## Experimental Section

**Labeled Esters.** These compounds were prepared with either methanol-*t* ($CH_2TOH$) or water-*t* (HOT), both from New England Nuclear, as a source of tritium. Procedures were as follows: equilibration of unlabeled methyl esters with methanol-*t*; reaction of methanol-*t* with acyl chloride; and reaction of diazomethane with RCOOT, prepared by exchange with HOT. For example, dimethyl terephthalate (2.53, 0.013 mol) was added to 26 mL of $CH_2TOH$ (1.8 $\mu$Ci mmol$^{-1}$) and the solution was left for 12 h at room temperature. Water (50 mL) was added, and the crystals were removed by filtration: 2.2 g (88%) of $CH_3O_2CC_6H_4CO_2CH_2T$, mp 140–141 °C (lit.[17] mp 141.5–141.8 °C for the unlabeled compound), was obtained. Alternatively, anisoyl chloride (7.1 g, 0.04 mol) was added to methanol-*t* (4 mL, 0.1 mol; 1.8 $\mu$Ci mmol$^{-1}$) and the mixture left for several days at room temperature. Then it was added to 100 mL of aqueous 5% $Na_2CO_3$; crystals were filtered out and recrystallized from 95% ethanol–water; yield of methyl anisate, 4.7 g (68%); mp 49–50 °C (lit.[18] mp 48 °C). Finally, benzoic acid (6.7 g, 0.05 mol) was allowed to stand for 3 h at room temperature in dioxane containing 1 mL of HOT (0.25 mCi/mL). The water and dioxane were pumped away, ether was added, and a solution of diazomethane in ether, prepared from nitrosomethylurea, was added. Methyl benzoate-*methyl-t* was distilled at 55–57 °C (0.5 mm); yield, 5.9 g (80%).

**(−)-Menthyl methyl carbonate** was prepared according to Salomaa[19] from (−)-menthol (15.6 g, 0.1 mol; Givaudan Delawanna, Inc.), which was converted to the alkoxide with sodium hydride in 200 mL of toluene. This was added dropwise to methyl chloroformate (13.6 g, 0.14 mol) in 100 mL of ether at 0 °C. Distillation and recrystallization from aqueous methanol yielded (−)-menthyl methylcarbonate, mp 32 °C (lit.[19] mp 31 °C).

**Exchange Kinetics and Radioassay.** Aliquots (1 mL) of reaction mixture were delivered by pipet into a separatory funnel containing 15 mL of xylene and 20 mL of water. After the mixture was shaken, the water was removed and the xylene layer extracted twice more with 20-mL portions of water and dried with sodium sulfate. A 10-mL aliquot of the xylene layer and a 10-mL aliquot of scintillation solution (10 g/L of 2.5-diphenyloxazole (PPO, Packard) in xylene or toluene) were combined in a Packard glass counting vial for radioassay. Packard-Tri-Carb or Beckman liquid scintillation counters were used. Observed radioactivities were fit to a first-order rate law by a weighted least-squares procedure. The first-order rate constants were then fit by a linear least-squares treatment to the methoxide concentrations to produce second-order rate constants.

**Methanolysis of (−)-Menthyl Methyl Carbonate.** Equal 1-mL volumes of substrate and sodium methoxide solutions were delivered by syringe into a thermostated 10-cm polarimeter cell (American Instrumental Co.), and the cell was quickly placed in a Perkin-Elmer digital polarimeter. Optical rotations (usually at 365 nm) were fit by a least-squares procedure to the first-order rate law. Second-order rate constants were obtained by linear least-squares as before.

**Registry No.** *p*-$MeOC_6H_4CO_2CH_2T$, 88229-69-0; *p*-$MeC_6H_4CO_2CH_2T$, 88229-70-3; $PhCO_2CH_2T$, 64935-86-0; *p*-$BrC_6H_4CO_2CH_2T$, 88229-71-4; *p*-$MeOCOC_6H_4CO_2CH_2T$, 88229-72-5; *m*-$O_2NC_6H_4CO_2CH_2T$, 88229-73-6; *p*-$O_2NC_6H_4CO_2CH_2T$, 88229-74-7; *o*-$MeOC_6H_4CO_2CH_2T$, 88229-75-8; *o*-$MeC_6H_4CO_2CH_2T$, 88229-76-9; *o*-$BrC_6H_4CO_2CH_2T$, 88229-77-0; $CH_3OCO_2CH_2T$, 88229-78-1; $CH_2TOH$, 20515-96-2; HOT, 13670-17-2; (−)-menthyl methyl carbonate, 22642-92-8; (−)-menthol, 2216-51-5; (−)-menthol sodium alkoxide, 27303-99-7; methyl chloroformate, 79-22-1; dimethyl terephthalate, 120-61-6; anisoyl chloride, 1300-64-7; benzoic acid, 65-85-0; diazomethane, 334-88-3.

