References and Notes

(1) Jorma K. Koskimies, Ph.D. Dissertation, University of North Carolina, Chapel Hill, N.C. 1976.
(2) E. L. Eliel, A. A. Hartmann, and A. G. Abatjoglou, *J. Am. Chem. Soc.*, **96**, 1807 (1974).
(3) The scheme shows the absolute configurations of the enantiomers in excess (a, *S* configuration at C-4; **b**, *R* configuration at C-6) used in the synthesis.
(4) K. Omura, A. K. Sharma, and D. Swern, *J. Org. Chem.*, **41**, 957 (1976), procedure A.
(5) THF had to be added in order to effect dissolution of **3a**.
(6) Four equivalents were used.
(7) A previous run with racemic **3a** had given a ratio of 94:6 (**4a/5a**), probably due to some moisture contained in the THF used.
(8) A diastereomeric mixture of **4a** and **5a** obtained by addition of racemic **1a**–Li to acetophenone served as reference.
(9) S. Takano, S. Hatakeyama, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, 68 (1977), and references there cited.
(10) Based on the rotation reported by L. Angiolini, P. Costa Bizzarri, and M. Tramontini, *Tetrahedron*, **25**, 4211 (1969), in MeOH for 82.1% optically pure ester (cf. ref 11), the optical purity of our material would be 43.8%.
(11) D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959).
(12) A previous experiment with racemic material had afforded **4b** in >99% diastereomeric purity; traces of moisture, again, may have caused the drop in diastereomeric purity; cf. note 7.
(13) L. N. Owen and M. U. S. Sultanbawa, *J. Chem. Soc.*, 3098 (1949).
(14) C. E. Hagberg and S. Allenmark, *Chem. Scr.*, **5**, 13 (1974).
(15) This value corresponds to 48% e.e., if the reported rotation[14] of $[\alpha]^{25}_D$ −17.1° (ethanol), is the true value for the optically pure compound. If so, some racemization must have occurred in the preparation of **1a** from the precursor acid.
(16) H. Schulz and V. du Vigneaud, *J. Am. Chem. Soc.*, **88**, 5015 (1966).
(17) Modification of a procedure by F. Aftallon, D. Lumbroso, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 1958 (1965).
(18) H. J. Backer and G. J. DeJong, *Recl. Trav. Chim. Pays-Bas*, **70**, 377 (1951).
(19) S. Yamaguchi and H. S. Mosher, *J. Org. Chem.*, **38**, 1870 (1973).
(20) Determined by an LSR experiment using $Eu(hfc)_3$.
(21) R. Roger, *J. Chem. Soc.*, 2168 (1932): $[\alpha]^{25}_D$ −126.2° ($CHCl_3$) for ethyl (*R*)-mandelate.
(22) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. I, Wiley, New York, N.Y., 1967, p 729: ½-h reflux in 2-propanol with Raney nickel, prepared according to the procedure therein described, led to complete desulfurization.
(23) $[\alpha]^{25}_D$ −0.349°, neat (i.e., the sample had been dissolved in 20.76 times its weight of racemic 4-methyl-2-pentanol). The rotation value indicates that some racemization (~45%) took place during desulfurization; cf. E. L. Eliel and S. Schroeter, *J. Am. Chem. Soc.*, **87**, 5031 (1965).
(24) P. A. Levene and A. Walti, *J. Biol. Chem.*, **94**, 367 (1931).
(25) Cf. note 12.
(26) E.g., B. M. Benjamin, H. J. Schaeffer, and C. J. Collins, *J. Am. Chem. Soc.*, **79**, 6160 (1957): 99% stereoselectivity. Reference 11: 90–92%. Reference 10: 100%.
(27) R. Méric and J.-P. Vigneron, *Bull. Soc. Chim. Fr.*, **327** (1973). These investigators have described a synthesis of **9** in 97% optical yield using manitol (which is consumed) as the chiral auxiliary reagent. They have also suggested (but not reduced to practice) a synthesis of the general type described here.

