Table III. Elemental Analyses for C, H, and N

	% found				% required		
	C	H	N	empirical formula	C	H	N
6a	78.7	6.7		$C_{14}H_{14}O_2$	78.5	6.54	
7a	78.7	6.6		$C_{14}H_{14}O_2$	78.5	6.54	
8a	66.0	8.0	4.6	$C_{17}H_{23}NO_2 \cdot HCl$	65.9	7.8	4.5
9a	65.9	8.0	4.4	$C_{17}H_{23}NO_2 \cdot HCl$	65.9	7.8	4.5
8b	61.2	9.1	5.0	$C_{14}H_{23}NO_2 \cdot HCl$	61.43	8.78	5.12
9b	61.5	9.1	5.0	$C_{14}H_{23}NO_2 \cdot HCl$	61.43	8.78	5.12
8c	57.4	7.9	4.0	$C_{14}H_{23}NO_2 \cdot (COOH)_2 \cdot {}^1/_2H_2O$	57.1	7.7	4.2
9c	71.0	9.9	5.9	$C_{14}H_{23}NO_2$	70.89	9.7	5.9

sponding proton of the trans isomer which is masked by the OCH_2 signal. This affords a rough guide for identifying threo and erythro isomers in this series.

The present synthesis offers a route to the threo and erythro isomers of 1-(aryloxy)-3-(alkylamino)butan-2-ols which is superior to existing routes in two respects: namely (1) it affords a more facile synthesis of the threo isomers via the readily accessible *threo*-(1-bromoethyl)oxirane **3** and (2) our conditions for the reactions of epoxides **6** and **7** with amines are much less severe and, in addition, the reaction times are considerably shorter.

Experimental Section

Melting points were obtained on an Electrothermal capillary melting point apparatus and are uncorrected. ^1H NMR spectra were run on a Varian HA-100 or Varian EM-390 spectrometer in $CDCl_3$ containing Me_4Si as an internal standard. IR spectra were recorded on a Perkin-Elmer 157 infrared spectrophotometer. TLC was performed on precoated silica gel plates (silica gel 60 F254, E. Merck, Darmstadt) developed in 5% EtOAc–$CHCl_3$ for oxiranes and a mixture of EtOAc–EtOH–Et_3N (80:20:9) for the α-methyl(aryloxy)propanolamines. Analytical data (C, H, N) are given in Table III.

erythro-(1-Bromoethyl)oxirane (4). A solution of bromine (63.3 g, 0.4 mol) in methylene chloride (50 mL) was added dropwise to a cooled, stirred solution of *cis*-crotyl alcohol (28.5 g, 0.4 mol) in methylene chloride (50 mL), and the mixture was stirred at room temperature for 30 min. The reaction mixture was washed successively with dilute aqueous sodium thiosulfate and water and then dried over anhydrous $MgSO_4$ and the methylene chloride was evaporated off. The residue was distilled under reduced pressure to give *threo*-2,3-dibromobutan-1-ol: bp 108–110 °C (13 mmHg); yield 65.1 g (71%); ^1H NMR ($CDCl_3$) δ 1.79–1.86 (d, 3 H, CH_3), 2.23 (s, 1 H, OH), 3.93–4.05 (m, 2 H, CH_2), 4.13–4.36 (m, 1 H, $CHBrCH_2$), 4.39–4.63 (m, 1 H, CH_3CHBr, J = 3 Hz).

A solution of *threo*-2,3-dibromobutan-1-ol (140 g, 0.60 mol) in diethyl ether (700 mL) and a solution of KOH (45 g, 0.80 mol) in water (400 mL) were vigorously stirred together for 6 h. The ethereal layer was separated and washed repeatedly with brine until the washings were no longer alkaline, dried over anhydrous $MgSO_4$, and evaporated to dryness. The residue was distilled under reduced pressure to give *erythro*-(1-bromoethyl)oxirane: bp 39–42 °C (20 mmHg); yield 58.1 g (64%); ^1H NMR ($CDCl_3$) δ 1.76–1.83 (d, 3 H, CH_3), 2.6–2.7 (m, 1 H, terminal oxirane proton cis to CHBr(Me) group), 2.84–2.95 (m, 1 H, terminal oxirane proton trans to CHBr(Me) group), 3.07–3.2 (m, 1 H, oxirane proton), 3.5–3.77 (m, 1 H, >CHBr).

