the NIH Facility for Biomedical Studies (Grant No. RR20092), located at Carnegie-Mellon University.

Supplementary Material Available. Full experimental details of this work will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2317.

References and Notes

(1) Part V: P. M. McCurry, Jr., and R. K. Singh, *J. Org. Chem.*, **39**, 2316 (1974).
(2) (a) E. W. Garbisch, Jr., *J. Org. Chem.*, **30**, 2109 (1965); (b) C. H. Depuy and K. L. Eilers, "Organic Syntheses," Collect. Vol. V, Wiley, New York, N. Y., 1973, p 326.
(3) G. Büchi and B. Egger, *J. Org. Chem.*, **36**, 2021 (1971).
(4) See paragraph at end of paper regarding supplementary material.
(5) For recent syntheses of *cis*-jasmone see (a) T. Mukaiyama, M. Araki, and H. Takei, *J. Amer. Chem. Soc.*, **95**, 4763 (1973); (b) K. Oshima, H. Yamamoto, and H. Nozaki, *ibid.*, **95**, 4446 (1973); (c) J. L. Herrmann, J. E. Richman, and R. H. Schlessinger, *Tetrahedron Lett.*, 3275 (1973); (d) A. I. Meyers and N. Nazarenko, *J. Org. Chem.*, **38**, 185 (1973); (e) P. A. Grieco, *ibid.*, **37**, 2363 (1972); (f) W. F. Berkowitz, *ibid.*, **37**, 341 (1972); (g) H. C. Ho, T. L. Ho, and C. M. Wong, *Can. J. Chem.* **50**, 2718 (1972); (h) R. A. Ellison and W. D. Woessner, *J. Chem. Soc., Chem. Commun.*, 529 (1972); (i) S. M. Weinreb and R. J. Cvetovich, *Tetrahedron Lett.*, 1233 (1972).
(6) Our material contained none of the trans isomer which was present in the authentic sample (~8%) kindly supplied to us by Professor P. Grieco who obtained it from International Flavors and Fragrances.
(7) The rate of polymerization of a bimolecular reaction is decreased in dilute solutions. Smaller volumes, oxygen, and increased [OH⁻] cause significant loss of material, whereas in more dilute base the rate of isomerization falls off drastically.
(8) (a) M. Stiles, R. R. Winkler, Y. Chang, and L. Traynor, *J. Amer. Chem. Soc.*, **86**, 3337 (1964); (b) K. Koelichen, *Z. Physik. Chem.*, **33**, 129 (1900).
(9) R. N. Lacey, *J. Chem. Soc.*, 1639 (1960).

Department of Chemistry **Patrick M. McCurry, Jr.***
Carnegie-Mellon University **Rajendra K. Singh**
Pittsburgh, Pennsylvania 15213

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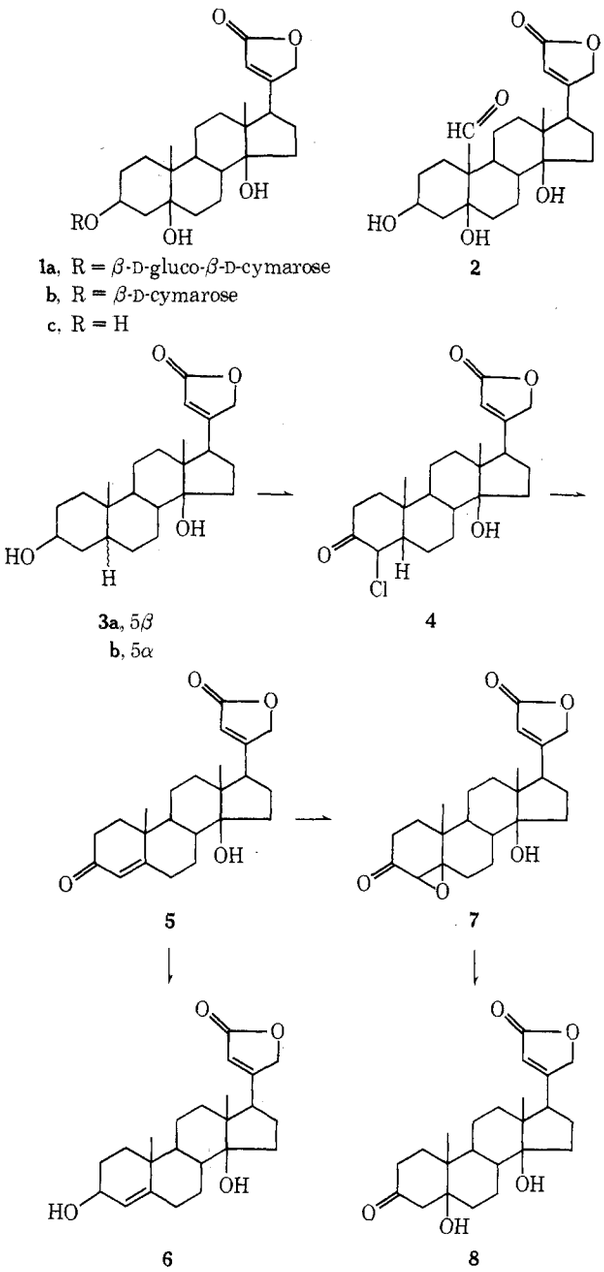
Steroids and Related Natural Products. 88. Synthesis of Periplogenin[1,2]

