plete and the product began to crystallize out of solution. The crystals were collected after cooling to −20 °C and washed with water, ethanol, and ether (59% yield, mp 219–220 °C). (In addition to other criteria, the identity of the products prepared by these methods was verified by mixture melting point determinations.) Anal. Calcd for $C_{13}H_{11}N_3O_3$: C, 60.70; H, 4.31; N, 16.33. Found: C, 60.71; H, 4.37; N, 16.33.

(15) In aquoeus alkaline solution this product was converted into 3,10-dimethyl-1-hydroxy-1,5-dideazaisoalloxazine (VI).[4b] Cleavage of the epoxide ring via Michael addition of OH^- at C-1 would yield a 1,5-dihydroxy-1,5-dihydro intermediate. Formation of VI and the associated lag phase could be accounted for by dehydration of this intermediate initiated by ionization at C-1 (pK = 6.8 for 1,5-dihydro-1,5-dideazaisoalloxazine[4b]).

(16) The rate constant observed for the reaction of thioxane (Aldrich, vacuum distilled) with H_2O_2 ($k = 6.7 \times 10^{-5}$ M^{-1} s^{-1} in methanol at 25 °C) is similar to the value previously reported under the same conditions. Dankleff, M. A. P.; Curci, R.; Edwards, J. O.; Pyun, H. Y. *J. Am. Chem. Soc.* **1968**, *90*, 3209–3218.

(17) Values of 8.7×10^{-2} and 9.6×10^{-2} M^{-1} s^{-1} were obtained for rate constants with IIIa and IIIb, respectively, in methanol at 25 °C. The same results were obtained with samples of IIIb prepared by different methods.[14]

(18) (a) Charpentier-Morize, M.; Laszlo, P.; Mayer, M. *Bull. Soc. Chim. Fr.* **1966**, 2264–2269. (b) Dullaghan, M. E.; Nord, F. F. *Mikrochim. Acta* **1953**, 17–21.

(19) (a) This instability, which is expected for an epoxide derivative, has previously been described.[4] (b) Rates of decomposition were determined in separate experiments under comparable conditions by monitoring the decrease in absorption at 330 nm observed immediately after preparing solutions of III in carbonate buffer.

(20) Cotton, F. A.; Wilkinson, G. "Advanced Inorganic Chemistry"; Interscience Publishers: New York, 1967; pp 308–310.

(21) Organic peroxy acids are generally weaker acids than the corresponding carboxylic acid, suggesting a similar relationship for the two ionizable protons in peroxycarbonic acid: Curci, R.; Edwards, J. O. In "Organic Peroxides", Swern, D., Ed.; Wiley-Interscience: New York, 1970; Vol. 1, pp 205–207.

Donald Vargo, Marilyn S. Jorns*

Department of Chemistry, The Ohio State University
Columbus, Ohio 43210

Received June 25, 1979

Total Synthesis of *dl*-Helenalin

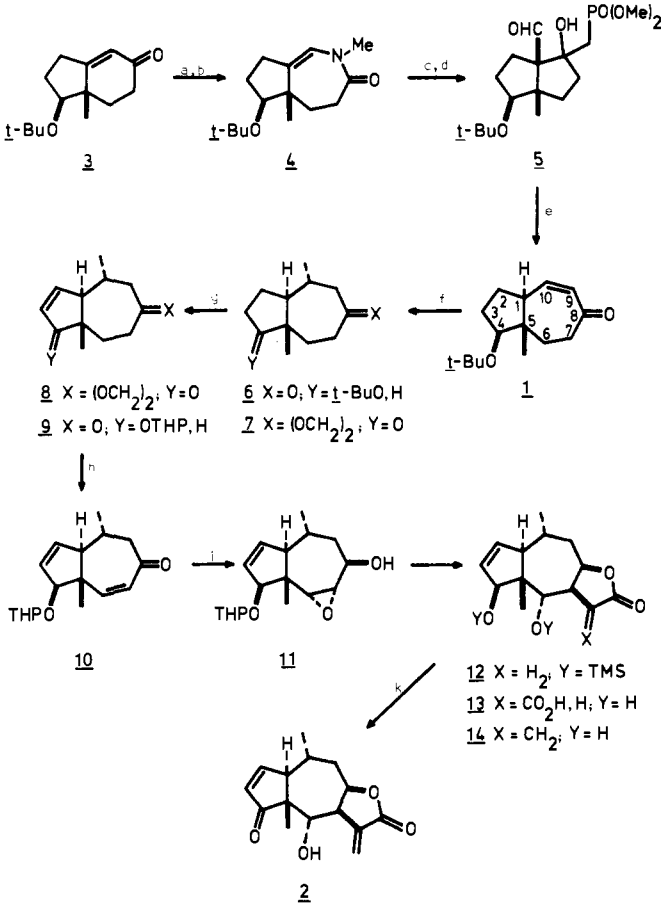
Sir:

