

- (6) We have prepared the two isomers of perfluorooctamethyltricyclo[4.2.0.0^{2,5}]-3,7-octadiene, Ia, mp 104–105°, and Ib, mp 207–208°. Isomer Ia was first prepared by treatment of *trans*-3-bromoperfluoro-1,2,3,4-tetramethylcyclobutene¹ with MeLi in ethyl ether at –125° and was postulated to be the *syn* isomer.⁷ However, Kobayashi et al. have concluded recently on the basis of preliminary x-ray structural data that isomer Ib (mp 204–205°) has the *syn* configuration.⁸ We have also obtained experimental results on the fluoride ion promoted equilibration of Ia and Ib, which support this assignment, i.e., that Ia is in fact the more stable and presumably *anti* isomer.⁹
- (7) W. T. Miller, R. J. ND L. F. Pelosi, pred in part at the 6th International Symposium on Fluorine Chemistry, Durham, England, July 1971; L. F. Pelosi, Ph.D. Thesis, Cornell University, 1973.
- (8) Y. Kobayashi, I. Kumadaki, A. Ohsawa, Y. Hanzawa, and M. Honda, *Tetrahedron Lett.*, 3001 (1975).
- (9) Unpublished work with W. M. Koppes.
- (10) A Hanovia 450-W high pressure quartz mercury vapor lamp was utilized. II and III were first isolated from cyclohexane and characterized but the major reaction involved the solvent. Good yields of C₆(CF₃)₃ isomers were recovered after irradiation in a mixture of 1,3- and 1,4-c-C₆F₁₀(CF₃)₂; ~20% II and 15% III were isolated after 36 h irradiation. In addition to being highly inert the fluorocarbon solvent further dissolved both reactants and products.
- (11) Perfluorooctamethylpentacyclo[4.2.0.0^{2,5}.0^{3,6}.0^{4,7}]octane (II): mp 253–254° (sealed tube); ir (gas) 135 (w), 1330 (vw), 1249 (w,sh), 1237 (vs), 1115 (vw) cm⁻¹ with no other appreciable absorption within the region of 3500–660 cm⁻¹; laser Raman¹³ (solid microsample) 1427 (m), 1256 (s), 1062 (m), 749 (vs), 560 (s), 324 (m), 303 (m), 261 (s), 230 (m) cm⁻¹; NMR ¹⁹F (c-C₆F₁₀) 64.4 (sharp singlet) ppm upfield from external CCl₃F; MS (70 eV) *m/e* 648 (very weak, C₁₆F₂₄⁺), 629 (15, C₁₆F₂₃⁺), 579 (15, C₁₅F₂₁⁺), . . . 69 (100, CF₃⁺).
- (12) Cubane is similarly transparent in the infrared with absorption bands only at 3000, 1231, and 851 cm⁻¹. P. E. Eaton and T. W. Cole, Jr., *J. Am. Chem. Soc.*, **86**, 3157 (1964).
- (13) Determined in the laboratories of the E. I. du Pont de Nemours & Co. by J. J. Jack through the courtesy of P. R. Resnick.
- (14) Perfluorooctamethylpentacyclo[5.1.0.0^{2,6}.0^{3,5}.0^{4,8}]octane (III): mp 186–187° (sealed tube, unchanged after 4 h at 200°); ir (gas) 1426 (vw), 1302 (w), 1261 (m), 1246 (m, sh), 1236 (vs), 1070 (vw) cm⁻¹; laser Raman¹³ (solid microsample) 1425 (vw), 970 (vw), 749 (s), 559 (w), 499 (vw), 312 (m), 259 (m), 233 (w) cm⁻¹; NMR ¹⁹F (C₆F₆) 53.1 (s), 57.2 (s), 60.9 (s) ppm upfield from external CCl₃F with areas of 1:2:1; MS (70 eV) *m/e* 648 (very weak, C₁₆F₂₄⁺), 629 (20, C₁₆F₂₃⁺), 579 (19, C₁₅F₂₁⁺), . . . 69 (100, CF₃⁺).
- (15) For a review of analogous interconversions of carbon–hydrogen compounds see L. T. Scott and M. Jones, Jr., *Chem. Rev.*, **72**, 181 (1972).
- (16) Perfluorooctamethylcyclooctatetraene (IV): mp 160–161°; ir (gas) 1310 (m), 1260 (vs), 1220 (vs), 729 (w) cm⁻¹; laser Raman¹³ (solid microsample) 1653 (s), 1214 (w), 1175 (vw), 1064 (m), 925 (vw), 905 (w), 771 (vw), 750 (vs), 619 (vw), 543 (vw), 336 (m), 260 (vs), 248 (m,sh), 169 (m) cm⁻¹; NMR ¹⁹F (C₆F₆) 59.7 (complex singlet) ppm upfield from external CCl₃F; MS (70 eV) *m/e* 647.9604 (5, C₁₆F₂₄⁺), 629 (37, C₁₆F₂₃⁺), 579 (26, C₁₅F₂₁⁺) . . . 69 (100, CF₃⁺).
- (17) The thermal conversions of II and III into IV appear to be the first such transitions to be established with a cubane and a cuneane.
- (18) J. W. Emsley, J. Feeney, and L. Y. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy", Vol. II. Pergamon Press, New York, N.Y., 1966.
- (19) G. W. King, "Spectroscopy and Molecular Structure", Rhinehart and Wilson, New York, N.Y., 1964, p 366.
- (20) An unknown structure,