Summary: Digitoxigenin (**3a**) was converted to canarigenin (**6**), periplogenin (**1c**), and uzarigenin (**3b**); the use of *tert*-butyl hypochlorite for oxidation of digitoxigenin (**3a**) to chloro ketone **4** and application of chromium(II) acetate for reduction of epoxy ketone **7** to hydroxy ketone **8** represented particularly convenient aspects of these synthetic transformations.

Sir: The digitalis-like cardiac activity of periplocin (**1a**)[3] was first reported in 1896 (in Russia) and isolation of this cardenolide in pure form was described the following year.[4] Some 30 years later Jacobs[5] began the careful structural studies of periplocymarin (**1b**) and periplogenin (**1c**) which were continued by Stoll[6] and brought by Reichstein[7] to a partial synthesis of periplogenin from strophanthidin (**2**). By 1960 periplogenin (**1c**) and its glycoside derivatives had been isolated from a number of plants of the *Asclepiadaceae* family and their structures were well established.[8] We now wish to report a formal total synthesis of periplogenin employing digitoxigenin (**3a**)[9] as relay. One of the synthetic intermediates (**5**) also formed the basis for completing convenient syntheses of canarigenin (**6**)[10] and uzarigenin (**3b**).[11]



Digitoxigenin (**3a**, 0.70 g) was simultaneously oxidized and chlorinated with *tert*-butyl hypochlorite[12] (in *tert*-butyl alcohol–hydrochloric acid, room temperature, 8 hr) to provide ketone **4** (0.50 g, mp 131–133°).[13] Dehydrohalogenation of ketone **4** (0.20 g) with lithium chloride in dimethylformamide (reflux 8 hr) led to canarigenone (**5**, 90 mg, mp 257–263°).[10] Careful reduction of α,β-unsaturated ketone **5** (0.10 g in THF) with lithium tri-*tert*-butoxyaluminum hydride (ice bath, 2 hr) gave (after silica gel chromatography and recrystallization from acetone–hexane) canarigenin (**6**, 71 mg, mp 259–261°, lit.[10] mp 260–262°). Further reduction of canarigenone (**5**, 0.16 g) with lithium borohydride in pyridine (ice bath, 5 hr) afforded a route to uzarigenin (**3b**, 0.12 g, mp 246–249° from methylene chloride–methanol, lit.[14] mp 230–246°).[11]

Oxidation of canarigenone (**5**, 40 mg) employing *m*-chloroperbenzoic acid in chloroform provided epoxy ketone **7** (10 mg, prisms from acetone–hexane, mp 229–

232°).[13] Chromium(II) acetate[15] in ethyl alcohol smoothly reduced epoxy ketone 7 (70 mg) to an easily separable mixture of hydroxy ketone 8 (42 mg, prisms from chloroform–methanol, mp 235–239°)[13] and canarigenone (19 mg). Selective reduction of ketone 8 (30 mg) in ethyl alcohol with Urushibara[16] nickel-A completed synthesis of periplogenin (**1c**, 26 mg, from methanol, mp 227–234°, lit.[7] mp 138–232°).