The group of sesquiterpenes called pseudoguaianolides has attracted considerable chemical attention not only because of their structurally challenging and esthetically pleasing nature, but also because of their cytotoxic properties.[1] Representatives of this class of natural products which have succumbed to total synthesis are the molecules helenalin,[2] confertin,[3] and damsin.[4] Our interest in these sesquiterpenes was stimulated by the desire to construct them from a common intermediate since they all possess a central seven-membered ring which holds the major elements of functionality and stereochemistry. Thus, we formulated the perhydroazulenone **1** containing an oxygen residue at C_8, an olefinic element between C_9 and C_{10}, and an angular methyl group at C_5. Acting in concert, these various aspects of **1** should permit stereoselective introduction of a methyl group at C_{10}, connection of the carbonaceous portion of a lactone residue at C_7, and oxygenation at C_6. Further, the oxygen atom borne at C_4 should allow functionalization at C_2 and C_3, when required. Herein, are described the preparation of **1** and its stereoselective conversion into helenalin (**2**). In the accompanying manuscript we report the synthesis of confertin and damsin from this same substance.

We commenced our preparation of **1** starting from the readily available enone **3**,[5] converting this material into the lactam **4** (mp 39–42 °C) using technology recently described by Barton and co-workers.[6] On reaction with lithio dimethyl methylphosphonate in THF at −78 °C,[7] lactam **4** was transformed into the pentalene-derived aldehyde **5** (mp 49–51 °C)[8] which in turn gave the desired enone **1** as the only reaction product (oil, 50% overall yield from **3**) on treatment with slightly less than 1 equiv of potassium *tert*-butoxide in *tert*-butyl alcohol[9] (Scheme I).

Elaboration of **1** into helenalin was initiated by conversion of the enone into its C_{10} α-methyl analogue **6** (mp 66.5–68 °C,

Scheme I[a]



[a] (a) MeNHOH·HCl, C_5H_5N, 40 °C. (b) TsCl, C_5H_5N, 22 °C. (c) $LiCH_2PO(OCH_3)_2$, THF, −78 °C. (d) NaOAc, HOAc, H_2O, Et_2O, 0 °C. (e) *t*-BuOH, *t*-BuOK, 22 °C. (f) MeMgBr, CuI, DMS, Et_2O, 0 °C; HCl, MeOH, 0 °C; *p*-TSA, C_6H_6, $HOCH_2CH_2OH$, 90 °C; PCC, NaOAc, CH_2Cl_2, 22 °C. (g) NaH, Ph_2S_2, DME, 45 °C; *m*-CPBA, CH_2Cl_2, 0 °C; toluene, $P(OMe)_3$, 110 °C; diisobutylaluminum hydride, toluene, −40 °C; MeOH, HCl, 0 °C; DNP, *p*-TSA, CH_2Cl_2, 0 °C. (h) LiHMDS, TMSCl, THF, −78 °C; $Pd(OAc)_2$, CH_3CN, 22 °C. (i) MeOH, NaOH, H_2O_2, H_2O, 40 °C; triisobutylaluminum, toluene, 0 °C. (j) $LiCH_2CO_2Li$, HMPA, THF, 50 °C; 6 N HCl; TMSCL, Et_3N, THF, 22 °C; MMC, 140 °C; 30% CH_2O, Et_2NH. (k) MnO_2, $CHCl_3$, 45 °C.

