A key feature of this pair of syntheses is the unambiguous manner in which stereochemistry has been introduced at a chiral center in one of three bridges of a [3.3.3]propellane relative to the other two (differently substituted) members. The sequences of reactions provide independent proof of both the structure and configuration of the natural product. Finally, it seems likely that the basic approaches outlined herein will prove applicable to other areas of propellane chemistry where stereochemical issues have been given scant attention.[20,21]

Acknowledgment. This research was made possible by the generous financial support of the National Institutes of Health (Grants AI-11490 and GM-28468) and the Eli Lilly Co.

Supplementary Material Available: IR, ^{1}H NMR, and MS data of compounds **2**, **3**, and **5-12** (3 pages). Ordering information is given on any current masthead page.

(20) (a) Paquette, L. A.; Thompson, G. L. *J. Am. Chem. Soc.* **1972**, *94*, 7118. (b) Thompson, G. L.; Heyd, W. E.; Paquette, L. A. *Ibid.* **1974**, *96*, 3177.

(21) Ginsburg, D. "Propellanes. Structure and Reactions"; Verlag Chemie: Weinheim/Bergstr., West Germany, 1975.

A Total Synthesis of a Racemic Eriolanin

M. R. Roberts and R. H. Schlessinger*

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

Received October 10, 1980

The lactones eriolanin (**1**) and eriolangin (**2**) are members of the rare 1,10-secoeudesmanolide class of sesquiterpenes. Isolated by Kupchan and co-workers from the chloroform extract of the plant *Eirophgllum lanatum* Forbes (Composite), these natural products were found to possess significant in vivo activity against P-388 leukemia in mice as well as in vitro activity against cell cultures derived from human carcinoma of the nasopharynx (KB).[1] The biological activity exhibited by **1** and **2** clearly reflects the presence of two α,β-unsaturated carbonyl residues in each molecule.[2] However, of much greater interest to the synthetic chemist is the stereochemistry of **1** and **2** which consists of three contiguous chiral centers within a cyclohexene ring along with an additional chiral center allylic and exocyclic to the ring—the entire array posing a provocative problem. In meeting this challenge, Grieco and co-workers have crafted an elegant solution ultimately resulting in total syntheses of both **1** and **2** as well as the third member of this class of natural products, ivangulin (**3**).[3] Herein, we describe the result of quite different synthetic reasoning demonstrated by the construction of eriolanin.

It occurred to us that base-induced ring opening of the bicyclooctenol **4** ought to afford the cyclohexenone **5** possessing the indicated stereochemistry.[4] Either stereoselective reduction or epoxidation of **5** would result in procurement of an intermediate readily convertible into the synthetic target. Our initial efforts to secure **4** utilized the obvious [4 + 2] cycloaddition reaction which unfortunately led to a low-yield production of all possible isomers of the corresponding adduct.[5] We were able, however, to stereoselectively secure **4** by using the sequence shown in Scheme I.

Treatment of the hydroxymethyl residue of the vinylogous ester **6** with chloromethyl methyl ether followed by hydrolysis with aqueous KOH at 50 °C gave the corresponding alcohol-protected vinylogous acid.[6] Refluxing this substance in a mixture of toluene and hexamethyldisilazane afforded the air-sensitive vinylogous silyl ester **7** [bp 110 °C (10^{-3} mm Hg)] in 70% overall yield from **6**.[7] A stereoselective tandem conjugate addition reaction of this substance to methyl crotonate was then carried out. Kinetic deprotonation of **7** with lithium diisopropylamide (LDA) in THF at −78 °C followed by addition of methyl crotonate gave the bicyclooctanone **8** as a single substance (mp 39.5–41 °C) in 74% yield.[8] A variety of methods for the conversion of **8** into **4** were examined, and by far the best route commenced with deprotonation of **8** with LDA followed by bromination of the enolate with elemental bromine. The bromo ketone was reduced with sodium borohydride to give a mixture of bromohydrins which were then treated with zinc in ethanol to afford **4** (oil); desilylation of the bridgehead alcohol occurs in the last reaction workup. The olefin alcohol was treated with a catalytic amount of potassium *tert*-butoxide in *tert*-butyl alcohol at 22 °C for 3 min to afford a single substance **5** (oil) in 74% overall yield from **8**.[9] Lithium tri-*tert*-butoxyaluminum hydride reduction of **5** gave a 92% yield of the β-allylic alcohol **9** contaminated with small amounts of the undesired α isomer.[10] Derivatization of **9** with *tert*-butylchlorodimethylsilane (TBSCl) followed by epoxidation with *N*-bromosuccinimide (NBS) in acetone/water/Na_2CO_3 afforded the *trans*-α-oxy epoxide **10** in 77% yield from **5**.[11] The fully decoupled ^{1}H spectrum of this substance at 400 MHz confirmed its relative stereochemistry.