- (21) An early report that IV was obtained as a thermal reaction product of perfluoro-2-butyne^a has been shown to be incorrect.^b (a) B. Ekstrom, *Chem. Ber.*, **92**, 749 (1959); (b) H. C. Brown, H. L. Gewanter, D. M. White and W. G. Woods, *J. Org. Chem.*, **25**, 634 (1960).

Lorenzo F. Pelosi, William T. Miller*

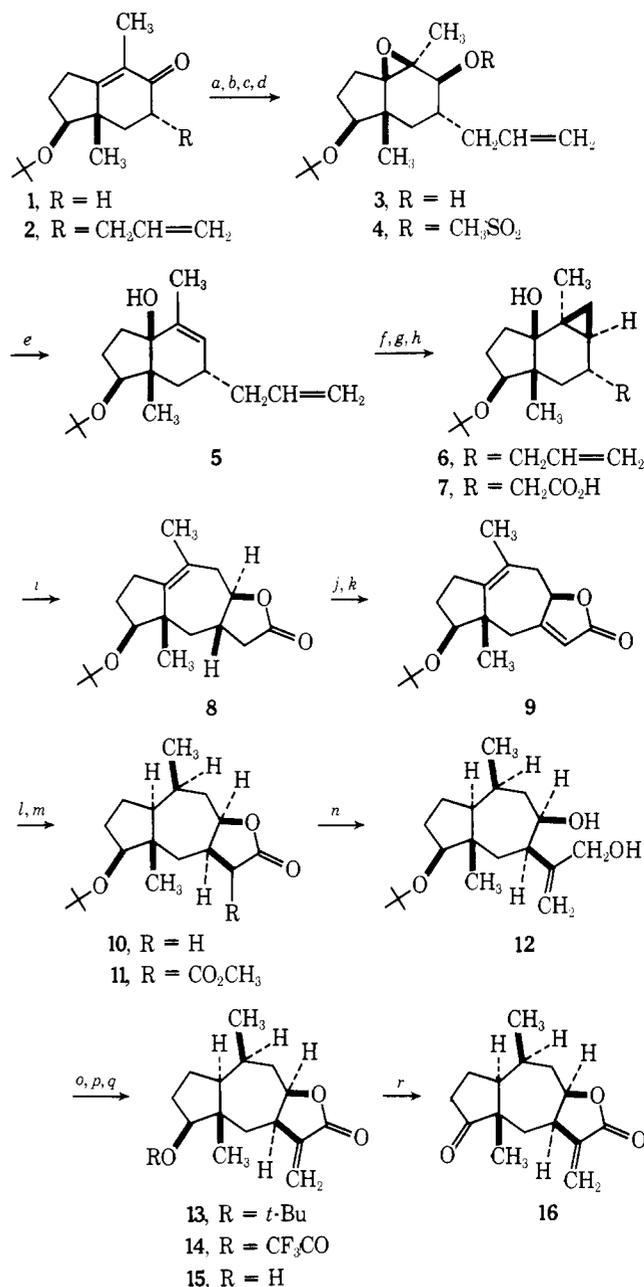
Department of Chemistry, Cornell University
Ithaca, New York 14853