87%) using methylmagnesium bromide in the presence of cuprous iodide–dimethyl sulfide.[10] Ketone **6** was then transformed into the ketal ketone **7** (mp 33–36 °C, 97% overall)[11] by sequential treatment with HCl–methanol (*tert*-butyl ether cleavage) followed by reaction with ethylene glycol (ketal formation) and finally oxidation with pyridinium chlorochromate buffered with sodium acetate.[12] The cyclopentanone residue of **7** was then converted into its cyclopentenone analogue **8** (mp 75–77 °C, 92% overall) by alkylation with diphenyl disulfide (NaH, DME), oxidation with *m*-chloroperbenzoic acid and sulfoxide elimination (110 °C, 30 h).[13] Lastly, **8** was transformed into the cycloheptanone **9** (oil, 84% overall) by diisobutylaluminum hydride reduction, ketal hydrolysis, and alcohol protection with dihydropyran.

In order to initiate the final stages of the synthesis, we intended to convert **9** into the cycloheptenone **10**, the latter substance serving as a vehicle for introduction of the lactone and hydroxyl residues. In our planning of this synthesis, we had examined molecular models of **9** and had tentatively concluded that proton abstraction from **9** might occur predominately at C_7—a result highly desirable to formulation of **10**.[14] We were pleased to find that **9** gave what appeared to be a single en-

0002-7863/79/1501-7626$01.00/0

olsilane product on deprotonation in the kinetic manner with lithium hexamethyldisilazane and trapping of the resulting enolate with trimethylsilyl chloride.[15] The structure of this substance was not forthcoming however, until it was treated with palladium acetate (trimeric) in anhydrous acetonitrile—whereupon the enone **10** (oil, 73%) was isolated.[16]

Basic hydrogen peroxide treatment of **10** and subsequent reduction of the α-epoxy ketone with triisobutylaluminum gave the *trans*-epoxy alcohol **11**.[17] This material, without purification, was submitted to epoxide ring opening using an excess of dilithioacetate in hexamethylphosphoramide and DME. Acid workup of the reaction served both to secure formation of the cis lactone and to hydrolyze the THP residue—this product was treated with trimethylsilyl chloride and then purified to give the tricyclic lactone derivative **12** (mp 121-122 °C, 55% from **10**).[18]

Methylenation of the lactone by treatment with methoxymagnesium carbonate (20 equiv, 140 °C, 2 h), followed by reaction of the resultant lactone acid **13** with 30% formalin solution containing diethylamine, afforded crystalline dihydrohelenalin, **14** (mp 156.5-157.5 °C) in 76% yield from **12**.[19] Lastly, oxidation of **14** with manganese dioxide gave crystalline racemic helenalin, mp 224-226 °C, in 6.6% overall yield from **3**. This material was found identical with a sample of synthetic helenalin kindly provided by Professor P. Grieco—further, the substance was found identical except for optical rotation to natural helenalin generously provided by Professor W. Herz.[20]

Acknowledgment. This work was supported by a Public Health Service Research Grant (CA 23257) from the National Cancer Institute. We also thank the Syntex and Hoffmann-La Roche Corporations for financial support as well as the Eastman Kodak Company for generous use of their 270-MHz NMR facility. Lastly, very special thanks to Drs. S. E. Normandin and C. S. Pogonowski for invaluable experiments which initiated this work.