Ernest L. Eliel,* Jorma K. Koskimies, Bruno Lohri

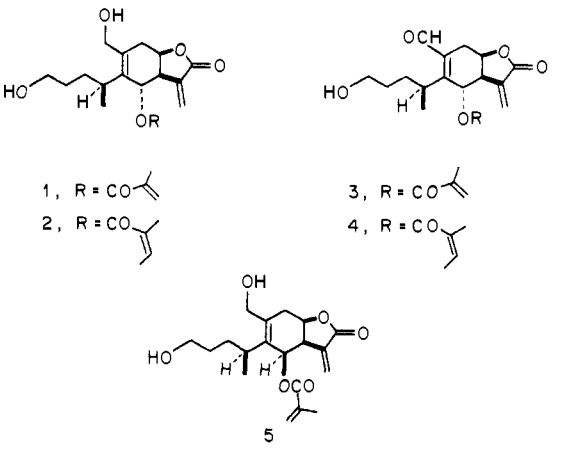
Department of Chemistry, University of North Carolina
Chapel Hill, North Carolina 27514

Received October 11, 1977

Total Synthesis of (±)-Eriolanin

Sir:

Eriolanin (**1**) and eriolangin (**2**) are novel antileukemic 1,10-*seco*-eudesmanolides which were isolated from *Eriophyllum lanatum* Forbes (Compositae) by Kupchan and coworkers during a search for tumor-inhibitory natural products from plant sources.[1] The structural elucidation of **1** and **2** involved a combination of NMR and mass spectral techniques along with x-ray analysis of a mixed crystal of dehydroeriolanin (**3**) and dehydroeriolangin (**4**).[2] Both eriolanin and eriolangin possess significant activity in vivo against P-388 leukemia in mice and in vitro against cell cultures derived from human carcinoma of the nasopharynx (KB). In this communication we wish to report a stereocontrolled total synthesis of (±)-eriolanin (**1**). In addition we report the stereospecific total synthesis of (±)-6-epieriolanin (**5**) which is more active than

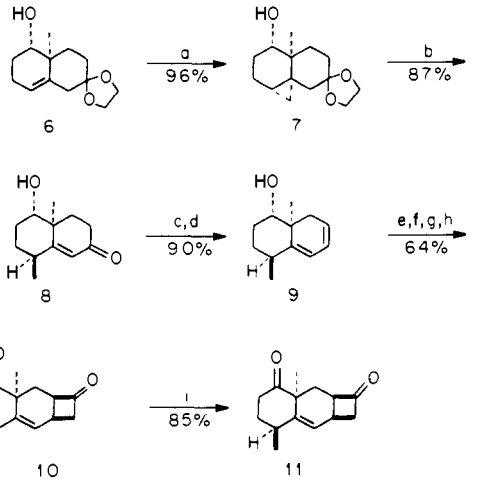


either **1** or **2** in vivo against the P-388 leukemia in mice.[3,4] (±)-6-Epieriolanin also exhibited significant activity (ED_{50} = 1.8 μg/mL)[5] in vitro against KB cells in tissue culture.

The key intermediate **11**, mp 111–112 °C, which can be converted into either racemic eriolanin or racemic 6-epieriolanin, was prepared in 41% overall yield by a nine-step sequence from the known octalol **6**[6] (Chart I). Cyclopropanation of octalol **6** employing the LeGoff modification[7] of the Simmons-Smith reaction gave the 4α,5α-methanodecalol **7** in 96% yield. Exposure of ketal **7** to 70% perchloric acid in methylene chloride resulted in cleavage of the cyclopropane ring and equilibration of the methyl group to the more stable equatorial position.[8] Tosyl hydrazone formation followed by treatment with excess lithium diisopropylamide in tetrahydrofuran gave in 90% yield the conjugated diene **9**[10] which was silylated in near-quantitative yield with *tert*-butyldimethylsilyl chloride in dimethylformamide containing imidazole.[11] As anticipated addition of dichloroketene[12] took place from the β face of the diene system providing, after dechlorination and cleavage of the silyl ether, cyclobutanone **10** (65%): IR (CCl_4) 3640, 3460, 1780 cm^{-1}. Oxidation of **10** with pyridinium chlorochromate[13] gave in 85% yield crystalline diketone **11**: IR (CCl_4) 1783, 1714 cm^{-1}.