***trans*-2-[(1-Naphthyloxy)methyl]-3-methyloxirane (7a).** A solution of *erythro*-(1-bromoethyl)oxirane (**6**) (2.2 g, 0.015 mol) in dimethoxyethane (10 mL) was added to a stirred solution of 1-naphthol (1.64 g, 0.011 mol) and NaOH (0.5 g, 0.012 mol) in water (50 mL), and the mixture was stirred at room temperature for ca. 70 h. The reaction mixture was extracted with petroleum ether (bp 60–80 °C) (2 × 25 mL) and the petroleum ether extracts were washed with brine and dried over anhydrous $MgSO_4$. Evaporation of the petroleum ether and crystallization of the crude epoxide from cyclohexane yielded *trans*-2-[1-(naphthyloxy)-methyl]-3-methyloxirane: mp 60–60.5 °C; yield 0.8 g (33%); ^1H NMR ($CDCl_3$) δ 1.27–1.39 (d, 3 H, CH_3), 2.8–3.09 (m, 2 H, oxirane 2-H and 3-H) 4.04–4.17 (m, 2 H, OCH_2), 6.6–8.3 (m, 7 H, aromatics). Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.50; H, 6.54. Found: C, 78.7; H, 6.6.

***erythro*-1-(1-Naphthyloxy)-3-(isopropylamino)butan-2-ol (9a).** A solution of *trans*-2-[(1-naphthyloxy)methyl]-3-methyloxirane (**7a**) (0.65 g) in 1:1 aqueous isopropylamine (20 mL) was heated under reflux for 4 h. The excess isopropylamine was removed under vacuum and the residue was acidified with 6 N HCl. The product hydrochloride precipitated out and was filtered off and dried. Crystallization from EtOH furnished *erythro*-1-(1-naphthyloxy)-3-(isopropylamino)butan-2-ol hydrochloride: yield 0.5 g (53%); mp 216–218.5 °C; ^1H NMR ($CDCl_3$) (for free base) δ 1.0–1.2 (m, 9 H, CH_3), 2.03–2.72 (broad, 2 H, OH and NH), 2.8–3.21 (m, 2 H, $CHNHCH(Me_2)$), 3.93–4.3 (m, 3 H, CH(OH)), 6.75–8.31 (m, 7 H, aromatics). Anal. Calcd for $C_{17}H_{23}NO_2 \cdot HCl$: C, 65.91; H, 7.75; N, 4.52. Found: C, 65.9; H, 8.0; N, 4.4.

An additional 100 mg (12%) of the free base was obtained from the acidic filtrate by basification with dilute NaOH and extraction with $CHCl_3$.

Acknowledgments. The author thanks Mr. B. Wright for his assistance in the interpretation of the ^1H NMR spectra and Mr. C. J. Howarth for providing the analytical data.

Registry No. **3**, 65702-01-4; **4**, 66125-04-0; **6a**, 70528-56-2; **6b**, 70528-57-3; **6c**, 70528-58-4; **7a**, 70528-59-5; **7b**, 70528-60-8; **7c**, 70528-61-9; **8a** HCl, 70528-62-0; **8b** HCl, 70528-63-1; **8c** oxalate, 70528-65-3; **9a**, 70528-66-4; **9a** HCl, 70528-67-5; **9b** HCl, 70528-68-6; **9c**, 70528-69-7; *cis*-crotyl alcohol, 4088-60-2; *threo*-2,3-dibromobutan-1-ol, 70528-70-0; 1-naphthol, 90-15-3.

