CH=C), 7.80–8.45 (m, 9, aromatic); exact mass calcd m/e 328.1464, found 328.1468.

Anal. Calcd for $C_{23}H_{20}O_2$: C, 84.12; H, 6.14. Found: C, 83.85; H, 5.89.

3-Methyl-4-(1-pyrenyl)butanoic Acid (3f). A mixture of 19.5 g (59.3 mmol) of **3e**, 150 mL of 40% aqueous KOH, and 50 mL of ethanol was heated at reflux for 3 h (alcoholic KOH is equally acceptable), cooled, and acidified with 6 N HCl. The precipitate was filtered off and recrystallized from benzene–ether to yield 16.0 g (89%) of the α,β-unsaturated acids (**3f**). A solution of 11.16 g (36.9 mmol) of **3f** and 1.7 g of 10% Pd/C in 150 mL of 9:1 ethyl acetate–acetic acid was hydrogenated (Parr shaker) at 3.5 atm for 24 h. Removal of catalyst by filtration and solvent under reduced pressure followed by recrystallization of the residue from benzene–petroleum ether afforded 9.9 g (87%) of **3g**: mp 124–129 °C (lit. mp 125–135 °C[2]); exact mass calcd m/e 302.1307, found 302.1314.

9-Methylbenzo[*a*]pyrene (1). The conversion of **3f** to **2** was accomplished as described[2] in 93% yield, mp 175.5–176 °C (lit. mp 176.5–177.5 °C[2]). To ketone **2** (7.0 g, 24.6 mmol) in 300 mL of 1:1 THF–ethanol was added 0.6 g (15.8 mmol) of $NaBH_4$ in three portions. After 20 h, hydrolysis was accomplished with saturated NH_4Cl, and the solution was concentrated. Extraction with 1:1 ether–benzene (2 × 100 mL) followed by washing the organic extracts with saturated NaCl, decolorization, gravity filtration through a cone of $MgSO_4$, and evaporation of the solvent afforded a yellow solid (one spot by TLC) which was used directly (4.79 g, 68%). Aromatization was accomplished as described[2] with 10% Pd/C (25% by weight), purifying by vacuum distillation directly from the reaction mixture followed by recrystallization from benzene–methanol. From 0.32 g of alcohol, 0.23 g of **1** was isolated (77%): mp 139–140 °C (lit. mp 139–140 °C[2]); ^1H NMR ($CDCl_3$) δ 2.62 (s, 3, CH_3), 7.08, 7.34, 7.48, 7.72, 7.88, 7.97, 8.03, 8.13, 8.22, 8.58, 8.70, 8.87 (m, 11, aromatics); UV (EtOH) λ_{max} (ϵ) 407 (6400), 386 (20 800), 384 (20 300), 379 (26 200), 367 (20 500), 350 sh (11 300), 335 sh (5200), 298 (57 200), 286 (44 200), 273 (30 500), 267 (48 900), 256 (37 700), 228 (24 700), 222 (23 100).

Registry No. **1**, 70644-19-8; **2**, 70644-20-1; **3a**, 129-00-0; **3b**, 3029-19-4; **3c**, 70644-21-2; **3d**, 70644-22-3; (*E*)-**3e**, 70644-23-4; (*Z*)-**3e**, 70644-24-5; **3f**, 70644-25-6; 7-hydroxy-9-methyl-7,8,9,10-tetrahydrobenzo[*a*]pyrene, 70644-26-7; diethyl 1-(methylthio)ethylphosphonate, 22966-40-1; ethyl trimethylsilylacetate, 4071-88-9.

Stereospecific Synthesis of *threo*- and *erythro*-1-(Aryloxy)-3-(alkylamino)butan-2-ols

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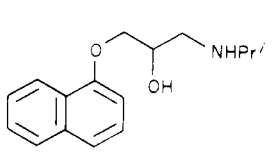
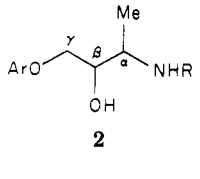
Received December 11, 1978

There is an extensive literature on the biological consequences of α-alkyl substitution in the ethanolamine moiety of β stimulants related to isoproterenol[1] and related β antagonists.[2] By contrast, relatively little structure–activity work has been reported on the effects of α-alkyl substitution on the biological properties of the medicinally important β antagonists related to propranolol (**1**). In