(16) Mitton, C. G.; Gresser, M.; Schowen, R. L. *J. Am. Chem. Soc.* **1969**, *91*, 2045.
(17) Legge, D. I. *J. Am. Chem. Soc.* **1947**, *69*, 2086.
(18) Kuhn, L. P.; Corwin, A. H. *J. Am. Chem. Soc.* **1948**, *70*, 3370.
(19) Salomaa, E. *Ann. Acad. Sci. Fenn., Ser. II* **1959**, *94*, 1; *Chem. Abstr.* **1961**, *54*, 5732g.

# Antibacterial Benzisoxazolones. An Unusual Rearrangement Product from *o*-Nitrostyrene Oxide en Route to the Photolabile Carbonyl Protecting Group (*o*-Nitrophenyl)ethylene Glycol

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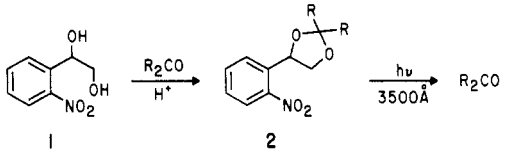
In the process of synthesizing the known, photolabile protecting group (*o*-nitrophenyl)ethylene glycol, we uncovered an acid-mediated rearrangement of *o*-nitrostyrene oxide to 1-(hydroxymethyl)-2,1-benzisoxazol-3(1*H*)-one. The structure was ascertained by IR, UV, $^1$H NMR, $^{13}$C NMR, MS, and X-ray crystallography. Also the benzisoxazolone was prepared by independent synthesis from an *o*-nitrobenzoate. Another novel transformation uncovered was the conversion of *o*-nitrostyrene oxide to 2-(*o*-nitrophenyl)ethanol with use of potassium hydroxide and 18-crown-6. Similar chemistry was insignificant with *p*-nitrostyrene oxide. The benzisoxazolone exhibited antibacterial and antileukemic activity (in vitro).

## Introduction

As part of a program in our laboratories on the design and use of photolabile prodrugs for the therapy of psoriasis and other proliferative skin disorders, we were interested in the (*o*-nitrophenyl)ethylene glycol group (**1**) as a photoreactive protecting group for carbonyl moieties. The (*o*-nitrophenyl)ethylene acetal or ketal (**2**), formed from the glycol and a carbonyl group, readily regenerates the carbonyl group[2-4] with high quantum efficiency. In the process of preparing **1** we uncovered an interesting rearrangement to a benzisoxazolone that exhibited in vitro antibacterial and antileukemic activity.[5]

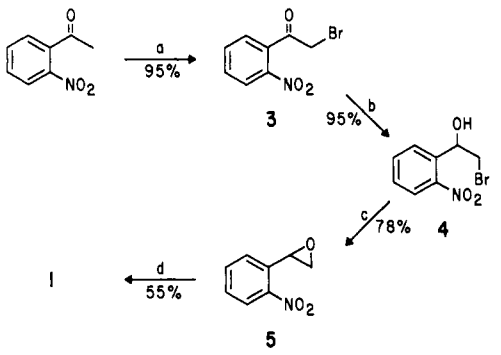



**1** **2**

(1) J. J. Voorhees and W. Wierenga, U.S. Patent 4 302 456 (7), 1981.
(2) J. Hebert and D. Gravel, *Can. J. Chem.*, **52**, 187 (1974).
(3) B. Amit, U. Zehavi, and A. Patchornik, *Isr. J. Chem.*, **12**, 103 (1974) (review).
(4) R. C. Kelly and I. Schletter, IUPAC Congress on Natural Products, Madison, WI, 1980 (June 15–20), reported the use of **1** for the protection and regeneration of a highly sensitive, polyunsaturated, β-hydroxy aldehyde.
(5) W. Wierenga, B. R. Evans, and G. E. Zurenko, *J. Antibiot.*, submitted.

0022-3263/84/1949-0438$01.50/0 

Scheme I[a]



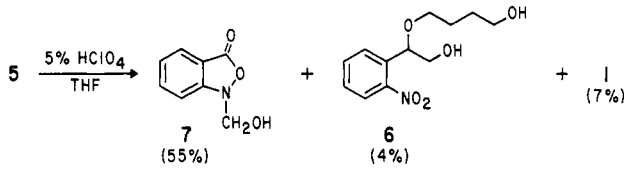

[a] (a) $Br_2$, $AlCl_3$, $Et_2O$; (b) $NaBH_4$, EtOH; (c) NaOH (aqueous); (d) $K_2CO_3$ dioxane $H_2O$, Δ.

## Results and Discussion

The use and preparation of **1** from *o*-nitrostyrene oxide (**5**) were first reported in a communication by Hebert and Gravel in 1974,[2] devoid of experimental details. We have developed a synthesis very similar to theirs and it is outlined in Scheme I.

Bromination of *o*-nitroacetophenone with catalytic aluminum trichloride and bromine, which was preferred in our hands to the bromine/acetic acid procedure,[6] cleanly afforded the known monobromo derivative **3**. Reduction to the bromohydrin and subsequent treatment with aqueous base gave the known oxide[11] (mp 62–63.5 °C from ethanol/water). $^1H$ and $^{13}C$ NMR spectral data were consistent with the assigned structure. Ring opening to the desired glycol **1** proceeded in reasonable yield with carbonate in refluxing aqueous dioxane or tetrahydrofuran (THF).