Direct Conversion of Carboxylic Acids into Amides

Paul A. Grieco,* Douglas S. Clark, and Gregory P. Withers

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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It has been demonstrated that treatment of carboxylic acids with phenyl thiocyanate and tri-*n*-butylphosphine in methylene chloride gives rise to the formation of activated thiol esters in high yield (eq 1).[1] We wish to report

$$RCOOH \xrightarrow[Bu_3P/THF]{C_6H_5SCN} RCOSC_6H_5 \qquad (1)$$

that treatment of carboxylic acids with *o*-nitrophenyl thiocyanate and tri-*n*-butylphosphine in tetrahydrofuran containing an amine results in the direct, high-yield conversion of acids into amides (eq 2).[2] This efficient,

$$RCOOH \xrightarrow[\substack{Bu_3P/THF \\ R'R''NH}]{o\text{-}O_2NC_6H_4SCN} RCONR'R'' \qquad (2)$$

(1) Grieco, P. A.; Yokoyama, Y.; Williams, E. *J. Org. Chem.* **1978**, *43*, 1283.

(2) For recent reports on the direct conversion of carboxylic acids into amides, see: Wilson, J. D.; Weingarten, H. *Can. J. Chem.* **1970**, *48*, 983. Pelter, A.; Levitt, T. E.; Nelson, P. *Tetrahedron* **1970**, *26*, 1539. Husson, H.-P.; Poupat, C.; Rodriguez, B.; Potier, P. *Tetrahedron Lett.* **1971**, 2697. Matsueda, R.; Maruyama, H.; Ueki, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.*, **1971**, *44*, 1373. Castro, B.; Dormoy, J.-R. *Bull. Soc. Chim. Fr.* **1971**, 3034. Barstow, L. E.; Hruby, V. J. *J. Org. Chem.* **1971**, *36*, 1305. Barton, D. H. R.; Comer, F.; Greig, D. G. T.; Sammes, P. G.; Cooper, C. M.; Hewitt, G.; Underwood, W. G. E. *J. Chem. Soc. C* **1971**, 3540. Yamada, S.-i.; Kasai, Y.; Shioiri, T. *Tetrahedron Lett.* **1973**, 1595. Hendrickson, J. B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, 277. Bald, E.; Saigo, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 1163. Mukaiyama, T.; Aikawa, Y.; Kobayashi, S. *ibid.* **1976**, 57. Collum, D. B.; Chen, S.-C.; Ganem, B. *J. Org. Chem.* **1978**, *43*, 4393.

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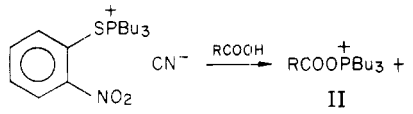
Table I. Preparation of Amides

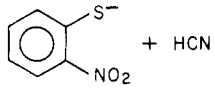
acid	amine	time, h	yield, %[a]
cyclohexanecarboxylic	allyl	7	100
cyclohexanecarboxylic	isobutyl	8	99
cyclohexanecarboxylic	diethyl	8	96
cyclohexanecarboxylic	benzyl	6.5	99
octanoic	allyl	7	98
octanoic	isobutyl	8	96
octanoic	diethyl	6	94
octanoic	benzyl	7	99
octanoic	piperidine	7	99
benzoic	allyl	5.5	100
benzoic	isobutyl	6.5	96
benzoic	diethyl	5.5	100
benzoic	benzyl	6.5	96
p-chlorobenzoic	allyl	4.5	92
p-chlorobenzoic	isobutyl	4	93
p-chlorobenzoic	diethyl	4.5	94
p-chlorobenzoic	benzyl	5.5	100
p-methoxybenzoic	benzyl	12	98

[a] Yields are based on pure compounds isolated by chromatography.

one-step procedure undoubtedly proceeds via the intermediacy of the acyl species II (generated from the thia-



I II



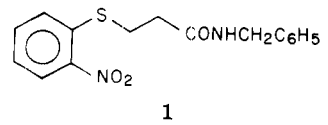
phosphonium cyanide I by reaction with the carboxylic acid), which reacts with the amine present to produce the corresponding amide and tri-*n*-butylphosphine oxide.