The syntheses of canarigenin, periplogenin, and uzarigenin just described should enhance the availability of these three cardenolides for biological evaluation.

References and Notes

(1) Part 87: G. R. Pettit and Y. Kamano, *J. Org. Chem.*, in press.
(2) We are pleased to acknowledge support of this investigation by the National Cancer Institute (performed pursuant to Contract Number NO1-CM-12308, with the Division of Cancer Treatment, National Cancer Institute, Department of Health, Education and Welfare) and Research Grant CA-10612-06 from the National Cancer Institute, the J. W. Kieckhefer Foundation, The Fannie E. Rippel Foundation, The Salt River Project of Arizona, Mrs. Virginia L. Bayless, and The Arizona Public Service Co. We are also grateful to Professor T. Reichstein for the authentic specimen of periplogenin and Dr. W. Haede for the authentic samples of canarigenin and uzarigenin.
(3) For leading references to cardenolide nomenclature and structural determination by mass spectrometry, refer to P. Brown, F. Bruschweiler, and G. R. Pettit, *Helv. Chim. Acta*, **55**, 531 (1972); P. Brown, F. Bruschweiler, G. R. Pettit, and T. Reichstein, *Org. Mass Spectrometry*, **5**, 573 (1971).
(4) E. Lehmann, *Arch. Pharm.*, **235**, 157 (1897).
(5) W. A. Jacobs and A. Hoffman, *J. Biol. Chem.*, **79**, 519 (1928).
(6) A. Stoll and J. Renz, *Helv. Chim. Acta*, **22**, 1193 (1939).
(7) P. Speiser and T. Reichstein, *Helv. Chim. Acta*, **32**, 1368 (1949). Later, 3β-acetoxystrophanthidin was converted to 3β-acetylperiplogenin: A. Katz, *ibid.*, **41**, 1399 (1958). Also, synthesis of periplogenin from 21-hydroxy-14-dehydroprogesterone has been described in communication form: R. Deghenghi, A. Philipp, and R. Gaudry, *Tetrahedron Lett.*, 2045 (1963).
(8) See, for example, E. Wyss, H. Jäger, and O. Schindler, *Helv. Chim. Acta*, **43**, 664 (1960).
(9) N. Danieli, Y. Mazur, and F. Sondheimer, *J. Amer. Chem. Soc.*, **84**, 875 (1962); C. R. Engel and G. Bach, *Steroids*, **3**, 593 (1964); G. Bach, J. Capitaine, and C. R. Engle, *Can. J. Chem.*, **46**, 733 (1968); W. Fritsch, W. Haede, K. Radscheit, and H. Ruschig, *Justus Liebigs Ann. Chem.*, **721**, 168 (1969); G. R. Pettit, L. E. Houghton, J. C. Knight, and F. Bruschweiler, *J. Org. Chem.*, **35**, 2895 (1970).
(10) A partial synthesis of canarigenin has been described by W. Fritsch, H. Kohl, U. Stache, W. Haede, K. Radscheit, and H. Ruschig, *Justus Liebigs Ann. Chem.*, **727**, 110 (1969).
(11) A synthesis of uzarigenin has been developed starting with 15α-hydroxy-5α-dihydrocortexone: U. Stache, W. Fritsch, W. Haede, and K. Radscheit, *Justus Liebigs Ann. Chem.*, **726**, 136 (1969). An earlier synthesis of uzarigenin acetate was described by M. Okada and Y. Saito, *Steroids*, 645 (1965).
(12) J. J. Beereboom, C. Djerassi, D. Ginsburg, and L. F. Fieser, *J. Amer. Chem. Soc.*, **75**, 3500 (1953).
(13) Each substance was purified by column chromatography or preparative layer chromatography employing silica gel. Elemental analyses and spectral data (mass, ir, and pmr) were consistent with each structural assignment. The mutual identity of synthetic and authentic samples was established by mixture melting point determination, ir spectral comparison, and thin layer chromatographic comparison.
(14) K. D. Roberts, E. Weiss, and T. Reichstein, *Helv. Chim. Acta*, **49**, 316 (1966).
(15) The use of chromium(II) acetate was suggested by the very useful investigation of C. H. Robinson and R. Henderson, *J. Org. Chem.*, **37**, 565, (1972). Experimental procedures for introducing the 5β-hydroxy group with chromium(II) acetate were first reported in the Robinson study.
(16) Y. Urushibara, S. Nishimura, and H. Uehara, *Bull. Chem. Soc. Jap.*, **28**, 446 (1955).