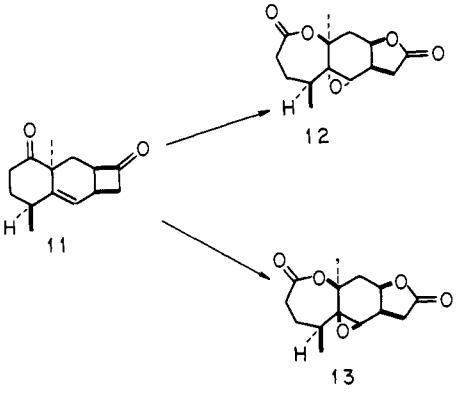
With the olefinic diketone **11** in hand we focused our attention on its direct oxidation to the dilactone epoxide **12** which having all chiral centers established would allow for its con-

Chart I[a]

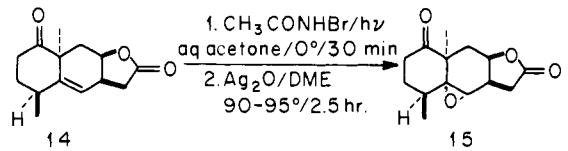


[a] a, Zn(Cu), CH_2I_2, Et_2O; b, 70% $HClO_4$, CH_2Cl_2, 0 °C (1 h) → room temperature (3 h); c, $TsNHNH_2$, $BF_3 \cdot Et_2O$, C_6H_6, room temperature (1 h); d, LDA (6.0 equiv), THF, −78 → 0 °C (1 h) → room temperature (4.5 h); e, *t*-Bu(Me)$_2$SiCl, DMF, imidazole; f, Cl_2-CHCOCl (2.7 equiv), Et_3N, hexane, room temperature (3.5 h); g, Zn, HOAc, 65 °C (4.5 h); h, 10% HCl, THF, room temperature (12 h); i, $C_5H_5NHCrO_3Cl$ (1.8 equiv), CH_2Cl_2, room temperature (2.5 h).

0002-7863/78/1500-1616$01.00/0

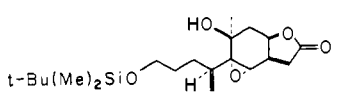


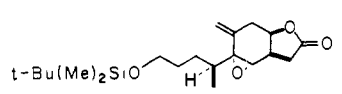
version to (±)-eriolanin. There was the possibility, however, that oxidation would lead to the corresponding dilactone epoxide **13.** Oxidation of **11** with 4.0 equiv of *m*-chloroperbenzoic acid in methylene chloride containing sodium bicarbonate gave rise to a single crystalline product (77%), mp 166–168 °C, which has been assigned structure **13.**[14] The structural assignment rests on the transformation of **13** into (±)-6-epieriolanin whose structure was determined by x-ray analysis (vide infra). The required epoxide **12** was successfully prepared via a four-step sequence of reactions. Treatment of **11** with *tert*-butyl hydroperoxide in tetrahydrofuran containing 10% aqueous sodium hydroxide at 0 °C for 30 min gave a single lactone (**14,** 83%): mp 107.5–109.5 °C; IR ($CHCl_3$) 1773, 1710 cm^{-1}. Submission of olefin **14** to bromohydrin formation

