(br s, 1 H), 7.20–8.00 (m, 6 H); ^{13}C NMR δ 170.0, 167.1, 134.1, 133.6, 131.7, 128.6, 127.2, 125.8, 85.4, 83.3, 56.3, 51.0, 28.8, 21.8. **9b**: mp 127–129 °C; IR (KBr) 3200, 3000, 1730, 1620, 1590 cm^{-1}; 60-MHz ^1H NMR δ 1.22 (d, 3 H), 1.35 (s, 9 H), 4.74–5.35 (m, 3 H), 5.82–6.08 (m, 2 H), 6.82 (br s, 1 H), 7.79 (br s, 1 H), 7.84–7.97 (m, 5 H); ^{13}C NMR δ 168.6, 167.3, 134.4, 133.8, 131.6, 128.4, 127.3, 126.7, 86.7, 82.8, 56.9, 51.5, 28.8, 21.8. **2b**: mp 224.5–225.5 °C; R_f = 0.43 (7:3 *n*-PrOH–H_2O); $[\alpha]^{25}_D$ +251 ± 2° (*c* 1.2, 1 N HCl); IR (KBr) 3250, 2840, 1660, 1500, 1300 cm^{-1}; ^1H NMR (D_2O, 360 MHz) δ 1.28 (d, 3 H, Me), 4.02 (d, 1 H, α-H), 5.14 (t, 1 H, 5-H), 5.44 (br s, 1 H, 2-H), 5.69 (d, 1 H, =CH), 6.19 (d, 1 H, =CH).

(8) The intermediacy of an epoxide under similar reaction conditions has been reported in the reaction of **3** with NaOAc in refluxing DMF: T. Ogawa, M. Matsui, H. Ohrui, H. Kuzuhara, and S. Emoto, *Agr. Biol. Chem.*, **36**, No. 9, 1655–1657 (1972).

(9) N. R. Williams, *Adv. Carbohydr. Chem.*, **25**, 155 (1970).

(10) Prepared according to L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. I, Wiley, New York, 1967, p 729.

(11) *tert*-Butylisonitrile was prepared by a modification of the procedure of Ugi et al. ("Organic Syntheses", Collect. Vol. V, Wiley, New York, 1973, p 300). Diphenyl ether was used instead of petroleum ether.

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(14) During these investigations, we have prepared the 5(*R*),2(*R*),α(*R*) isomer which was presumed to be identical with natural furanomycin. The physical properties of this isomer are different from those of the natural product: mp 204–205 °C dec; R_f = 0.41 (7:3 *n*-PrOH–H_2O), $[\alpha]^{25}_D$ +47.4 ± 2° (*c* 1, 1 N HCl); IR (KBr) 3270, 3000, 2890, 2600, 1620, 1520, 1490, 1405, 1370, 1345, 1330, 1312, 1110, 1087, 1060, 1007, 980 cm^{-1}; ^1HNMR (D_2O, 360 MHz) δ 1.31 (d, 3 H, Me), 4.01 (d, 1 H, α-H), 5.03 (m, 1 H, 5-H), 5.32 (br m, 1 H, 2-H), 5.71 (d, 1 H, =CH), 6.13 (d, 1 H, =CH). Full details pertaining to the cis series will be reported in a forthcoming publication.

(15) A recent communication from Professor Morris J. Robins at the University of Alberta informed us that he had also synthesized the 5(*R*),2(*R*),α(*R*) isomer from ribose and that this compound did not have the same physical properties as natural furanomycin.