References and Notes

(1) (a) For representative examples, see T. K. Devon and A. I. Scott, "Handbook of Naturally Occurring Compounds", Vol. II, Academic Press, New York, 1972; H. Yoshika, T. J. Mabry, and B. N. Timmerman, "Sesquiterpene Lactones", University of Tokyo Press, Japan, 1973. (b) Pertinent references to the biological activity of these systems include E. Rodriguez, G. H. N. Towers, and J. C. Mitchell, *Phytochemistry*, **15**, 1573 (1976); K. H. Lee, T. Ibuka, R. Y. Wu, and T. A. Geissman, *ibid.*, **16**, 1177 (1977); K. H. Lee, E. C. Mar, M. Okamoto, and I. H. Hall, *J. Med. Chem.*, **21**, 819 (1978); G. R. Pettit, C. L. Herald, G. F. Judd, L. D. Vanell, E. Lehto, and C. P. Pase, *Lloydia*, **41**, 29 (1978); F. J. Evans and C. J. Soper, *ibid.*, **41**, 193 (1978).

(2) Y. Ohfune, P. A. Grieco, D. L. J. Wang, and G. Majetich, *J. Am. Chem. Soc.*, **100**, 5946 (1978).

(3) (a) J. A. Marshall and R. H. Ellison, *J. Am. Chem. Soc.*, **98**, 4312 (1976); (b) M. F. Semmelhack, A. Yamashita, J. C. Tomesch, and J. Hirotsu, *ibid.*, **100**, 5565 (1978); (c) P. A. Wender, M. A. Eissenstat, and M. P. Filosa, *ibid.*, **101**, 2196 (1979).

(4) (a) R. Kretchmer and W. J. Thompson, *J. Am. Chem. Soc.*, **98**, 3379 (1976); (b) P. De Clercq and M. Vanderwalle, *J. Org. Chem.*, **42**, 3447 (1977); (c) P. A. Grieco, Y. Ohfune, and G. Majetich, *J. Am. Chem. Soc.*, **99**, 7397 (1977); (d) ref 3c.

(5) We thank Dr. P. Wehrli of the Roche Corporation for a very generous sample of this material as well as detailed instruction for its preparation.

(6) D. H. R. Barton, M. J. Day, R. H. Hesse, and M. M. Pechet, *J. Chem. Soc., Perkin Trans. 1*, 1764 (1975).

(7) C. A. Henrick, E. Böhme, J. A. Edwards, and J. H. Fried, *J. Am. Chem. Soc.*, **90**, 5926 (1968).

(8) Compound **5** must be formed in the following manner: lithio dimethyl methylphosphonate adds to the carbonyl group of lactam **4**—either under the reaction conditions or under workup conditions this adduct rearranges, by ring opening, into the *N*-methyl imine analogue of **5**. Although normally not isolated, this imine has been fully characterized as have all other compounds reported herein.

(9) Compound **1** arises from **5** by base-induced retro-aldol ring opening of the latter followed by protonation of the resultant aldehyde enolate and subsequent intramolecular condensation between the β-ketophosphonate enolate and the aldehyde residue. We assumed that the critical trans geometry required for **1** would result via stereoselective protonation of the aldehyde enolate from the side opposite that occupied by the adjacent methyl group. Implicit in this stereochemical outcome is the assumption that both the oxy-*tert*-butyl residue and the side chain bearing the phosphonate moiety would occupy equatorial positions while the methyl group would reside in an axial environment. The stereochemistry of **1** was demonstrated to be trans with respect to $C_1 \rightarrow C_5$ ring fusion by reduction of it into its C_9-C_{10} dihydro analogue. Compound **1** also was treated with DBU to give the C_1-C_{10} β,γ-unsaturated ketone. The latter material was then reduced to give a 4:1 mixture of trans and cis saturated ketones, respectively—a result anticipated from previous work carried out by Marshall and co-workers.[3a] The 270-MHz NMR spectra of trans and cis ketones are clearly different and consistent with the structures assigned them.

(10) We had originally intended to use the reagent lithium dimethylcuprate to carry out this reaction; in this instance, however, a 4:1 ratio of **6** and its β-methyl analogue was obtained. These isomeric substances proved difficult to separate, and, thus, we resorted to the magnesium derived reagent. Our development of this reagent was guided by literature reports from P. R. McGuirk, A. Marfat, and P. Helquist, *Tetrahedron Lett.*, 2973 (1978), and G. L. van Mourik and H. J. Pabon, *ibid.*, 2705 (1978).