The procedure is generally carried out employing 1.5 equiv of amine in tetrahydrofuran containing 1.5 equiv of *o*-nitrophenyl thiocyanate and 1.5 equiv of freshly distilled tri-*n*-butylphosphine. The reaction, which proceeds under mild conditions, has been performed on both aryl and alkyl carboxylic acids utilizing both primary and secondary amines (Table I).

Reaction of 3-methyl-2-butenoic acid with benzylamine in anhydrous tetrahydrofuran containing tri-*n*-butylphosphine and *o*-nitrophenyl thiocyanate afforded a 96% yield of the corresponding amide as a crystalline compound, mp 62–63 °C (eq 3). In contrast, acrylic acid, when

$$(CH_3)_2C{=}CHCOOH \xrightarrow[o\text{-}O_2NC_6H_4SCN]{C_6H_5CH_2NH_2} \xrightarrow[Bu_3P/THF]{} (CH_3)_2C{=}CHCONHCH_2C_6H_5 \quad (3)$$

subjected to the same reaction conditions, gave rise to only a 17% yield of *N*-benzylacrylamide, mp 46.0–47.5 °C. The major product (61%) was the amide 1, mp 129–130 °C.



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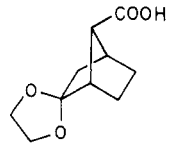


2

Application of the above procedure to the bicyclo[2.2.1]heptanecarboxylic acid 2[3] using benzylamine gave

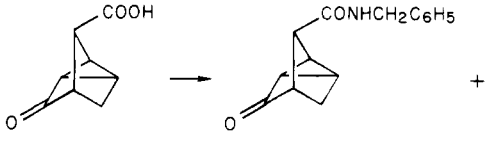
(3) Unpublished results of D. R. Moore, University of Pittsburgh.

Table II. Preparation of Lactams

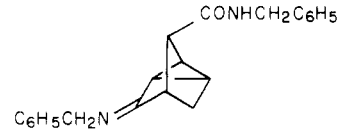
amino acid	time, h	yield, %[a]
4-aminobutyric acid	19	88
6-aminocaproic acid	23	97
5-aminovaleric acid	22	73

[a] Yields were determined by VPC analysis.

the corresponding amide in 99% yield as a crystalline solid, mp 115.5–116.5 °C. Treatment of keto acid 3[4] with 1.0



3 4



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equiv each of benzylamine, *o*-$O_2NC_6H_4SCN$, and Bu_3P generated, in addition to the anticipated amide 4, mp 116.5–117.5 °C (70%), benzylimine 5 (15%).

The application of the above method to lactam synthesis employing ω-aminocarboxylic acids was briefly examined. The reactions were carried out in dimethylformamide using 1.5 equiv of *o*-$O_2NC_6H_4SCN$ and 1.5 equiv of tri-*n*-butylphosphine. As indicated in Table II the yields for the five-, six-, and seven-membered ring lactams were uniformly high. We have, however, been unsuccessful in our attempts to prepare larger ring lactams by this method.

Experimental Section

Reactions were run under an atmosphere of nitrogen. Tri-*n*-butylphosphine was distilled before use. Tetrahydrofuran was distilled from lithium aluminum hydride prior to use. Dimethylformamide was distilled from calcium hydride. Melting points were determined in a Fischer-Johns hot-stage melting point apparatus and are uncorrected.

General Procedure for Conversion of a Carboxylic Acid into an Amide. A solution of 202 mg (1.4 mmol) of octanoic acid in 10 mL of tetrahydrofuran containing 379 mg (2.1 mmol) of *o*-nitrophenyl thiocyanate[5] was treated with 230 μL (2.1 mmol) of benzylamine and 524 μL (2.1 mmol) of freshly distilled tri-*n*-butylphosphine. After 7 h at room temperature the solvent was removed in vacuo and the residue was chromatographed on 80 g of silica gel. Elution with benzene (230 mL) followed by hexane–ether (1:1) gave 325 mg (99%) of crystalline *N*-benzyloctamide, mp 65.0–65.5 °C, identical in all respects with an authentic sample.

Acknowledgments. This investigation was supported by Public Health Service Research Grant CA 13689-07 from the National Cancer Institute.