Prior to successfully exploiting these hydrolysis conditions, we explored several other procedures to generate the glycol **1**. Treatment of **5** with mild acid in THF afforded three products: 7% isolated yield of the desired glycol **1**, 4% of a glycol **6** whose $^1H$ NMR was consistent with the incorporation of a molecule of THF, and 55% of 1-(hydroxymethyl)-2,1-benzisoxazol-3(1*H*)-one (**7**).




The structure of this unusual rearrangement product is based on IR, $^1H$ and $^{13}C$ NMR, MS, and elemental analysis. Since this benzisoxazolone was unknown,[7] additional structure confirmation was achieved by single-crystal X-ray analysis.

Figure 1 shows conformation and numbering of **7**. The figure also shows bond distances and angles about the nitrogen atom, which has a pyramidal configuraton and

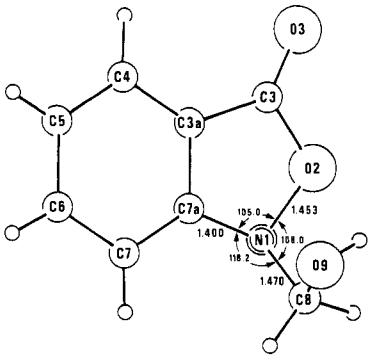



**Figure 1.** Numbering and conformation of **7**.

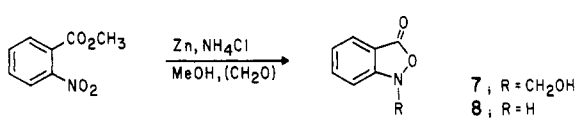
Table I. Final Atomic Coordinates (×10⁴) for 7

| atom | x | y | z |
|---|---|---|---|
| N(1) | 507 (2) | 8404 (2) | 7992 (2) |
| O(2) | -332 (2) | 7016 (2) | 6286 (1) |
| C(3) | 627 (3) | 7881 (2) | 4847 (2) |
| O(3) | 76 (2) | 7004 (2) | 3293 (1) |
| C(3A) | 2184 (2) | 9803 (2) | 5588 (2) |
| C(4) | 3599 (3) | 11265 (2) | 4739 (2) |
| C(5) | 4978 (3) | 12938 (3) | 5839 (2) |
| C(6) | 4959 (3) | 13129 (3) | 7736 (2) |
| C(7) | 3552 (3) | 11686 (2) | 8591 (2) |
| C(7A) | 2147 (3) | 10022 (2) | 7470 (2) |
| C(8) | 1001 (3) | 7379 (3) | 9146 (2) |
| O(9) | 2566 (2) | 6730 (2) | 8417 (1) |

is substantially (0.12 Å) out of the plane of the rest of the atoms in the fused rings. The N1–C7A bond is somewhat shorter, and the N1–O2 bond somewhat longer than would be expected for single bonds if one assumes bond lengths of 1.47 Å for C–N[8] and 1.43 Å for N–O.[9] Fractional coordinates for **7** are listed in Table I.

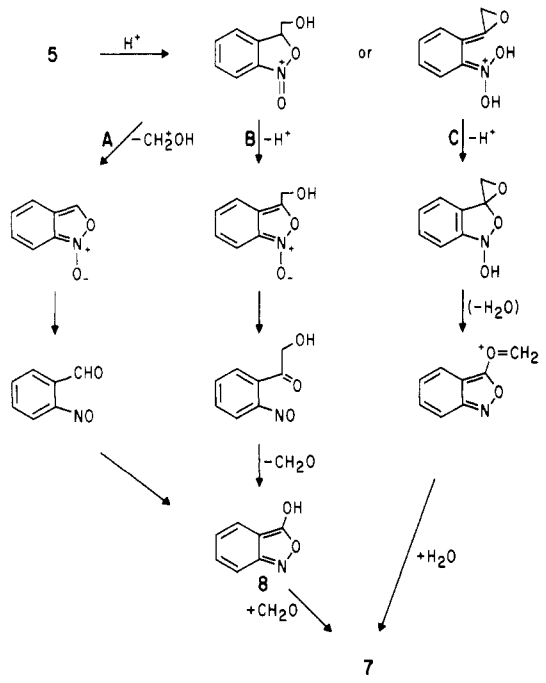
Pairs of molecules interact by means of hydrogen bonds between the hydroxyl and the carbonyl in centrically related molecules (O3–O9 = 2.757 Å). The molecules pack in parallel planes, with molecules in adjacent planes staggered so that the carbonyl of one molecule is directly above the benzene ring of another. Packing distances between aromatic carbons are a little less than would be predicted frm the van der Waals half-thickness of aromatic molecules, 1.70 Å.[10] Distances between C3 and atoms C3A and C4 in molecules related by a center of symmetry but not hydrogen bonded together are 3.265 and 3.274 Å, respectively.