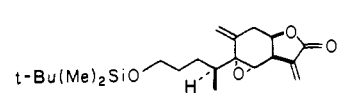


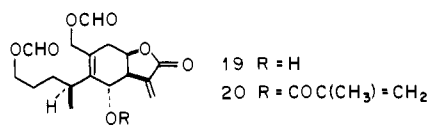
followed by treatment with silver oxide afforded a crystalline epoxide (**15**), mp 173–174 °C, in 74% yield. Baeyer–Villiger oxidation of of ketone **15** with *m*-chloroperbenzoic acid in methylene chloride containing lithium carbonate (96 h) provided the desired dilactone epoxide **12** (mp 164–165.5 °C; IR ($CHCl_3$) 1775, 1732 cm^{-1}) in 45% yield (60% based on consumed ketone).

Dilactone **12** was converted to the γ-lactone **16** via a three-step sequence (1, Dowex 50W-X8 (H^+), aqueous acetone, 48 h, 25 °C; 2, diborane, THF, −20 °C (3 h) → −10 °C (5 h) → 25 °C (1 h); 3, *t*-Bu(Me)$_2$SiCl, DMF, imidazole) in 72% overall yield. Treatment of the tertiary alcohol **16** with thionyl chloride in benzene containing pyridine at room tem-









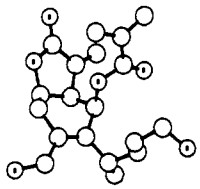


Figure 1. The C_4 (*S*) enantiomer of (±)-6-epieriolanin. Oxygen atoms are denoted by small dots at their centers. The orientation is arbitrary.

perature for 25 min gave a 42% yield of pure exocyclic olefin **17** after chromatography on SilicAR CC-7. Introduction of the α-methylene unit, carried out in 60% overall yield via hydroxymethylation,[15] mesylation, and β-elimination (DBU), provided the α-methylene-γ-butyrolactone **18:** IR (CCl_4) 1782, 1645 cm^{-1}; NMR (CCl_4) δ 6.21 (d, 1 H, J = 3 Hz), 5.61 (d, 1 H, J = 3 Hz), 5.26 (br s, 2 H). The crucial S_N2' opening of epoxide **18** was effected by Dowex 50W-X8 (H^+) suspended in chloroform containing formic acid.[16a] The product (**19**) upon treatment (25 °C, 30 min) with the anhydride of methacrylic acid in tetrahydrofuran containing triethylamine and a catalytic amount of 4-dimethylaminopyridine afforded, after chromatography on SilicAR CC-7, methacrylate **20** (mp 90–91 °C; IR (CCl_4) 1778, 1730, 1720, 1640 cm^{-1}) in 63% overall yield from **18.** Deformylation[16b] was carried out (96%) using Dowex 1-X8 (OH^- form) in methanol at 0 °C (1 h) providing (±)-eriolanin, mp 114.5–115.5 °C, identical with a sample of natural eriolanin by comparison of spectral properties (IR, NMR)[17] and thin-layer mobility in several solvent systems.[18]

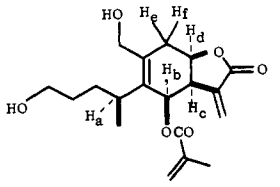
Epoxide **13,** which we had obtained directly from diketo olefin **11** as described above, was converted to (±)-6-epieriolanin (**5**),[20,21] mp 124–125 °C, in 20% overall yield from **13** with only minor modification of the reactions employed above for the conversion of **12** → (±)-eriolanin. Determination of the structure and relative configuration of (±)-6-epieriolanin was effected through a single-crystal x-ray analysis.[22] The conformation of 6-epieriolanin is shown in Figure 1. Among a number of striking conformational features of 6-epieriolanin is the axial nature of the C-6 substituent located on the boat-shaped cyclohexene ring.