Received December 15, 1975

The Stereoselective Total Synthesis of Pseudoguaianolides: Confertin

Sir:

The pseudoguaianolide family of sesquiterpenes is a widely distributed class of natural products whose diverse structures and medicinal properties have been of increasing interest in recent years.¹ A major problem in the synthesis of represen-



^a LiN(*i*-Pr)₂, CH₂=CHCH₂Br. ^b LiAlH₄. ^c *m*-ClC₆H₄CO₂H. ^d CH₃SO₂Cl. ^e Li, NH₃. ^f CH₂I₂, Zn(Cu). ^g O₃. ^h Ag₂O. ⁱ H₃O⁺. ^j LiN(*i*-Pr)₂, (PhSe)₂. ^k H₂O₂. ^l H₂/Pd-C, EtOAc. ^m KH, CH₃OCO₂CH₃. ⁿ KH, LiAlH₄. ^o MnO₂, C₆H₆. ^p CF₃CO₂H. ^q *i*-PrOH, NaOH. ^r CrO₃(C₂H₅N)₂, CH₂Cl₂.

tative members of this structural class has been rigid control of stereochemistry in flexible hydroazulene ring systems.² In this report we describe a highly stereoselective synthesis of confertin (**16**) by an approach which should be applicable to other pseudoguaianolides as well.

Keto ether **1** obtained in 75% overall yield from 2-methyl-1,3-cyclopentanedione^{3,4} was alkylated with allyl bromide using lithium diisopropylamide in tetrahydrofuran (THF)-hexamethylphosphoric triamide (HMPA) to give the dienone **2**. Attempts at reduction-elimination of the corresponding α , β -epoxy ketone to alcohol **5** via the Wharton method⁵ were totally unsuccessful. Therefore the alternative sequence of lithium aluminum hydride reduction and epoxidation to epoxy alcohol **3** followed by lithium-ammonia reduction of the mesylate derivative **4** was developed to circumvent this problem. The overall yield of this modified sequence was 75%.

Allylic alcohol **5** underwent Simmons-Smith cyclopropanation⁶ in 80% yield to the cyclopropylcarbinol **6** (contaminated with 15% of the bicyclopopyl compound). The stereochemistry of the cyclopropanation can be assigned on the basis of the well-established directing influence on such reactions by allylic alcohol substituents.⁷ The stereochemistry of alcohol **5**, in turn, depends upon the analogous directing effect on epoxidation by the secondary allylic alcohol grouping⁸ of the precursor to epoxide **3**. The stereochemistry of this allylic alcohol grouping is based on the known preference for metal hydride reductions of enones such as **2** to give equatorial alcohols.⁹