Benzisoxazol-3(1*H*)-one (**8**) itself has been described by Bamberger and Pyman[12] as the product of the zinc reduction of *o*-nitrobenzoates. Later, Barton et al.[1] reported the zinc-mediated liberation of alcohols from *o*-nitrobenzoates, as protecting groups, affording benzisoxazolone as the byproduct. In utilizing this chemistry as an independent synthetic route to **7**, we realized only a 10% yield of benzisoxazolone (**8**). These experiments included dilute conditions, inverse addition, and different forms of activated zinc. Benzisoxazolone (**8**) can be readily converted to **7** with formaldehyde in the presence of acid or base. However, **7** was produced directly in 45% yield when formaldehyde was added to the reaction mixture.



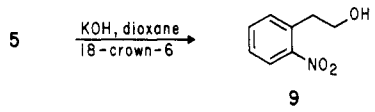

(6) Gerekoht, *Justus Liebigs Ann. Chem.*, **221**, 323 (1883).
(7) Previous workers have shown the conversion of *o*-nitrostyrene oxide to (*o*-nitrosobenzoyl)methanol in the presence of formic acid (see ref 23, p 673, and T. W. M. Spence and G. Tennant, *J. Chem. Soc., Perkin Trans. 1*, 98, 1972). Also, acid-catalyzed conversion of *o*-nitrophenyl glycidic esters and β-(*o*-nitrophenyl)-α,β-epoxy ketones to 2,1-benzisoxazoles (anthranils) and *N*-hydroxyquinolones, respectively, has been reported (see A. Schillinger and S. Wleugel, *Chem. Ber.*, **16**, 222 (1883) and T. W. M. Spence and G. Tennant, *J. Chem. Soc.*, 3712 (1971).
(8) J. E. Wollrab and V. W. Laurie, *J. Chem. Phys.*, **48**, 5058 (1968).
(9) A. P. Cox and R. L. Kuczkowski, *J. Am. Chem. Soc.*, **88**, 5071 (1966).
(10) L. Pauling, "The Nature of the Chemical Bond," 3rd ed., Cornell University Press: Ithaca, NY, 1960, p 260.
(11) C. O. Guss, *J. Org. Chem.*, **17**, 678 (1952).
(12) E. Bamberger and F. L. Pyman, *Ber.*, **42**, 2297 (1909).
(13) D. H. R. Barton, I. H. Coates, and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, 599 (1973).

Scheme II

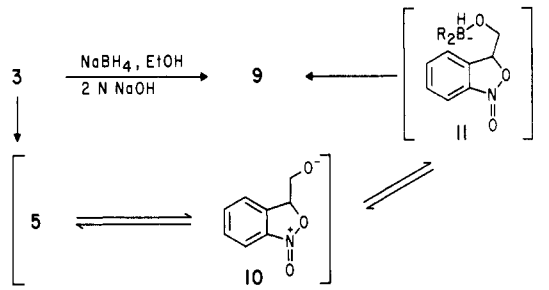


Several possible mechanisms are projected in Scheme II for the acid-promoted derivation of **7** from oxide **5**. They are all basically nuances on the same theme of *o*-nitro group participation in the initial solvolysis[14,15] followed by loss and readdition of the elements of formaldehyde at some point. *o*-Nitrosobenzaldehyde has been claimed as an isolable entity (see path A). Although we have not attempted to distinguish among these possible pathways, we have demonstrated that the addition of excess formaldehyde does not enhance the conversion of **5** to **7**. In addition, interpretation of experiments designed to trap free formaldehyde (e.g., phenylhydrazine) was complicated by the fact that **7** also reacts with the trapping agents under the reaction condition. The intermediacy of benzisoxazoles is rationalized on the basis of their solvolytic derivation from *o*-nitrobenzyl precursors.[17]

Another procedure targeting the glycol **1** from *o*-nitrostyrene oxide involved the use of potassium hydroxide and crown ether. The only product isolated (73% yield) was 2-(*o*-nitrophenyl)ethanol (**9**) presumably formed via an electron-transfer–protonation process.



This interesting product was also the result of an abortive shortcut in the synthesis of **1** (Scheme I). We attempted to produce **1** directly from α-bromo-*o*-nitroacetophenone with use of sodium borohydride in basic media. Instead 2-(*o*-nitrophenyl)ethanol (**9**) was the sole product (56% isolated yield). Assuming the initial step is reduction to the alkoxide followed by ring closure to the styrene oxide,[18] one could then invoke participation of the *o*-nitro to form a cyclic nitronate (**10**). Reductive conversion to the primary alcohol may be facilitated by a penultimate, alkoxyborohydride species (**11**) to deliver hydride intramolecularly in a solvolytic, two-stage process. Treatment of 5-(bromoacetyl)uracil under similar conditions affords the corresponding primary alcohol as well.[18]



A consistent theme in the several examples delineated above is the participation of the proximate nitro group in a reaction pathway to alter the usual chemistry.[23] To demonstrate that this is not just an electronic or inductive effect, we prepared the corresponding *p*-nitrophenyl compounds (Scheme III).