1

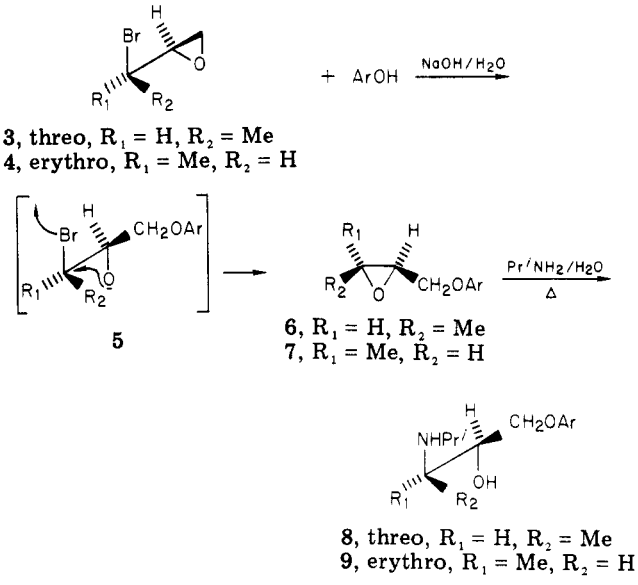


2

(1) R. T. Brittain, D. Jack, and A. C. Ritchie, *Adv. Drug Res.*, **5**, 197 (1970).

(2) R. Howe, *J. Med. Chem.*, **12**, 642 (1969), and references cited therein.

Scheme I



studying this problem we devised a route for the stereoselective synthesis of the threo and erythro isomers of 1-(aryloxy)-3-(alkylamino)butan-2-ols (**2**) starting from the simple precursors *cis*- and *trans*-crotyl alcohol. Recent reports on the synthesis of α- and γ-methyl(aryloxy)propanolamines[3,4] have prompted us to report our own findings.

We discovered that phenols reacted with both *threo*- and *erythro*-(1-bromoethyl)oxirane[5] (**3** and **4**, respectively) under basic conditions at room temperature to give in each case a single oxirane product to which we have assigned the cis and trans structures **6** and **7** (see reaction Scheme I). The *threo*-(1-bromoethyl)oxirane (**3**) was prepared from *trans*-crotyl alcohol as described by Hiskey et al.;[6] the erythro isomer (**4**) was obtained from *cis*-crotyl alcohol by an analogous method. In practice, **3** and **4** are considerably less reactive than the related demethyl analogue chloromethyloxirane, and there is still ca. 10% phenol present after 3 days' stirring. We usually stopped the reaction at this stage and the excess phenol was easily removed by extraction with dilute caustic soda.

In principle the reaction of oxirane **3** with a nucleophile can occur at carbon atoms 1, 2, or 3. Attack at carbon 2 was ruled out since this could not yield an oxirane and moreover there is ample precedent[7] that nucleophiles attack oxiranes at the least substituted carbon atom. A direct S_N2 attack on carbon 3 with displacement of the bromine atom would have given a terminal oxirane whereas the ^1H NMR spectra of the products **6a–c** clearly show signals for two vicinal oxirane protons and for the OCH_2 group. Attack at carbon 1 is consistent with the findings of Hiskey et al.,[6] who showed that **3** reacted with sodium acetylide at carbon 1, and also of Waters et al.,[8] who showed that sodium methoxide attacked (1-bromoethyl)oxirane at carbon 1. Interestingly Waters et al.

(3) G. Shtacher, R. Rubenstein, and P. Somani, *J. Med. Chem.*, **21**, 678 (1978).

(4) T. L. Lemke, R. L. Boblitt, G. A. Capiton, L. A. Cates, and G. E. Martin, *J. Org. Chem.*, **43**, 2079 (1978).

(5) A more precise nomenclature for *threo*-(1-bromoethyl)oxirane (**3**) is 2(*SR*)-[1(*SR*)-bromoethyl]oxirane and likewise the erythro isomer (**4**) is 2(*SR*)-[1(*RS*)-bromoethyl]oxirane.

(6) C. F. Hiskey, H. L. Slates, and N. L. Wendler, *J. Org. Chem.*, **21**, 429 (1956).

(7) R. E. Parker and N. S. Isaacs, *Chem. Rev.*, **59**, 737 (1959).

(8) R. C. Waters and C. A. Van Der Werf, *J. Am. Chem. Soc.*, **76**, 709 (1954).

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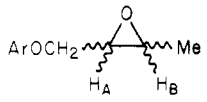
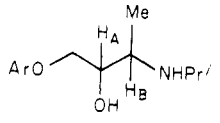
Table I. 2-[(Aryloxy)methyl]-3-methyloxiranes



	Ar	isomer	mp or bp, °C	yield,[a] %	chem shifts, ppm: oxirane protons H_A, H_B	chem shifts, ppm: OCH_2 protons
6a	1-naphthyl	cis	72-72.5	46	3.08-3.53	4.2-4.26
7a	1-naphthyl	trans	60-60.5	33	2.8-3.09	4.02-4.18
6b	*m*-tolyl	cis	98-100 (0.9 mm)	65	3.05-3.39	4.0-4.13
7b	*m*-tolyl	trans	*b*		2.9-3.11	3.87-4.24
6c	*p*-tolyl	cis	98-101 (1 mm)	71	2.97-3.34	4.0-4.12
7c	*p*-tolyl	trans	111-113 (6.5 mm)	32	2.82-3.11	3.78-4.19

[a] Yields have not been optimized. [b] The oxirane was not purified and its structure was confirmed by ^1H NMR.

