to increase the degree of conversion to about 60% to obtain the (*S*) form in high optical purity. Conversely, to obtain the (*R*) form in high optical purity the reaction was stopped at about 40% conversion.

Compared with the mammalian lipases, bacterial Lipase Amano P displayed a higher catalytic activity. As shown in Table I, the time required for optimal conversion was much shorter when using Lipase P.

Also, in the case of the lipase-catalyzed transesterification, the two mammalian lipases showed good stereospecificity at 50% conversion (see Table II). Both the (*R*) and (*S*) forms of the substrate were converted to their esters, but the rates were different: with pancreatin, at 60% conversion, the ee of the (*S*) form was ≥95%, while the ee of the (*R*) form was 60%.

It is worth noting that much less enzyme was necessary to get satisfactory reaction rates upon its adsorption on Celite (see footnotes *e* and *g* in Table II).

The bacterial lipase was not as efficient as the mammalian one in the transesterification reaction, and a high ee was obtained only at a much higher degree of conversion (ca. 80%). The data on Tables I and II show that sometimes the ee's approached 100% for the two forms (*R*) and (*S*); moreover, the stereospecificity of the enzymatic hydrolysis in aqueous solution was preserved in organic solvent in the case of the transesterification reaction.

The (*R*) form reacted faster than the (*S*) form in both reactions; with short reaction times it was therefore possible to obtain the (*R*) form in high ee as an alcohol by the hydrolysis procedure and as an ester by the transesterification procedure.

The two procedures are thus complementary with respect to the final product composition, and the method can easily be tailored to suit synthetic needs.

Experimental Section

Melting points were determined on a Kofler apparatus and are uncorrected. ^{1}H NMR spectra were recorded for $CDCl_3$ solution [$(CH_3)_4Si$ internal standard] on a Bruker AM 300 instrument. The ee values were obtained by integration of the OCH_3 signals of the MTPA (Moshers' acid) amides. GLC analyses were carried out on a Carlo Erba HRGC 5300 chromatograph with a 2 m × 4 mm SP 2100 3% column at 100–250 °C and with a flame-ionization detector. IR spectra were recorded on a Perkin-Elmer 1420 spectrophotometer. All hydrolytic reactions were performed with a Metrohm pH-stat. Optical rotations were measured in neat form or on ethanol solutions with a Perkin-Elmer 241 polarimeter.

Steapsin (11 U/mg) was purchased from Sigma Chemical Co., pancreatin (57 U/mg) was purchased from Unibios, and Lipase Amano P (30 U/mg) was a gift from Amano Chemical Co.

Preparations of 2-[*N*-(Alkoxycarbonyl)amino] 1-Alcohols 2a,c. To a solution in water (300 mL) of 2-amino 1-alcohol (0.6 mol) and sodium carbonate (63.6 g, 0.6 mol) was added ethyl chloroformate (0.6 mol) dropwise over a 0.5-h period at 0–5 °C. The reaction mixture was stirred an additional 2 h at room temperature and extracted with chloroform. The organic layer was dried and evaporated to dryness to give the desired product in 90–100% yield.

2-[*N*-(Ethoxycarbonyl)amino]-1-butanol (2a): 98% yield; mp 39–40 °C; ^{1}H NMR δ 0.96 (3 H, t, J = 7.5 Hz), 1.25 (3 H, t, J = 7.4 Hz), 1.40–1.70 (2 H, m), 3.48–3.72 (4 H, m), 4.12 (2 H, q, J = 7.4 Hz), 5.25 (1 H, br s); IR (Nujol) ν 3300, 1685 cm^{-1}.

2-[*N*-(Ethoxycarbonyl)amino]-1-propanol (2c): 94% yield; mp 20–22 °C; ^{1}H NMR δ 1.17 (3 H, d, J = 7.0 Hz), 1.24 (3 H, t, J = 7.3 Hz), 3.40–3.72 (4 H, m), 4.12 (2 H, q, J = 7.3 Hz), 5.05 (1 H, br s); IR ν 3310, 1690 cm^{-1}.