*p*-Nitrophenacyl bromide, in contrast to the *o*-nitro analogue, afforded *p*-nitrostyrene oxide (**12**) with borohydride under basic conditions. No 2-(*p*-nitrophenyl)ethanol was detected. We were able to detect some 2-(*p*-nitrophenyl)ethanol with the KOH/18-crown-6 procedure, but the yield was substantially reduced relative to the *o*-nitro series. Acid hydrolysis proceeded in the expected fashion to produce (*p*-nitrophenyl)ethylene glycol and the THF-incorporated glycol product.

## Experimental Section

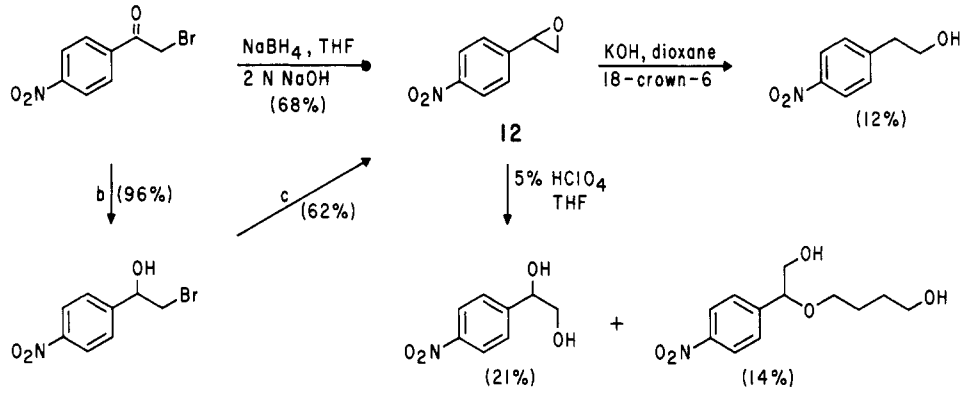
**General Methods.** All solvents employed were reagent grade and used as received. $^1$H NMR spectra were recorded on either a Varian FT-80 or EM-390 instrument. $^{13}$C NMR spectra were recorded on a Varian CFT-20 instrument. All data is relative to internal $Me_4Si$. IR spectra were obtained on a Perkin-Elmer Model 197 instrument. UV spectra were recorded on a Perkin-Elmer Lambda 3 instrument. Melting points were obtained with a Thomas-Hoover Unimelt apparatus and are uncorrected.

***o*-Nitrostyrene Oxide (5).** This was prepared in 70% overall yield from *o*-nitroacetophenone by the procedures of Gerekoht[6] and Guss[11] except that the initial bromination employed the standard bromine/aluminum trichloride procedure rather than bromine/acetic acid. The α-bromo-*o*-nitroacetophenone and bromohydrin were identified by IR and $^1$H NMR and by melting point comparisons with literature values.[5,11] *o*-Nitrostyrene oxide similarly was identified by $^1$H NMR: $^1$H NMR ($CDCl_3$) δ 8.3–8.1 (m, 1 H), 7.8–7.3 (m, 3 H), 4.49 (dd, 1 H), 3.30 and 2.69 (dd, 2 H); $^{13}$C NMR ($Me_2SO$) 151.84 ($C_1$), 138.46, 132.92, 130.67 and 128.48 ($C_{3-6}$), 138.07 ($C_2$), 54.02 ppm ($C_{7,8}$-superimposed d and t on off-resonance); mp 62–63.5 °C (lit.[6] mp 64–5 °C).

**(*o*-Nitrophenyl)ethylene Glycol (1).** To 4.4 g (26.7 mmol) of *o*-nitrostyrene oxide in 20 mL of dioxane was added 2.4 g of potassium carbonate in 20 mL of water. The solution was heated at reflux for 24 h and then cooled and diluted with 50 mL of water.

(14) W. B. Dickinson, *J. Am. Chem. Soc.*, **86**, 3580 (1964).
(15) S. S. Ball, L. J. Andrews, and R. M. Keefer, *J. Org. Chem.*, **44**, 525 (1979), and references cited therein.
(16) E. Bamberger and F. Elger, *Liebigs Ann. Chem.*, **371**, 319 (1909). See also H. Mauser and H. Heitzer, *Z. Naturforsch.*, **216**, 109 (1966), and J. M. Bakke and H.-J. Engan, *Acta Chem. Scand., Ser. B*, **32**, 230 (1978).
(17) See, for example, C. A. Grob and O. Weissbach, *Helv. Chim. Acta*, **44**, 1748 (1961), and T. J. McCord, D. R. Smith, J. K. Swan, A. M. Goebel, D. E. Thornton, C. C. Yakshe, and A. L. Davis, *J. Heterocycl. Chem.*, **16**, 1249 (1979).
(18) R. C. Bleackley, A. S. Jones, and R. T. Walker, *Tetrahedron*, **32**, 2795 (1976).
(19) D. J. Duchamp, "Algorithms for Chemical Computation", American Chemical Society, Washington, DC, 1977, Ser. No. 46, pp 98–121.
(20) The CRYM system of crystallographic programs and the direct methods program DIREC were written by David J. Duchamp, The Upjohn Co.
(21) "International Tables for X-Ray Crystallography", Vol. 3, Kynoch Press, Birmington, England, 1962, pp 202, 205.
(22) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).
(23) P. N. Preston and G. Tennant, *Chem. Rev.*, **72**, 627 (1972).