Acknowledgments. This investigation was supported by Public Health Service Research Grants CA 13689-06, HL 15378, and AM 19856. Proton magnetic resonance (250 MHz) spectra were obtained on the National Institutes of Health NMR Facility supported by PHS Grant RR-00292. We are deeply indebted to Professor A. T. Sneden (Virginia Commonwealth University) for gifts of natural eriolanin and eriolangin, and for obtaining the biological data on (±)-6-epieriolanin. We are grateful to Dr. Alan F. Thomas (Firmenich) for a generous gift of pure angelic acid. Figure 1 was drawn on PROPHET, an NIH supported computing network.

References and Notes

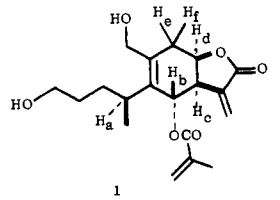
(1) S. M. Kupchan, R. L. Baxter, C.-K. Chiang, C. J. Gilmore, and R. F. Bryan, *J. Chem. Soc., Chem. Commun.*, 842 (1973).
(2) R. F. Bryan and C. J. Gilmore, *Acta Crystallogr., Sect. B,* **31,** 2213 (1975).
(3) Antileukemic and in vitro cytotoxicity were assayed under the auspices of the National Cancer Institute by the procedure described in *Cancer Chemother. Rep.*, **25,** 1 (1962).
(4) (±)-6-Epieriolanin (**5**) demonstrated activities of 128–168% test/control (T/C) at dose levels ranging from 8.0 to 16.0 mg/kg in the PS test system. Eriolanin (**1**) and eriolangin (**2**) exhibited PS activities of 109–152% T/C and 114–128% T/C, respectively, at doses ranging from 16.0 to 32.0 mg/kg. We are indebted to Professor A. T. Sneden for providing us with the latter data.
(5) It should be noted that the ED_{50} value of (±)-epieriolanin compares favorably with the ED_{50} values of 2.5 μg/ml for eriolanin and 10 μg/ml for eriolangin.
(6) C. H. Heathcock and R. Ratcliffe, *J. Am. Chem. Soc.*, **93,** 1746 (1971).
(7) E. LeGoff, *J. Org. Chem.*, **29,** 2048 (1964).
(8) The olefinic proton of enone 8 appeared as a doublet at δ 5.68 with a

coupling constant of J = 1.8 Hz which is in complete agreement with the predicted value of 1.6–1.8 Hz.[9]
(9) D. J. Collins, J. J. Hobbs, and S. Steinhell, *Aust. J. Chem.*, **16**, 1030 (1963).
(10) For a review of the Shapiro olefin forming reaction, see R. H. Shapiro, *Org. React.*, **23**, 405 (1976).
(11) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972).
(12) H. C. Stevens, D. A. Reich, D. R. Brandt, K. R. Fountain, and E. J. Gaughan, *J. Am. Chem. Soc.*, **87**, 5257 (1965); L. Ghosez, R. Montaigne, and P. Mollet, *Tetrahedron Lett.*, 135 (1966); A. Hassner and V. R. Fletcher, *ibid.*, 5053 (1970); P. A. Grieco and K. Hiroi, *ibid.*, 3467 (1974).
(13) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(14) We were not able to assign a structure to the dilactone epoxide, mp 166–168 °C, on the basis of NMR analysis at 250 MHz.
(15) P. A. Grieco and K. Hiroi, *J. Chem. Soc., Chem. Commun.*, 1317 (1972); P. A. Grieco, M. Nishizawa, T. Oguri, S. D. Burke, and N. Marinovic, *J. Am. Chem. Soc.*, **99**, 5773 (1977).
(16) (a) The desired opening of epoxide **18** was accompanied by cleavage of the silyl ether and conversion of the resultant alcohol into its formyl ester. (b) Attempted hydrolysis of the two formate esters with anhydrous potassium carbonate in methanol at varying temperatures gave, in addition to hydrolysis of the two formyl groups, the product derived from Michael addition of methanol to the α-methylene-γ-butyrolactone moiety. The methacrylate unit appeared not to suffer 1,4 addition.
(17) (±)-Eriolanin: IR ($CHCl_3$) 3440, 1758, 1710, 1660, 1635 cm^{-1}; NMR (250 MHz) δ ($CDCl_3$) 6.45 (d, 1 H, J = 2.5 Hz), 6.08 (s, 1 H), 6.05 (d, 1 H, J_{bc} =