Ozonolysis of the allyl substituted tricyclic **6** followed by workup with silver oxide afforded acid **7** which readily and stereospecifically rearranged upon treatment with aqueous perchloric acid to the hydroazulene lactone **8** (80% overall yield).¹⁰ Conversion to the butenolide **9** was achieved by subsequent treatment with diphenyl diselenide and lithium diisopropylamide followed by hydrogen peroxide.¹¹ Catalytic hydrogenation (Pd/C, ethyl acetate) then gave the crystalline *cis*-lactone **10** in 70% yield. Earlier synthetic studies have shown that hydrogenations involving positions 1, 7, and 10 of the pseudoguaiane ring system are strongly directed by the proximate C-5 quaternary methyl grouping.¹²

Introduction of the α -methylene moiety by the Minato-Horibe sequence¹³ involving formylation, reduction, tosylation, and elimination, although successful for damsin-type pseudoguaianolides,¹² could not be effectively accomplished with the regioisomeric lactone **10**. Therefore an alternative method was examined.¹⁴ To that end, the crystalline carbomethoxy derivative **11** obtained from lactone **10** with dimethyl carbonate-potassium hydride was converted to the enolate and reduced with lithium aluminum hydride to yield the diol **12**. Oxidation with manganese dioxide afforded the desired α -methylene- γ -butyrolactone **13**. Cleavage of the *tert*-butyl ether with trifluoroacetic acid led to the trifluoroacetate **14** which was saponified in isopropyl alcohol to minimize addition to the conjugated double bond by solvent-derived alkoxide.¹⁵ Oxidation of the resulting alcohol **15** by the modified Collin's procedure¹⁶ yielded (\pm)-confertin (**16**) whose spectral properties were identical with those of the natural product.^{1,17}

References and Notes

- (1) For a recent compilation of structures see H. Yoshioka, T. J. Mabry and B. N. Timmermann, "Sesquiterpene Lactones", University of Tokyo Press, Tokyo, 1973.
- (2) Cf. J. A. Marshall, *Synthesis*, 517 (1972).
- (3) D. J. Crispin, A. E. Vanstone, and J. S. Whitehurst, *J. Chem. Soc. C*, 10 (1970).
- (4) R. A. Micheli, Z. G. Hajos, N. Cohen, D. R. Parrish, L. A. Portland, W. Sciannama, M. A. Scott, and P. A. Wehrli, *J. Org. Chem.*, **40**, 675 (1975).
- (5) P. S. Wharton and D. H. Bolen, *J. Org. Chem.*, **26**, 3615 (1961).
- (6) H. E. Simmons and R. D. Smith, *J. Am. Chem. Soc.*, **80**, 5323 (1958).
- (7) S. Winstein and J. Sonnenberg, *J. Am. Chem. Soc.*, **83**, 3235 (1961).
- (8) H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1958 (1957).
- (9) Cf. H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, Menlo Park, Calif., 1972, pp 54-64.
- (10) J. A. Marshall and R. H. Ellison, *J. Org. Chem.*, **40**, 2070 (1975).
- (11) H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.*, **97**, 5434 (1975).
- (12) J. A. Marshall and W. R. Snyder, *J. Org. Chem.*, **40**, 1656 (1975). We have recently learned that Professor R. A. Kretschmer has effected a similar hydrogenation in a synthesis of (\pm)-damsin. We are indebted to Professor Kretschmer for a preprint of this work.
- (13) H. Minato and I. Horibe, *J. Chem. Soc. C*, 1575 (1967).
- (14) J. A. Marshall and N. Cohen, *J. Org. Chem.*, **30**, 3475 (1965).
- (15) Cf. G. H. Kulkarni, G. R. Kelkar, and S. C. Bhattacharyya, *Tetrahedron*, **20**, 2639 (1964).
- (16) R. Ratcliffe and R. Rodehurst, *J. Org. Chem.*, **35**, 4000 (1970).
- (17) This investigation was supported by Grant Number 5R01 CA1108914, awarded by the National Cancer Institute, DHEW.