Scheme III




The solution was extracted twice with 100 mL of ethyl acetate, and the combined organic phases were washed with brine, dried over sodium sulfate, and concentrated to a brown solid (3.7 g). This was recrystallized from methylene chloride to give 2.1 g (43%), mp 94–96 °C (lit.[2] mp 95–96 °C). The mother liquors were chromatographed on 150 g of silica gel with 25% ethyl acetate/hexane eluent to afford 0.55 g of starting material (12%) and 0.6 g of product (12%) for a total yield of 63% (based on recovered starting material): $^1$H NMR ($(CD_3)_2CO$) δ 8.1–7.3 (m, 4 H), 5.30 (dd, 1 H), 3.68 (dd, 2 H), 4.6 and 3.8 (br s, 2-OH); $^{13}$C NMR ($Me_2SO$) 149.43 ($C_1$), 138.11 ($C_2$), 133.71, 129.75, 128.98, 124.56 ($C_{3-6}$), 70.59 ($C_7$), 67.76 ppm ($C_8$); IR (Nujol) 3300, 3200 cm$^{-1}$ (OH).

**1-(Hydroxymethyl)-2,1-benzisoxazol-3(1*H*)-one (7).** To 4.4 g (26.6 mmol) of *o*-nitrostyrene oxide in 20 mL of THF was added 25 mL of 5% perchloric acid. The solution was stirred for 20 h at room temperature and then diluted with 150 mL of ethyl acetate. The solution was then washed with saturated sodium bicarbonate and water and dried over sodium sulfate. Chromatography on silica gel with 30% ethyl acetate/hexane eluent afforded 2.4 g (55%, $R_f$ 0.47) of the product; recrystallization from ethyl acetate/hexane gave the product with mp 116–117 °C. A lower $R_f$ (0.41) product was also eluted (0.3 g, 7% yield), which had identical $R_f$ (TLC) and NMR data with that of *o*-nitrophenyl)ethylene glycol. The lowest $R_f$ (0.17) product (0.2 g, 4% yield) exhibited an NMR consistent with **6** ($CDCl_3$) δ 8.1–7.3 (m, 4 H), 5.05 (m, 1 H), 4.1–3.3 (m, 8 H), 1.62 (t, $J$ = 6 Hz, 2 H). **7**: $^1$H NMR (acetone-$d_6$) δ 7.9–7.6 (m, 2 H), 7.5–7.2 (m, 2 H), 5.27 (s, 2 H); $^{13}$C NMR ($Me_2SO$) 167.83 (CO), 155.04 (CN), 135.37, 124.98, 124.57, 113.26 (aromatic CH), 113.89 (aromatic C), 94.85 ppm ($CH_2$); MS, $m/e$ 165 (40, $M^+$), 148 (29, $M^+$ – OH), 135 (100, $M^+ - CH_2O$), 104 (30, $C_6H_4CO$). Anal. Calcd for $C_6H_7NO_3$: C, 57.49; H, 4.22; N, 8.38. Found: C, 57.77; H, 4.25; N, 8.20.

**Reduction of Methyl *o*-Nitrobenzoate to 1-(Hydroxymethyl)-2,1-benzisoxazol-3(1*H*)-one (7).** To methyl *o*-nitrobenzoate (2 g, 11 mmol) in 50 mL of THF was added ammonium chloride (4 g, 75 mmol) in 50 mL of water. To this mixture were added zinc dust (1.7 g, 26 mmol), sodium carbonate (0.6 g, 5.7 mmol), and 37% aqueous formaldehyde (11 mL). After 1.5 h 1 mL of formaldehyde solution was added. The mixture was filtered after an additional hour, diluted with ethyl acetate (EtOAc), washed with dilute aqueous sodium carbonate (3 × 30 mL) and brine, dried, and concentrated to a pale yellow solid (1.8 g). Crystallization from EtOAc/hexane gave colorless crystals (0.8 g, 44% yield, mp 115–117 °C). This was identical with the acid-catalyzed rearrangement product from *o*-nitrostyrene oxide.

**2-(*o*-Nitrophenyl)ethanol (9) from *o*-Nitrostyrene Oxide.** To 1.51 g (9.1 mmol) of *o*-nitrostyrene oxide in 20 mL of dioxane (THF also works) were added under $N_2$ with stirring 350 mg of 18-crown-6 and 1.52 g (25 mmol) of potassium hydroxide. The dark solution was stirred for 48 h at room temperature. The reaction was neutralized with acetic acid, taken up in ethyl acetate, washed with saturated sodium bicarbonate, water, and brine, and dried over sodium sulfate to give 1.1 g of crude product (73%). The NMR and *Rf* (TLC) showed it to be identical with that of the alternately prepared 2-(*o*-nitrophenyl)ethanol (vide infra).