(11) Reaction sequences for which an overall yield is reported normally were carried out using crude intermediates—only the final product of the sequence was chromatographically purified.

(12) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).

(13) For an excellent leading reference on this methodology, see B. M. Trost, T. N. Salzmann, and K. Hivoi, *J. Am. Chem. Soc.*, **98**, 4887 (1976).

(14) Removal of the α proton at C_7 appeared to be the most likely experimental result given that **9** would occupy a minimal energy configuration at −78 °C and that carbon–hydrogen bond rupture would yield a filled p orbital (anion) maximally oriented for interaction with the carbonyl residue.

(15) Several alkylation reactions in addition to that described have been carried out with this anion—all of these products are regioselectively formed. Deprotonation of **9** with lithium hexamethyldisilazane in the thermodynamic mode followed by various enolate trapping reactions affords regioindiscriminate products.

(16) This methodology is described in detail by Y. Ito, T. Hirao, and T. Saegusa, *J. Org. Chem.*, **43**, 1011 (1978). The structure of **10** logically follows from its IR and NMR spectrum. NMR spectra of crude reaction mixtures indicate **10** to be the only product formed in this reaction. Sulfide alkylation of the kinetic enolate of **9**, followed by oxidative elimination[13] also affords **10**, but in lower yield.

(17) For an example of this methodology, see M. R. Roberts, W. H. Parsons, and R. H. Schlessinger, *J. Org. Chem.*, **43**, 3970 (1978).

(18) Very similar reaction sequences which appeared during the course of our work have been reported by Grieco[2] and by P. Kok, P. De Clercq, M. Vanderwalle, J. P. De Clercq, G. Germain, and M. Van Meerssche, *Tetrahedron Lett.*, 2063 (1979). For other examples of α-oxy epoxide ring-opening reactions, see S. Danishefsky, M. Y. Tsai, and T. Kitahara, *J. Org. Chem.*, **42**, 394 (1977); G. R. Kieczykowski, M. R. Roberts, and R. H. Schlessinger, *ibid.*, **43**, 788 (1978).

(19) For a detailed description of this methodology see W. H. Parker and F. J. Johnson, *J. Org. Chem.*, **38**, 2489 (1973).

(20) Comparisons were based on the IR, 270-HMz NMR, mass spectra, TLC, and melting points of these materials.

M. R. Roberts, R. H. Schlessinger*

Department of Chemistry, University of Rochester
Rochester, New York 14627

Received August 13, 1979

Total Syntheses of *dl*-Confertin and *dl*-Damsin

Sir:

In the preceeding manuscript we described the stereoselective conversion of the perhydroazulenone **1** into the sesquiterpene helenalin; herein, we report the transformation of **1** into the pseudoguaianolides confertin (**2**)[1] and damsin (**3**).[2] Introduction of a β-oriented methyl group at C_{10} and attachment of an acetic acid residue at C_7 are required for the elaboration of **1** into confertin, whereas a 1,3 transposition of oxygen from C_8 to C_6 together with the previously stipulated manipulations at C_{10} and C_7 are demanded for obtaining damsin from **1**.

The synthesis of **2** and **3** commences by addition of lithium dimethylcuprate to **1** followed by trapping of the resulting enolate with chlorotrimethylsilane.[3] Reaction of this enolsilane with palladium acetate (trimeric) in anhydrous acetonitrile[4] smoothly affords the enone **4** (mp 59-60 °C) in 83% overall yield from **1**.[5] Establishment of the β-configured C_{10} methyl group was then secured by reduction of the enone with rhodium on alumina in ethanol—a reaction which gives essentially pure **5** (mp 98-98.5 °C) in 95% yield.[6] By this route, quantities of **5** were readily available, and the conversion of this substance into confertin and damsin is outlined below.

Molecular models suggested that deprotonation of **5** in the kinetic manner would occur at C_7 thereby generating an eno-

0002-7863/79/1501-7627$01.00/0