Preparations of 2-[*N*-(Alkoxycarbonyl)amino] 1-Alcohol Esters 3a–c. To a solution in chloroform (150 mL) of **2a,c** (0.24 mol) and pyridine (0.27 mol) under nitrogen atmosphere was added dropwise the acid chloride (0.27 mol) at 0 °C over a 0.5-h period. The mixture was stirred an additional 2 h at room temperature and then washed with water, 5% $NaHCO_3$, and 5% HCl and water (2 × 30 mL each). The organic layer was dried and evaporated to dryness to give the desired product in 90–100% yield.

2-[*N*-(Ethoxycarbonyl)amino]butyl acetate (3a): 93% yield; bp 114–116 °C (3 mmHg); ^{1}H NMR δ 0.96 (3 H, t, J = 7.5 Hz), 1.24 (3 H, t, J = 7.4 Hz), 1.42–1.63 (2 H, m), 2.07 (3 H, s), 3.80 (1 H, br s), 4.03–4.17 (4 H, m), 5.00 (1 H, br s); IR ν 1720 cm^{-1}.

2-[*N*-(Ethoxycarbonyl)amino]butyl butyrate (3b): 96% yield; bp 115–117 °C (0.5 mmHg); ^{1}H NMR δ 0.90–1.82 (13 H, m), 2.28 (2 H, t, J = 7.0 Hz), 3.78 (1 H, br s), 3.90–4.10 (4 H, m) 5.00 (1 H, br s); IR ν 1720 cm^{-1}.

2-[*N*-(Ethoxycarbonyl)amino]propyl acetate (3c): 92% yield; bp 87–88 °C (0.5 mmHg); ^{1}H NMR δ 1.19 (3 H, d, J = 7.0 Hz), 1.23 (3 H, t, J = 7.4 Hz), 2.08 (3 H, s), 3.90–4.25 (5 H, m), 4.80 (1 H, br s); IR ν 1720 cm^{-1}.

Adsorption of Enzymes on Celite. Celite 577 (1 g) was washed with water and 0.1 N phosphate buffer and then added to a solution of 250 mg of enzyme in 4 mL of 0.1 N phosphate buffer. The mixture was spread on a watch glass and left to dry at room temperature with occasional mixing until visibly dry.

Lipase-Catalyzed Hydrolysis of 2-[*N*-(Alkoxycarbonyl)-amino] 1-Alcohol Esters 3a–c. The following procedure is representative. To a magnetically stirred solution of 2-[*N*-(ethoxycarbonyl)amino]butyl acetate (**3a**) (3.05 g, 15 mmol) in 0.1 N phosphate buffer (40 mL) at 25 °C was added pancreatin (100 mg, 5700 U), and the solution was maintained at pH 7 with 1 N aqueous NaOH by using a pH-stat. The hydrolysis was allowed to proceed to 53% conversion (8 h). The reaction mixture was extracted with ethyl acetate (3 × 40 mL), and the organic layer was dried over sodium sulfate and evaporated to dryness. Flash chromatography on SiO_2 with *n*-hexane/ethyl acetate (1:1) afforded 1.28 g (42%) of (*S*)-(−)-**3a** [$[\alpha]^{20}_D$ −27.0° (*c* 2, ethanol)] and 1.07 g (44%) of (*R*)-(+)-2a [$[\alpha]^{20}_D$ +31.7° (*c* 2, ethanol)].

The above ester (*S*)-(−)-**3a** (1.1 g, 5.4 mmol) was heated for 2 h at 80 °C in 4 mL of 30% NaOH. The reaction mixture was extracted with chloroform (5 × 10 mL). The organic extract was dried over sodium sulfate, evaporated to dryness, and distilled to give 410 mg (85%) of (*S*)-(+)-2-amino-1-butanol: 94% ee;[13] $[\alpha]^{20}_D$ +9.5° (neat) (lit. $[\alpha]^{20}_D$ +10.1° (neat); ^{1}H NMR δ 0.95 (3

(11) In the hydrolytic reaction of **3a**, esterase from porcine liver (Sigma) and lipase from *Aspergillus niger* (Amano) were not stereospecific; lipase from *Rhizopus delemar* (Amano) gave no reaction at all, and lipase from *Candida cylindracea* (Sigma) enabled us to obtain products of only moderate ee (unhydrolyzed ester of 50% ee at 60% conversion).