5

3 Hz), 5.61 (s, 1 H), 5.27 (d, 1 H, J = 2.5 Hz), 5.05 (dt, 1 H, J_{cd} = 8 Hz, J_{de} = 2.5 Hz, J_{df} = 3 Hz), 4.23 (AB q, 2 H, $\Delta\nu_{AB}$ = 21.2 Hz, J = 12 Hz, CH_2OH), 3.4–3.6 (m, 3 H, $-CH_2CH_2OH$, H_c), 2.80 (AM portion of an AMX system, 2 H, $\Delta\nu_{AM}$ = 80.4 Hz, J_{af} = 16 Hz, J_{de} = 2.5 Hz, J_{df} = 3 Hz), 2.77 (m, 1 H, H_a), 1.93 (s, 3 H), 1.0–1.4 (m, 4 H, $-CH_2CH_2-$), 0.90 (d, 3 H, J = 7 Hz).
(18) After the submission of this manuscript, alcohol **19** was converted in two steps (1, angelic anhydride,[19] Et_3N, THF, 4-dimethylaminopyridine, room temperature, 23 h; 2, Dowex 1X-8 (OH^- form), methanol, 0 °C, 1.5 h) into (±)-eriolangin (**2**), mp 90–91 °C, which was shown to be identical in all respects with an authentic sample of natural eriolangin.
(19) L. B. Bos and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **82**, 168 (1963).
(20) The NMR spectrum[21] of compound **5** at 250 MHz revealed that it was not identical with the NMR spectrum of natural eriolanin; however, it was obvious that all functional groups were present. Unfortunately, NMR analysis did not permit assignment of structure **5** to racemic 6-epieriolanin.
(21) (±)-6-Epieriolanin: IR ($CHCl_3$) 3620, 3450, 1762, 1712, 1665, 1640 cm^{-1}; NMR (250 MHz) δ ($CDCl_3$) 6.36 (d, 1 H, J = 2 Hz), 6.00 (s, 1 H), 5.97 (d, 1 H, J_{bc} = 5 Hz), 5.77 (d, 1 H, J = 2 Hz), 5.56 (s, 1 H), 4.85 (q, 1 H, J_{cd} = J_{de} = J_{df} = 8 Hz), 4.22 (AB q, 2 H, $\Delta\nu_{AB}$ = 18.4 Hz, J = 12 Hz, $-CH_2OH$), 3.51 (t, 2 H, $-CH_2CH_2OH$), 3.25 (m, 1 H, H_a), 2.88 (m, 1 H, H_c), 2.86 (AM portion of an AMX system, 2 H, $\Delta\nu_{AM}$ = 55.7 Hz, J_{af} = 16 Hz, J_{de} = 8 Hz, J_{df} = 8 Hz), 1.87 (s, 3 H), 1.2–1.5 (m, 4 H, $-CH_2CH_2-$), 1.07 (d, 3 H, J = 7 Hz).



1

(22) Crystals of racemic 6-epieriolanin are monoclinic, space group $P2_1/c$, with cell constants a = 9.4729 (6), b = 12.064 (1), c = 16.426 (2) Å; β = 97.60 (1)°; V = 1860.7 Å^3; ρ_0 = 1.257 g cm^{-3}, ρ_c = 1.26 g cm^{-3} (for Z = 4). A total of 3804 reflections were measured, of which 2229 are considered observable ($I > 2\sigma_I$). The structure was determined by routine multisolution direct methods[23] and refined to a current residual of R = 0.067.
(23) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(24) Fellow of the Alfred P. Sloan Foundation.