We then turned our attention to the C_1 homologation of the side chain of **10** and found that several standard methods of accomplishing this were unsatisfactory. By recourse to reduction of the ester with diisobutylaluminum hydride and conversion of the resulting alcohol into its corresponding iodide (via the mesylate), we were able to add a C_2 unit employing (divinylcopper)lithium, thereby obtining the olefin **11** in 85% yield from **10**. The lactone residue was then appended onto **11** by removal of the silyl residue with triethylamine hydrofluoride, reaction of the epoxy alcohol with dilithioacetate, and lactonization mediated by *p*-toluenesulfonic acid.[12] The lactone **12** (mp 75–76 °C) was obtained in 72% yield from **11**.

(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) T. A. Giessman and M. A. Irwin, *Pure Appl. Chem.*, **21**, 167 (1970); S. M. Kupchan, *ibid.*, **21**, 227 (1970); S. M. Kupchan, M. A. Eakin, and A. M. Thomas, *J. Med. Chem.*, **14**, 1147 (1971); A. Rosowsky, N. Papathanasopaulos, H. Lazarus, G. E. Foley, and E. J. Modest, *ibid.*, **17**, 672 (1974); G. A. Howie, I. K. Stamos, and J. M. Cassady, *ibid.*, **19**, 309 (1976); P. A. Grieco, J. A. Noguez, Y. Masaki, K. Hiroi, M. Nishizawa, A. Rosowsky, S. Oppenheim, and H. Lazarus, *ibid.*, **20**, 71 (1977).

(3) For total syntheses of **1** and **2**, see P. A. Grieco, T. Oguri, S. Gilman, and G. T. DeTitta, *J. Am. Chem. Soc.*, **100**, 1616 (1978); P. A. Grieco, T. Oguri, and S. Gilman, *ibid.*, **102**, 5886 (1980). For the isolation of **3**, see W. Herz, Y. Sumi, V. Sudarsanam, and D. Raulais, *J. Org. Chem.*, **32**, 3658 (1967). For a total synthesis of **3**, see P. A. Grieco, T. Oguri, C.-L. J. Wang, and E. Williams, *J. Org. Chem.*, **42**, 4113 (1977).

(4) During the course of this work, W. C. Still and M.-Y. Tsai [*J. Am. Chem. Soc.*, **102**, 3654 (1980)] reported a similar ring-opening reaction in their elegant total synthesis of (±)-trichodermol.

(5) For some examples of similar difficulties with the Diels–Alder reaction, see A. J. Birch, P. L. MacDonald, and V. H. Powell, *Tetrahedron Lett.*, **5**, 351 (1969); T. Ibuka, Y. Mori, and Y. Isubushi, *ibid.*, **36**, 3169 (1976); T. Ibuka, Y. Mori, T. Aoyama, Y. Isubushi, *Chem. Pharm. Bull.*, **26**, 456 (1978).

(6) Compound **6** is readily prepared from trimethylgallic acid. Yields much higher than that reported in the literature can be realized by rapid reaction workup: O. L. Chapman and P. Fitton, *J. Am. Chem. Soc.*, **85**, 41 (1963), and references cited therein. Also see W. Nagata, S. Hirai, T. Okumura, and K. Kawata, *ibid.*, **90**, 1650 (1968).

(7) S. Torkelson and C. Ainsworth; [*Synthesis*, 722 (1976)] describe the use of hexamethyldisilane with imidazole for silylation of 1,3-dicarbonyl compounds. The use of bis(trimethylsilyl)acetamide has been described for this type of reaction by J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Am. Chem. Soc.*, **88**, 3390 (1966).

(8) Tandem conjugate addition reactions starting from the kinetic enolates of unsaturated cyclic ketones have been described in detail by K. B. White and W. Reusch, *Tetrahedron*, **24**, 2439 (1978). A single reaction of this kind starting from the kinetic enolate derived from a cyclic vinylogous ester has been reported by M. L. Quesada, R. H. Schlessinger, and W. H. Parsons, *J. Org. Chem.*, **43**, 3968 (1978).

(9) The singularity of this material was demonstrated by the ^{1}H spectrum of this substance at 400 MHz together with its ^{13}C spectrum.