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(13) The product was converted into MTPA amide (see ref 7) and the ee determined by integration of the OCH_3 signals in the 300-MHz ^{1}H NMR spectrum: 2-amino-1-butanol *R* form δ 3.40, *S* form δ 3.46; 2-amino-1-propanol *R* form δ 3.46, *S* form δ 3.52.

H, t, J = 6.5 Hz), 1.31–1.58 (2 H, m), 2.51–2.89 (1 H, m), 3.01 (3 H, br s), 3.32–3.74 (2 H, m); IR ν 3400, 2950, 1590, 1470 cm^{-1}.

The alcohol (*R*)-(+)-**2a** (950 mg, 5.9 mmol) was treated similarly to give 430 mg (82%) of (*R*)-(−)-2-amino-1-butanol: 90% ee;[13] $[\alpha]^{20}_D$ −9.2° (neat); spectral characteristics as reported above.

Lipase-Catalyzed Transesterification of 2-[*N*-(Alkoxycarbonyl)amino] 1-Alcohols 2a,c. The following procedure is representative. To a magnetically stirred solution of 2-[*N*-(ethoxycarbonyl)amino]-1-butanol (**2a**; 3.22 g, 20 mmol) in ethyl acetate (120 mL) at 25 °C was added steapsin (0.2 g, 2200 U) supported on Celite 577 (1.0 g), and the reaction mixture was stirred at 25 °C.

Periodically 1-μL aliquots of the liquid phase were withdrawn and analyzed by gas chromatography. After 48 h, approximately 50% conversion was reached and the reaction stopped. The solid enzyme was filtered off and the solution evaporated to dryness. Flash chromatography on SiO_2 with *n*-hexane/ethyl acetate (1:1) afforded 1.3 g (40%) of (*S*)-(−)-**2a** [$[\alpha]^{20}_D$ −32.2° (*c* 2, ethanol)] and 1.65 g (40%) of (*R*)-(+)-**3a**; [$[\alpha]^{20}_D$ +27.6° (*c* 2, ethanol)].

The ester (*R*)-(+)-**3a** (1.3 g, 6.4 mmol) was treated as described above to give 440 mg (77%) of (*R*)-(−)-2-amino-1-butanol: 95% ee;[13] $[\alpha]^{20}_D$ −9.6° (neat); spectral characteristics as already described.

The alcohol (*S*)-(−)-**2a** (1.0 g, 6.2 mmol) was treated as described above to give 430 mg (78%) of (*S*)-(+)-2-amino-1-butanol; 92% ee;[13] $[\alpha]^{20}_D$ +9.3° (neat); spectral characteristics as described above.

Lipase-Catalyzed Transesterification of 2-Amino-1-butanol (1a). To a magnetically stirred solution of (*RS*)-2-amino-1-butanol (**1a**; 2.0 g, 22.5 mmol) in ethyl acetate (120 mL) at 25 °C was added steapsin (1.0 g, 11 000 U) and the reaction mixture stirred at 25 °C.

Periodically, 1-μL aliquots of the liquid phase were withdrawn and analyzed by gas chromatography. After 72 h, about 35% conversion was reached and the reaction stopped. The enzyme, which appeared as a gummy substance, was filtered off and the solution evaporated to dryness. Flash chromatography on SiO_2 with *n*-hexane/ethyl acetate (1:1) afforded 810 mg (27%) of racemic 2-(acetylamino)-1-butanol [^1H NMR δ 0.95 (3 H, t, J = 7.2 Hz), 1.40–1.70 (2 H, m), 2.00 (3 H, s), 3.1–4.2 (4 H, m), 6.80 (1 H, br s); IR ν 3290, 1650, 1560 cm^{-1}] and 1.0 g (50%) of racemic 2-amino-1-butanol.