Paul A. Grieco,*[24] Tomei Oguri, S. Gilman
Department of Chemistry, University of Pittsburgh
Pittsburgh, Pennsylvania 15260

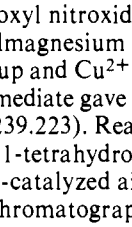
George T. DeTitta
Medical Foundation of Buffalo
Buffalo, New York 14203
Received October 12, 1977

A New Series of Minimum Steric Perturbation Nitroxide Lipid Spin Labels

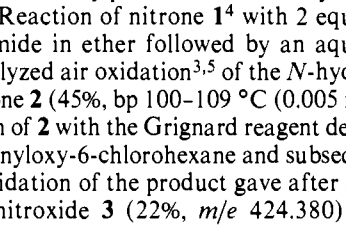
Sir:

A continuing concern in the study of biological and other systems by the nitroxide spin-labeling technique has been the extent to which the system is perturbed by the steric bulk of the nitroxide moiety.[1] We describe herein a new series of "minimum steric perturbation" nitroxide lipid spin labels which we term azethoxyl nitroxides.[2] The nitroxyl nitrogen atom and two of the pyrrolidine ring carbon atoms of the azethoxyl nitroxides are integrated into the lipid chain. Additionally, both bent and straight chain structures can be prepared corresponding to cis (e.g., **11**) and trans (e.g., **10**) isomers about the pyrrolidine ring. Since the cis azethoxyl nitroxides appear from molecular models to resemble quite well the geometry about a cis carbon-carbon double bond, one has in effect a near-ideal ESR probe for the motion and environment experienced by a cis double bond in lipids. On the other hand, models suggest that the trans azethoxyl nitroxides are a reasonably good analogue of a saturated chain.

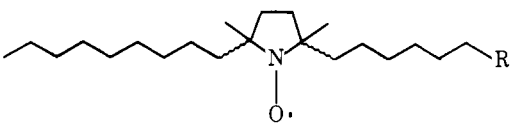
The synthesis of representative trans and cis azethoxyl fatty acid derivatives **10** and **11** closely parallels our recent synthesis of proxyl nitroxides.[3] Reaction of nitrone **1**[4] with 2 equiv of nonylmagnesium bromide in ether followed by an aqueous workup and Cu^{2+} catalyzed air oxidation[3,5] of the *N*-hydroxy intermediate gave nitrone **2** (45%, bp 100–109 °C (0.005 mm); *m/e* 239.223). Reaction of **2** with the Grignard reagent derived from 1-tetrahydropyranyloxy-6-chlorohexane and subsequent Cu^{2+}-catalyzed air oxidation of the product gave after silica gel chromatography nitroxide **3** (22%, *m/e* 424.380) as a mixture of cis-trans isomers. Hydrolysis (0.1 M HCl in MeOH) of **3** gave alcohols **4** (76%, *m/e* 340.321) which were



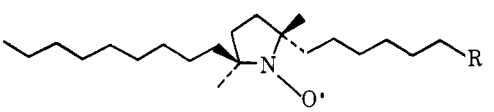
1



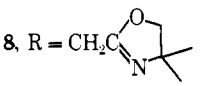
2



3, R = OTHP
4, R = OH
5, R = OMs

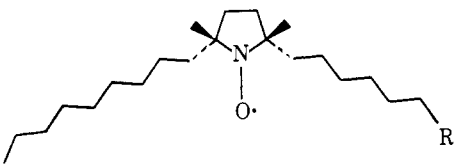


6, R = I

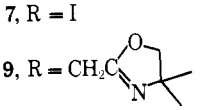


8, R = CH_2C

10, R = CH_2CO_2H



7, R = I



9, R = CH_2C

11, R = CH_2CO_2H

0002-7863/78/1500-1618$01.00/0