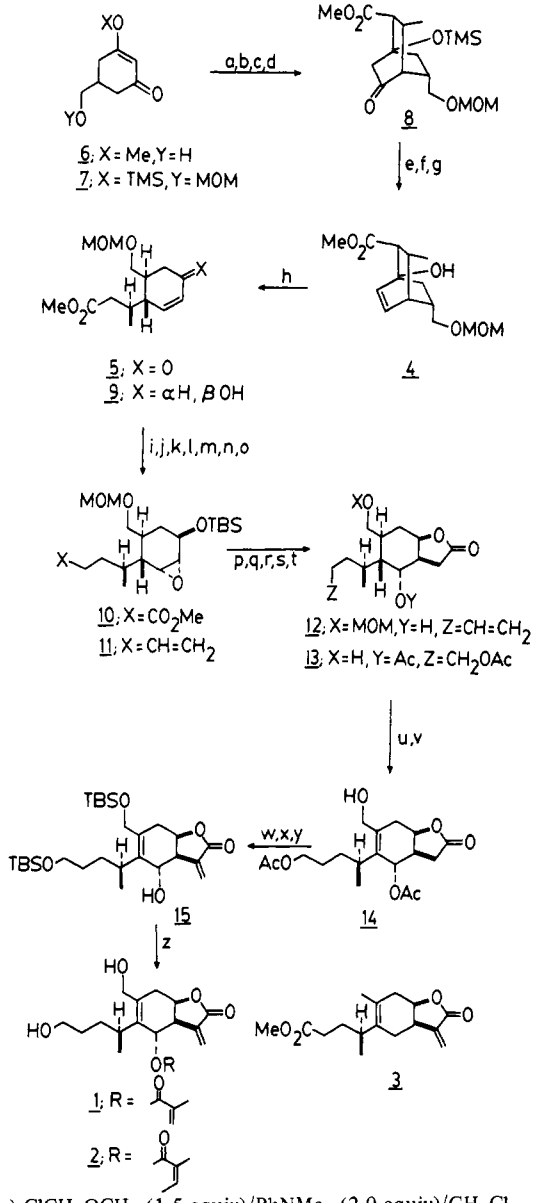
(10) The stereochemical course of this reaction was anticipated on the basis of literature precedence summarized by E. Toromanoff, *Top. Stereochem.*, *2*, 157 (1967).

(11) While a varity of methods to secure *trans*-α-oxy epoxides are available, the method described therein proved considerably superior in this instance. For other examples, see C. G. Chavdarian and C. H. Heathcock, *Synth. Commun.*, **6**, 277 (1976).

(12) For several examples of the reaction of dilithio acetate with α-oxy expoxides, see S. Danishefsky, M.-Y. Tsai, and T. Kitahara, *J. Org. Chem.*, **42**, 396 (1977).

0002-7863/81/1503-724$01.00/0

Scheme I



[a] (a) $ClCH_2OCH_3$ (1.5 equiv)/$PhNMe_2$ (2.0 equiv)/CH_2Cl_2 (1.5 M)/22 °C, 48 h; (b) KOH/H_2O/50 °C; Me_6Si_2/toluene/110 °C; (d) LDA (1.0 equiv), 1 M in THF/methyl crotonate (1.1 equiv)/-78 °C, 10 min/-20 °C for 8 h; (e) LDA, 1 M in THF/rapid addition of Br_2 (10 equiv) in CH_2Cl_2 (3 M) at -78 °C/stirring 1 min/inverse quench into aqueous $NaHCO_3$ and Na_2SO_3; (f) $NaBH_4$/EtOH/22 °C, 2 h; (g) Zn^0/EtOH/75 °C, 10 h/H^+; (h) *t*-BuOK (0.1 equiv) 0.25 M in *t*-BuOH/1 min; (i) $(t\text{-BuO})_3$-AlLiH (1.1 equiv)/THF (1 M)/22 °C, 8 h; (j) TBSCl/DMF/imidazole/22 °C, 2 h; (k) NBS (1.1 equiv)/acetone-H_2O (0.5 M)/0 °C, 1 h; MeOH/K_2CO_3/22 °C, 10 h; (l) DiBAl-H, 1 M in hexane diluted to 0.5 M with THF/-78 °C, 10 min/0 °C, 10 min; (m) MsCl (1.3 equiv)/THF (1 M)/Et_3N (2.0 equiv)/0 °C, 1 h; (n) NaI (5.0 equiv)/acetone (0.3 M)/40 °C, 2 h; (o) $(CH_2{=}CH)_2CuLi$, 0.5 M in THF/-78 °C, 30 min/-20 °C, 10 min/0 °C, 10 min; (p) Et_3NHF (2.1 equiv) in CH_3CN (0.4 M)/Et_3N (1.0 equiv)/60 °C, 10 h; (q) $LiCH_2CO_2Li$ (7 equiv)/THF (0.5 M)/HMPA (7 equiv)/50 °C, 6 h/*p*-TSA (0.01 equiv)/benzene (0.25 M)/80 °C, 4 h; (r) O_3/CH_3OH (0.1 M)/-78 °C, 5 min/$NaBH_4$/-20 °C, 20 min; (s) Ac_2O (3 equiv)/pyridine (0.4 M)/DMAP (0.2 equiv)/22 °C, 8 h; (t) $(CH_2SH)_2$ (2.0 equiv)/BF_3Et_2O (2.0 equiv)/CH_2Cl_2 (0.5 M)/0 °C, 1 h; (u) PCC (1.1 equiv)/CH_2Cl_2 (0.5 M)/22 °C, 10 h; (v) PhSeCl (4.4 equiv)/EtOAc (0.25 M)/60 °C, 8 h/workup with H_2O and CH_2Cl_2/$NaBH_4$/EtOH/0 °C, 5 min; (w) K_2CO_3 (2.2 equiv)/CH_3OH (0.1 M)/0 °C, 30 h; (x) TBSCl (3.2 equiv)/pyridine (0.4 M)/imidazole (2.0 equiv)/0 °C, 2 h/TMe_3SiCl (3.4 equiv)/0 °C, 40 min; (y) LDA (1.1 equiv)/THF (1 M)/CO_2/40% CH_2O/Et_2NH/HOAc; (z) methacrylic anhydride (1.05 equiv)/pyridine (0.5 M)/DMAP (2.0 equiv)/22 °C, 8 h.