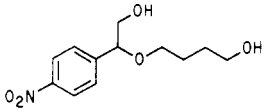
**2-(*o*-Nitrophenyl)ethanol (9) from α-Bromo-*o*-nitroacetophenone.** To 483 mg (2 mmol) of *o*-nitrophenacyl bromide in 3 mL of ethanol and 3 mL of THF at 5 °C with stirring were added 100 mg of sodium borohydride and 1.6 mL of 2 N sodium hydroxide. The solution was allowed to come to room temperature and stirred for 2 h and then quenched with acetic acid (to pH 6). After dilution with water, the reaction solution was extracted twice with ether. The combined organic phases were dried over magnesium sulfate and concentrated to give 350 mg of crude product. Chromatography on silica gel (25% EtOAc/hexane) afforded 188 mg (56%): $^1$H NMR ($CDCl_3$) δ 8.1–7.8 (m, 1 H), 7.6–7.2 (m, 3 H), 3.89 (t, $J$ = 6 Hz, 2 H), 3.12 (t, $J$ = 6 Hz, 2 H), 2.8 (br s, 1 H); IR (neat) 3550 cm$^{-1}$ (OH); UV (ethanol) $\lambda_{max}$ 204 (13 350), 257 (4600). Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.81; H, 5.53; N, 8.46. To 108 mg (0.64 mmol) of 2-(*o*-nitrophenyl)ethanol in 2 mL of pyridine was added 100 L of benzoyl chloride, and the solution was stirred under $N_2$ for 18 h. Ice was added and the solution extracted twice with 25 mL of ether. The combined organic phases were washed with 1 N HCl, water, and brine and dried over magnesium sulfate. The crude product obtained after concentrating to dryness was recrystallized from methylene chloride/hexane to give 97 mg of product benzoate, mp 53–55 °C (lit.[5] mp 55 °C). Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.56; H, 4.86; N, 5.08.

***p*-Nitrostyrene Oxide (12).** *p*-Nitrophenacyl bromide, mp 99.5–101 °C (lit.[6] mp 97–99 °C), prepared from *p*-nitroacetophenone analogous to the previously described *o*-nitroacetophenone, was converted to the bromohydrin with $NaBH_4$,[6] mp 86–87 °C, which in turn was closed to the oxide with aqueous sodium hydroxide; recrystallization from ethanol/water gave the product with the following: mp 79–81 °C (lit.[6] mp 82–85 °C); $^1$H NMR (acetone-$d_6$) δ 7.92 and 7.26 (4 H, $A_2B_2$), 4.07 (m, 1 H), 3.20 and 2.83 (2 H, m).

***p*-Nitrostyrene Oxide (12) from *p*-Nitrophenacyl Bromide.** To 3.76 g (13.4 mmol) of *p*-nitrophenacyl bromide in 10 mL of methanol and 12 mL THF were added 200 mg of sodium borohydride and 14 mL of 2 N NaOH. After stirring at 5 °C for 35 min, the reaction mixture was quenched with acetic acid (pH ~6), diluted with 150 mL of ethyl acetate, and washed with saturated sodium bicarbonate and water, and dried over sodium sulfate. The residue (3.4 g) was crystallized from 75% ethanol (water) to afford 1.50 g of *p*-nitrostyrene oxide (68% yield, mp 79–81 °C; NMR and TLC $R_f$ identical with that of the authentic compound).

**(*p*-Nitrophenyl)ethylene Glycol.** To 4.23 g (25.6 mmol) of *p*-nitrostyrene oxide in 257 mL of THF was added 25 mL of 5% perchloric acid for 20 h at room temperature. The reaction solution was taken up in ethyl acetate and washed thoroughly with water and then dried over sodium sulfate and concentrated. The residue was chromatographed on 350 g of silica gel with 40% EtOAc/hexane → 100% ethyl acetate gradient to recover in decreasing $R_f$ 1.0 g (21%, mp 79–81 °C) of the product glycol and 880 mg (14%) of a more polar product identified by NMR as ii: (acetone-$d_6$) δ 8.24 and 7.65 (4 H, $A_2B_2$), 4.55 (t, $J$ = 6 Hz, 1 H), 3.9–3.3 (8 H, m), 1.64 ("t", $J$ = 6 Hz, 4 H); IR (neat) 3300 cm$^{-1}$. (*p*-Nitrophenyl)ethylene glycol: $^1$H NMR (acetone-$d_6$) δ 8.20 and 7.71 (4 H, $A_2B_2$), 4.88 (2 H, m, CHO and OH), 4.13 (1 H, t, $J$ = 5 Hz, CHO), 2.71 (2 H, m, CHO, OH); IR (neat) 3350 cm$^{-1}$ (OH).

**2-(*p*-Nitrophenyl)ethanol.** To 445 mg (2.7 mmol) of *p*-nitrostyrene oxide was added 8 mL of dioxane followed by 200



(ii)

mg of 18-crown-6 and 360 mg of potassium hydroxide. The solution was stirred under $N_2$ for 48 h, then quenched with acetic acid (pH ~6), and diluted with water and ethyl acetate. The organic phase was separated, washed with water and brine, and dried over sodium sulfate. Chromatography of the concentrated multicomponent residue on silica gel (40% EtOAc/hexane) yielded 55 mg of the known product (12% yield): $^1$H NMR ($CDCl_3$) $\delta$ 8.13 and 7.38 (4 H, $A_2B_2$), 3.88 (t, $J$ = 6 Hz, 2 H), 2.93 (t, $J$ = 6 Hz, 2 H), 2.3 (br s, 1 H).