Acknowledgment. We thank Dr. Silvia Spera of Istituto G. Donegani for her valuable help and discussion concerning NMR analysis.

Registry No. (*R*)-**1a**, 5856-63-3; (*S*)-**1a**, 5856-62-2; (±)-**1a**, 13054-87-0; (*R*)-**1c**, 35320-23-1; (*S*)-**1c**, 2749-11-3; (±)-**1c**, 6168-72-5; (*R*)-**2a**, 110418-25-2; (*S*)-**2a**, 110418-29-6; (±)-**2a**, 110455-82-8; (*R*)-**2c**, 110418-26-3; (*S*)-**2c**, 83197-71-1; (±)-**2c**, 110455-83-9; (*S*)-**3a**, 110418-22-9; (*R*)-**3a**, 110418-27-4; (±)-**3a**, 110455-84-0; (*S*)-**3b**, 110418-23-0; (±)-**3b**, 110455-85-1; (*S*)-**3c**, 110418-24-1; (*R*)-**3c**, 110418-28-5; (±)-**3c**, 110507-76-1; triacylglycerol lipase, 9001-62-1; pancreatin, 8049-47-6; (±)-2-(acetylamino)-1-butanol, 71501-68-3.

A Cyclization Approach to Functionalized Seven-Membered Carbocycles

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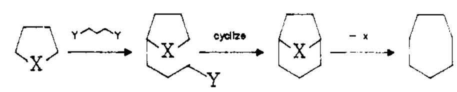
Functionalized seven-membered carbocycles are prepared by dialkylative cyclization of masked butadienes with 2-alkylidene-1,3-dihalopropanes. 3-Sulfolenes are essential intermediates acting as aids to constrain the conformation of the butadiene part during the cyclization step.

Seven-membered carbocyclic compounds are generally more difficult to prepare by cyclization reactions than their lower homologues (ring sizes of five and six) because of conformational flexibility and entropic reasons.[1] One attractive way to solve these problems is to make use of the rigidity of a preexisting ring to lessen the conformational flexibility during the cyclization process. As illustrated in Scheme I, one can imagine a bicyclo[3.2.*n*] system **3** to be synthesized by attaching a three-carbon unit to a cyclic compound **1** containing a four-carbon unit via a 2,2′-dialkylation process. Because of the conformational rigidity of the preexisting ring, the disfavored entropic effect usually encountered for seven-membered ring cyclization (from **2** to **3**) should be minimized. The bridge of the bicyclic compound **3** (noted as X) can be removed afterward to yield the desired seven-membered product **4**. The prerequisite for the success of this strategy is to have a good conformationally constrained four-carbon unit containing a readily removable functional group that facilitates the connection of a three-carbon unit to the molecule at correct positions.

Scheme I



1 2 3 4

3-Sulfolenes appear to be qualified candidates for conformationally constrained four-carbon units because they are susceptible to smooth deprotonation/alkylation reactions[2] and the activating group, SO_2, can normally be removed by mild thermolysis.[3] More importantly, the

(1) For a review of a cycloaddition approach to seven-membered rings, see: Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1.

(2) (a) Chou, T. S.; Tso, H. H.; Chang, L. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 515. (b) Chou, T. S.; Tso, H. H.; Chang, L. J. *J. Chem. Soc., Chem. Commun.* **1984**, 1323. (c) Chou, T. S.; Tso, H. H.; Chang, L. J. *J. Chem. Soc., Chem. Commun.* **1985**, 236. (d) Chou, T. S.; Tso, H. H.; Lin, L. C. *J. Org. Chem.* **1986**, *51*, 1000. (e) Chou, T. S.; Tso, H. H.; Tao, Y. T.; Lin, L. C. *J. Org. Chem.* **1987**, *52*, 244.

(3) (a) Mock, W. L. *J. Am. Chem. Soc.* **1975**, *97*, 3666. (b) McGregor, S. D.; Lemal, D. L. *Ibid.* **1966**, *88*, 2858. (c) Kellogg, R. M.; Prins, W. L. *J. Org. Chem.* **1974**, *39*, 2366.