Ozonolysis of the olefinic side chain of **12** followed by reductive workup gave the corresponding side-chain alcohol, and it along with the secondary ring alcohol were acylated with acetic anhydride in pyridine containing (dimethylamino)pyridine (DMAP). Removal of the methoxymethyl moiety was readily accomplished by employing ethanedithiol and $BF_3{\cdot}Et_2O$: the product, **13** (oil), was obtained in 70% yield from **12**. We now commenced introduction of the ring olefin by pyridinium chlorochromate oxidation of **13**. The unstable aldehyde formed in this reaction was immediately combined with phenylselenyl chloride in ethyl acetate at 65 °C. Contrary to the usual course of this reaction, selenylation under these conditions was accompanied by loss of the elements of PhSeH under nonoxidizing conditions, and a mixture of unsaturated aldehydes became the ultimate products of this reaction.[13] Without purification, these substances were reduced with sodium borohydride in ethanol and the desired alcohol **14** (mp 124-125.5 °C) was isolated after chromatography in 40% yield from **13**.

The terminating steps of the synthesis (α-methylenation of the lactone residue and esterification of the secondary ring alcohol) were addressed starting with removal of the acetate residues of **14** by using K_2CO_3 in methanol at 0 °C for 30 h. The resulting crude triol was then selectively protected in a single-flask operation by initial treatment with TBSCl in a mixture of pyridine and imidazole (primary alcohols react) followed by addition of Me_3SiCl (secondary alcohol reacts). The lithium enolate of this substance (LDA, THF, -78 °C) was carbonated with CO_2 and the resulting acid lactone treated with a mixture of 40% formalin and diethylamine to afford the corresponding α-methylene lactone.[14] Treatment of this substance with acetic acid hydrolyzed the Me_4Si protecting group of the secondary alcohol, giving rise to **15** (mp 121-122.5 °C) in 51% yield from **14**. Esterification of **15** with methacrylic anhydride in pyridine containing DMAP followed by removal of the TBS groups with 10% HCl in ethanol gave synthetic eriolanin (**1**) in 90% yield (mp 113-114 °C; lit.[15] mp 113-114.5 °C). The physical properties of this substance were identical with those of a sample of synthetic eriolanin kindly provided us by Professor Paul Grieco.[16]

Additional examples of tandem conjugate addition reactions potentially useful in the construction of natural products will be reported in the future.

Acknowledgment. This work was supported by a Public Health Service Research Grant (CA 23257) from the National Cancer Institute. We also thank the Syntex Corporation for financial support.

(13) This type of reaction, under similar conditions, has been observed by Professor Dennis Liotta, Department of Chemistry, Emory University. We thank Professor Liotta for sharing his results with us.

(14) For a detailed description of this highly useful methylenation sequence, see W. H. Parker and F. J. Johnson, *J. Org. Chem.*, **38**, 2489 (1973).

(15) See ref 3.

(16) We thank Professor Paul Grieco, Department of Chemistry, Indiana University, for a generous sample of synthetic eriolanin as well as spectral data on natural eriolanin.

Concerted Mechanism of Intramolecular 1,1-Cycloaddition Reaction of Allyldiazomethane[1]

Tsutomu Miyashi, Yôsuke Fujii, Yoshinori Nishizawa, and Toshio Mukai*

Department of Chemistry, Faculty of Science
Tohoku University, Sendai 980, Japan

Received June 12, 1980

In our previous report,[2] we demonstrated a novel intramolecular reactivity of the terminal nitrogen of diazomethane, that is, various

(1) Organic Thermal Reaction, part 50. For part 49, see ref 2.