Registry No. 1, 70659-78-8; 2, 70659-79-9; 2 benzyl amide, 70659-82-4; 3, 70748-53-7; 4, 70659-80-2; 5, 70659-81-3; 3-methyl-2-butenoic acid, 541-47-9; *N*-benzyl-3-methyl-2-butenamide, 67264-80-6; acrylic acid, 79-10-7; *N*-benzylacrylamide, 13304-62-6; *o*-nitrophenyl thiocyanate, 2769-30-4; tri-*n*-butylphosphine, 998-40-3; cyclohexanecarboxylic acid, 98-89-5; octanoic acid, 124-07-2; benzoic acid, 65-85-0; *p*-chlorobenzoic acid, 74-11-3; *p*-methoxybenzoic acid, 100-09-4; 4-aminobutyric acid, 56-12-2; 6-aminocaproic acid, 60-32-2;

(4) Bindra, J. S.; Grodski, A.; Schaaf, T. K.; Corey, E. J. *J. Am. Chem. Soc.* **1973**, *95*, 7522. Peel, R.; Sutherland, J. D. *J. Chem. Soc., Chem. Commun.* **1974**, 151.

(5) Wagner-Jauregg, T.; Helmut, E. *Ber. Dtsch. Chem. Ser. B* **1942**, *75*, 935.

5-aminovaleric acid, 660-88-8; allylamine, 107-11-9; isobutylamine, 78-81-9; diethylamine, 109-89-7; benzylamine, 100-46-9; piperidine, 110-89-4; *N*-allylcyclohexanecarboxamide, 70659-83-5; *N*-isobutylcyclohexanecarboxamide, 70659-84-6; *N,N*-diethylcyclohexanecarboxamide, 5461-52-9; *N*-benzylcyclohexanecarboxamide, 35665-26-0; *N*-allyloctanamide, 70659-85-7; *N*-isobutyloctanamide, 70659-86-8; *N,N*-diethyloctanamide, 996-97-4; *N*-benzyloctanamide, 70659-87-9; 1-octanoylpiperidine, 20299-83-6; *N*-allylbenzamide, 10283-95-1; *N*-isobutylbenzamide, 5705-57-7; *N,N*-diethylbenzamide, 1696-17-9; *N*-benzylbenzamide, 1485-70-7; *N*-allyl-*p*-chlorobenzamide, 5866-99-9; *N*-isobutyl-*p*-chlorobenzamide, 7461-33-8; *N,N*-diethyl-*p*-chlorobenzamide, 7461-38-3; *N*-benzyl-*p*-chlorobenzamide, 7461-34-9; *N*-benzyl-*p*-methoxybenzamide, 7465-87-4; 2-pyrrolidinone, 616-45-5; hexahydro-2*H*-azepin-2-one, 105-60-2; 2-piperidinone, 675-20-7.

Communications

Studies in Macrolide Synthesis: Control of Remote Stereochemistry by Sulfenic Acid Cyclization and 2,3-Sigmatropic Ring Expansion

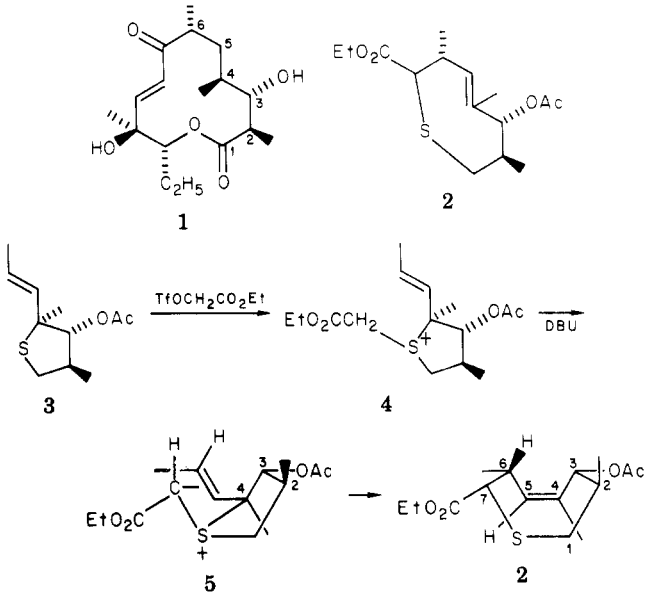
Summary: Three asymmetric centers are generated stereospecifically by cyclization of a γ,δ-unsaturated sulfenic acid derivative, **7**, to give an α-alkenyl tetrahydrothiophene, **9a**, the starting material for stereospecific synthesis of a 4-thiacyclooctene, **2**.