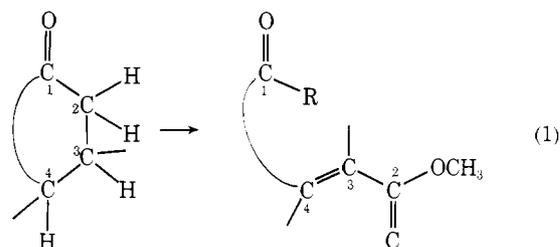
James A. Marshall,* Robert H. Ellison

Department of Chemistry, Northwestern University
Evanston, Illinois 60201
Received April 16, 1976

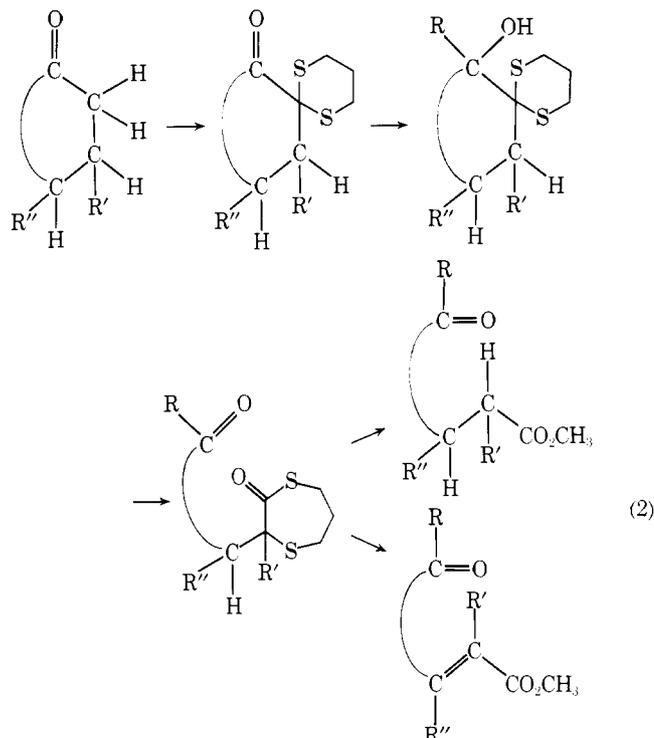
New Synthetic Reactions. Oxidative Seco Rearrangement

Sir:

We wish to report a new type of ring cleavage method that allows selective functionalization of C-1, -2, -3, and -4 of a cycloalkanone as illustrated in eq 1. The key step involves an intriguing oxidative cleavage that is accompanied by rearrangement of a 2,2-dithiocycloalkan-1-ol. The cleavage of functionalized rings serves as a major approach in the design of the total synthesis of many natural products.¹ Marshall developed an elegant approach to ring fission based upon the hydroxide induced cleavage of α,α -trimethylenedithiocycloalkanones;² however, the method is restricted to use of "naked" hydroxide and to ketone cleavages (i.e., the hydroxyl derivatives do not cleave). We developed an alternative approach based upon 1-hydroxy-2-phenylthiocycloalkanes;³ however, this method is restricted to rings possessing some strain energy such as those of four or five members. The approach reported herein, as summarized in eq 2, further overcomes the limitations of these two methods and is applied to the synthesis of the queen's substance that is found in several species of insects.



The carbonyl group of dithiane **12a** can be reduced (NaBH_4 ,



ethanol, room temperature) or undergo addition of an organometallic (CH_3Li , ether-THF, 0°) to produce the hydroxy dithianes **2**.⁴ Subjection of **2** to 2.6 equiv of lead tetraacetate (PhH , 50 - 55° , 15 h) leads to the ring cleaved and rearranged products **3**⁴ in excellent yields (**3a**, mp 61° , 80%; **3b**, mp 62° , 95%). The structures of **3** were indicated by their elemental compositions, spectral properties, and further conversions. In addition to the aldehyde (1728 cm^{-1}) and ketone (1718 cm^{-1}) carbonyl groups of **3a** and **b**, respectively, a thioester carbonyl