Table II. 1-(Aryloxy)-3-(alkylamino)butan-2-ols



	Ar	isomer	chem shifts, ppm: OCH_2	chem shifts, ppm: H_A	J_{AB}, Hz	mp, °C	salt	yield,[a] %	formula[c]
8a	1-naphthyl	threo	4.13-4.24	3.53-3.77	6.9	213.5-216	HCl	71	$C_{17}H_{24}NO_2Cl$
9a	1-naphthyl	erythro	3.9-4.3[d]		5.4	216-218.5	HCl	53	$C_{17}H_{24}NO_2Cl$
8b	*m*-tolyl	threo	3.95-4.06	3.4-3.61	6.9	102-103	HCl	53	$C_{14}H_{24}NO_2Cl$
9b	*m*-tolyl	erythro	3.75-4.09[d]		3.6	180-181	HCl	54	$C_{14}H_{24}NO_2Cl$
8c	*p*-tolyl	threo	3.92-4.07	3.38-3.62	6.6	115-118	$(COOH)_2$	60	$C_{16}H_{25}NO_6$
9c	*p*-tolyl	erythro	3.8-4.04[d]		3.8	96-98	base	24[b]	$C_{14}H_{23}NO_2$

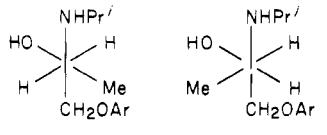
[a] Yields are based on oxirane. [b] Yield based on phenol. [c] All compounds were analyzed for C, H, and N and the results were within ±0.4% theory. [d] H_A was overlapped by the OCH_2 signal.

reasoned from the products of LAH reduction of their starting oxirane that it was the threo isomer and that the product of reaction with sodium methoxide was the erythro isomer although they presented no evidence to support this.

We propose that reaction proceeds by attack of phenoxide anion at carbon 1 to give an alkoxide intermediate (**5**) which undergoes intramolecular displacement of bromine to give the oxiranes **6** and **7**. The cis oxirane proton signals are found at lower field than the signals for the corresponding trans protons (see Table I) and this is consistent with reports[9] that for alkyl-substituted oxiranes the alkyl group shields an adjacent cis proton and deshields a trans proton. The structures of the *cis*- and *trans*-2-[(aryloxy)methyl]-3-methyloxiranes (**6** and **7**) were confirmed by their ^1H NMR spectra. In the spectrum of *cis*-2-[1-(naphthyloxy)methyl]-3-methyloxirane (**6a**) the individual oxirane protons fortuitously appeared at different chemical shifts and the coupling constant (~5 Hz) falls within the range quoted for J_{cis} of 2.2–5.2 Hz.[9] Finally, the ^1H NMR spectrum for *trans*-2-phenoxymethyloxirane prepared by our route agrees with data published by Shtacher et al.[3] for the same compound unambiguously prepared by peroxidation of the corresponding *trans*-crotyl ether.

The *cis*- and *trans*-oxiranes **6** and **7** reacted with aqueous isopropylamine at reflux temperature in 4–5 h to give the corresponding *threo*- and *erythro*-1-(aryloxy)-3-(isopropylamino)butan-2-ols **8** and **9**, respectively. We found that the drastic conditions used by Shtacher et al. (140 °C for 40 h in the presence of phenol) were unnecessary. The only product formed[10] arose from attack of isopropylamine on carbon 3 of the oxiranes **6** and **7** presumably because attack at carbon 2 is hindered by the adjacent bulky aryloxy group.

In general $J_{erythro}$ is greater than J_{threo}[9] unless there is hydrogen bonding, when other factors may intervene.[11] Our observed values for J_{threo} and $J_{erythro}$ are in the range 6.6–6.9 and 3.6–5.4 Hz, respectively (see Table II) Shtacher et al. have shown in their IR data that there is considerable hydrogen bonding in these (aryloxy)butanolamines and this being so, one would expect the preferred conformations of the threo and erythro isomers to be **10** and **11**,



10 threo **11** erythro

respectively, in which the OH and $NHPr^i$ groups are adjacent and the bulkiest groups are trans to one another. In the threo case (**10**) the protons have a trans relationship whereas in the erythro case (**11**) they are gauche. Since J_{trans} is greater than J_{gauche}, then for this series J_{threo} is greater than $J_{erythro}$, as observed.

An examination of the ^1H NMR spectra of free bases **8a–c** and **9a–c** run in $CDCl_3$ showed that for the threo isomers, the proton adjacent to the OH group occurs as an isolated multiplet at higher fields than the corre-

(9) H. Booth, *Prog. Nucl. Magn. Reson. Spectrosc.*, **5**, 180–186 (1971).

(10) No trace of the isomeric 4-(aryloxy)-3-(isopropylamino)butan-2-ols was observed when the ^1H NMR of the crude reaction product was recorded.

(11) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Oxford, 1969, pp 291–292.

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

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Received February 13, 1979

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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