Sir: Synthetic approaches to macrolide antibiotics must solve the difficult problem of stereochemical control at remote asymmetric centers. In this communication we outline the construction of a sulfur heterocycle **2** which incorporates the C_1–C_7 segment of methynolide **1** with the natural stereochemistry at C_2, C_3, and C_6. Our main purpose is to describe a synthesis of the tetrahydrothiophene **3** by a remarkably stereospecific sulfenic acid cyclization and to show that the C_4 stereochemistry of **3** can be transformed into the C_6 stereochemistry of **2** (Scheme I). The latter process is achieved by taking advantage of the predictable geometry of 2,3-sigmatropic ring expansion reactions.[1] A description of strategy for conversion of **2** into methynolide precursors will be deferred to subsequent publications.

Ylides derived from α-alkenyl tetrahydrothiophenes rearrange to 4-thiacyclooctenes.[1a] The major product from stabilized ylides is invariably the cis double bond isomer of an eight-membered ring, so the transition state geometry for ylide ring expansion can be drawn as the tub conformation **5**. The required cisoid propenyl rotamer is then constrained to rearrange to **2** with predictable stereochemistry at C_6 as shown. It is the relative stereochemistry of C_4 with respect to C_3 and C_2 which ultimately controls C_6; if C_4 were inverted, it would be necessary to use an analogue of **5** having a *cis*-propenyl group to afford the same stereoisomer **2**. Inspection of **5** suggests that C_7 geometry can also be predicted since the ester will undoubtedly prefer an exo orientation with respect to the bicyclo[3.3.0]octane-type transition state.

The synthesis of **3** is outlined in Scheme II. A sulfenic acid precursor **6** is available by a simple, precedented sequence which controls the geometry of the trisubstituted double bond.[2] Slow addition of **6** to refluxing 1:1 acetic acid–acetic anhydride (boron trifluoride etherate catalyst) gives a single volatile product **9a** (81%) isolated by simple distillation. As shown by Morin and co-workers, thermolysis of *tert*-alkyl sulfoxides in acetic anhydride generates sulfenic acetates via initial fragmentation to the sulfenic acid.[3] Electrophilic addition of the sulfenic acetate **7** to the internal double bond is responsible for the formation of **9a**.

Scheme I



To convert acrylate derivative **9a** into the desired α-propenyl tetrahydrothiophene structure, a two-stage operation was performed. First, methanolysis of the acetate (K_2CO_3) and alcohol protection (dihydropyran, TsOH) gave **9b**. Without isolation of intermediates, **9b** was reduced (DIBAL) to an allylic alcohol and mesylated (BuLi; MsCl), and the sensitive allylic mesylate was converted into a propenyl derivative **9c** by $Li^+Et_3{}^-BH$[4] (35% overall from **9a**).

The crucial cyclization of sulfenic acetate **7** was expected to give **9a** according to the following argument. Morin cyclizations are believed to involve episulfonium ion intermediates,[3] and two such species, **8A** and **8B**, are possible depending on which face of the double bond is attacked by electrophilic sulfur. The undesired intermediate **8B** is strongly destabilized relative to **8A** by a severe *endo*-methyl–*endo*-methyl interaction, and also suffers from steric congestion along the path for S_N2 attack by acetate

(1) (a) E. Vedejs, J. P. Hagen, B. L. Roach, and K. L. Spear, *J. Org. Chem.*, **43**, 1185 (1978); (b) E. Vedejs, M. J. Arco, D. W. Powell, J. M. Renga, and S. P. Singer, *ibid.*, **43**, 4831 (1978).

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