Cancer Research Laboratory and Department of Chemistry, Arizona State University, Tempe, Arizona 85281
Yoshiaki Kamano, George R. Pettit*

Department of Chemistry, School of Medicine, The Jikei University, Tokyo, Japan
M. Tozawa

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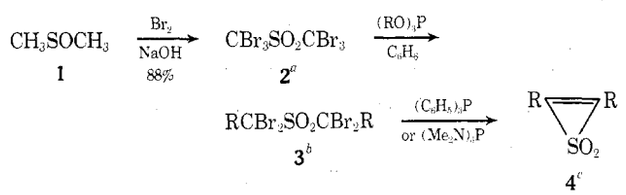
Synthesis of Alkyl-Substituted Thiirene Dioxides

Summary: A new synthesis of dialkylthiirene 1,1-dioxides *via* debromination of bis(α,α-dibromoalkyl) sulfones by means of trisubstituted phosphines is reported.

Sir: Previously the synthesis of the theoretically interesting and synthetically useful diaryl, aryl alkyl, and dialkylthiirene 1,1-dioxides has been described.[1] Unfortunately, derivatives bearing alkyl substituents have been obtained so far only *via* sulfene and diazoalkane intermediates and therefore are not readily available on a large scale either for an extensive study of their properties or as precursors of other useful synthetic intermediates. With this deficiency in mind we now describe a new route to the dialkyl thiirene dioxides **4** which makes these compounds as easily obtainable as the diaryl analogs. Central to the new approach is the 1,3-elimination[2] of bromine from a bis(α,α-dibromoalkyl) sulfone by means of triphenylphosphine or a tris(dialkylamino)phosphine [*e.g.*, **3** → **4**; R = CH_3 (50%); R = CH_3CH_2 (89%)].

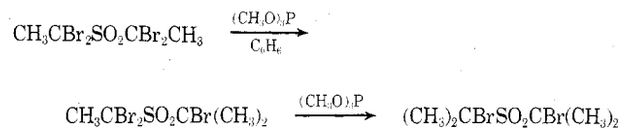
Scheme I



[a] Prepared by a modification of the methods of W. V. Farrar [*J. Chem Soc.*, 508 (1956)] and H. Liebig and H. Pfetzing [German Patent 1,256,216; *Chem. Abstr.*, **69**, 18609 (1968)]. [b] **R** = Et, 70% yield; mp 101.5–102°; nmr ($CDCl_3$) δ 1.42 (t, 3 H), 3.02 (q, 2 H). [c] R = Et, 89% *via* $(Me_2N)_3P$ at −70°; liquid; nmr ($CDCl_3$) δ 1.30 (t, 3 H), 2.75 (q, 2 H). Thermolysis (100°) gave 3-hexyne (90%).

To be useful this method requires a simple synthesis of the tetrabromo sulfones **3**, and such a method has now been developed on the basis of a novel but obscure reaction first described in the patent literature.[3] Adapting Szabo's method for the synthesis of the corresponding tetrachloro analogs, reaction of trimethyl and triethyl phosphite with bis(tribromomethyl) sulfone (**2**) gives sulfone **3** (R = Me or Et). In addition to its importance for the preparation of the vinylene sulfones, this unique method of carbon–carbon bond formation combined with conversion to **4** and subsequent facile thermal cycloelimination of sulfur dioxide represents a useful route to internal acetylenes. Although it was not possible to stop the alkylation of **2** by trimethyl phosphite with the introduction of a single methyl group, it was thereafter possible to introduce selectively the third and fourth methyl groups (Scheme II). Tri- and dibromo sulfones such as **5** and **6** are potentially of interest as precursors of olefins by extension of the present process.

Scheme II



[a] Yield 80%; mp 126–127°; nmr ($CDCl_3$) δ 2.48 (s, 6 H), 3.01 (s, 3 H). [b] Yield 90%; mp 129–130°; nmr ($CDCl_3$) δ 2.30 (s).