**X-ray Study of 7.** Crystal data for 7 ($C_8H_7NO_3$) were as follows: triclinic, space group $P\bar{1}$, $Z$ = 2, $a$ = 7.038 (1) Å, $b$ = 7.718 (2) Å, $c$ = 7.556 (1) Å, $\alpha$ = 104.50 (2)°, $\beta$ = 83.11 (1)°, $\gamma$ = 115.10 (5)°, $D_{measd}$ = 1.45 g cm$^{-3}$, $D_{calcd}$ = 1.52 g cm$^{-3}$, $\mu$(Cu K$\alpha$) = 9.0 mc$^{-1}$, 1087 reflections, of which 1033 were greater than one standard deviation. Intensity data for all reflections with $2\theta$ 138° were collected by using the step-scan technique at −150 °C on a Syntex $P2_1$ diffractometer controlled by a Harris computer using graphite monochromatized Cu K$\alpha$ radiation ($\lambda$ = 1.5418 Å). Standard deviations in observed intensities were approximated by the function $\sigma^2(I) = \sigma^2$(counting statistics) + $(0.017I)^2$, where the coefficient of $I$ was calculated from intensities of 10 reflections monitored throughout the data collection, considering deviations in intensities that were not explained by counting statistics.[19] The structure was solved by direct methods by using DIREC.[20]

Coordinates, hydrogen coordinates, and anisotropic thermal parameters of non-hydrogen atoms were refined minimizing the function $\sum w(F_o^2 - F_c^2)^2$ where weights w were taken as the reciprocals of the variances $\sigma^2(F_o^2)$. Atomic form factors were from "International Tables for X-Ray Crystallography"[21] except hydrogen form factors which were taken from Stewart et al.[22] The final agreement index $R$, ($R = \sum||F_o| - |F_c||/\sum F_o$), was 0.035. All calculations were carried out on an IBM 3033 computer using the CRYM system of crystallographic programs.[20]

**Registry No.** 1, 51673-59-7; 3, 6851-99-6; 4, 88057-15-2; 5, 39830-70-1; 6, 88057-17-4; 7, 88057-16-3; 9, 15121-84-3; 9 (benzoate), 88057-18-5; 12, 6388-74-5; 12 (bromohydrin), 19922-82-8; ii, 88057-20-9; (*p*-nitrophenyl)ethylene glycol, 88057-19-6; 2′-nitroacetophenone, 577-59-3; methyl 2-nitrobenzoate, 606-27-9; *p*-nitrophenacyl bromide, 99-81-0; 4′-nitroacetophenone, 100-19-6; 4-nitrobenzeneethanol, 100-27-6.

**Supplementary Material Available:** Tables II–VII, anisotropic thermal parameters, hydrogen coordinates, bond distances, bond angles, torsion angles, and short intermolecular distances (5 pages). Ordering information is given on any current masthead page.

# Regiospecific Two-Step Synthesis of Optically Active Allylic Terpenyl Thiols

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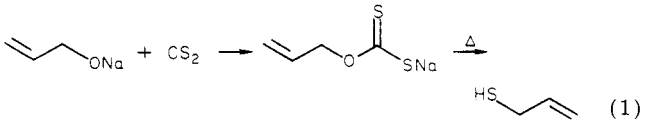
Allylic thiols were prepared in 70–90% yields by treatment of mono- and sesquiterpenes with $C_6H_5SO_2N{=}S{=}O$ followed by $LiAlH_4$ reduction of the ene adducts.

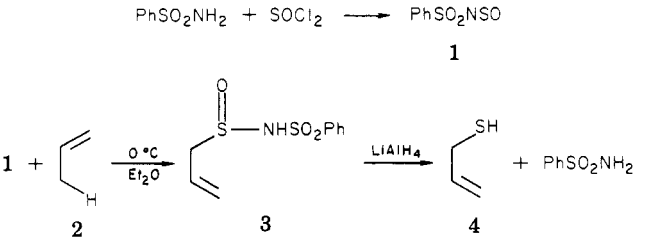
Allylic thiols are of interest as synthesis intermediates because they can be converted into allylic dianions that

react preferentially in the $\gamma$-position with a variety of electrophiles.[1] In addition, terpene thiols are constituents of fruit flavors and of perfumes.[2-6] Allylic thiols can be prepared by treating an alkali metal allylic alcoholate with $CS_2$ followed by thermal degradation of the resulting metal xanthogenate[3] (eq 1).



(1)

Scheme I



This reaction has been applied to the preparation of terpene thiols from geraniol, pulegol, carveol, and myrtenol. However, it is not regioselective (or stereoselective), presumably because of a double rearrangement similar to the one that has been observed with sulfodiimides.[7] We here present a new regiospecific synthesis of optically active terpene thiols in two steps from readily available terpene hydrocarbons.

*N*-Sulfinylbenzenesulfonamide (1), which is a potent enophile and dienophile,[8-10,16] undergoes an ene reaction

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