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A Total Synthesis of *dl*-Pentalenolactone†

Sir:

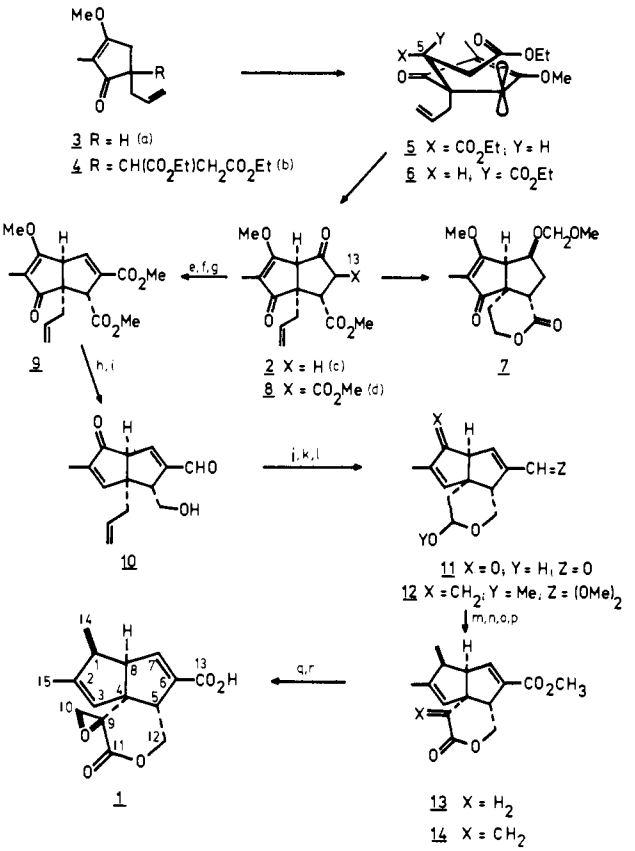
In 1970 an UpJohn group described the isolation and characterization of an acidic lipophilic antibiotic, pentalenolactone (**1**)—a substance which possesses a highly compacted tricyclic structure and which exhibits cytotoxic activity.[1] These interesting properties elicited considerable chemical activity culminating in an intriguing total synthesis of **1** by Danishefsky and co-workers.[2] Herein, we describe a quite different synthetic route to **1** which commences with a brief formulation of the pentalene system **2**, followed by an interlude of functional group reorganization, and concluding with the introduction of carbons 14 and 10.[3]

The vinylogous ester 3-methoxy-2-methylcyclopentenone[4] was kinetically deprotonated at −78 °C with lithium diisopropylamide (LDA), and the enolate thus formed was alkylated with allyl bromide to give **3** [90%, bp 70–75 °C (4×10^{-6} Torr)] (Scheme I).[5] Compound **3** was further appended by deprotonation with LDA and subsequent reaction with diethyl maleate. The resulting adduct, **4** (mp 88–89 °C), was determined by ^1H NMR to be a 1:1 mixture of epimers about C_5. Hence, enolate generation stemming from the vinylogous ester residue of this substance would yield two anions, **5** and **6**, with differing configurations about C_5. Molecular models suggested that **5** would undergo cyclization into the pentalene **2**—a material possessing the desired cis relationship between the allyl group and the carboxylate residue at C_5. A significant inhibition to cyclization was indicated for **6** stemming from a serious interaction between the five-membered-ring vinylogous ester enolate and the C_5 carboxylate residue. Therefore, we anticipated that only compound **2** would result from cyclization of **4** and were gratified to find that treatment of the latter with a mixture of sodium hydride, dimethyl carbonate, and DME at 0–22 °C for 1 h did indeed yield **2** [bp 145–155 °C (4×10^{-6} Torr), mp 72–73.5 °C, 75% yield from **3**].[6] The ^1H NMR spectrum of **2** indicated it to be a single compound, and its relative stereochemistry was readily confirmed by high yield conversion into the cis lactone **7**.[7]

The C_{13} carboxyl residue present in the natural product was next introduced by deprotonation of **2** at −78 °C with potassium hexamethyldisilazane (thermodynamic mode) followed by carbonation (CO_2) of the cyclopentanone derived enolate.[8] Acidification of this reaction mixture at −15 °C with 3% HCl, rapid extraction with methylene chloride, and esterification with diazomethane at −78 °C gave the diester **8**. Methanolic sodium borohydride reduction of **8**, mesylation of the resulting β-hydroxy ester, and elimination of the elements of methanesulfonic acid (collidine, 180 °C) afforded the acrylate ester **9** (mp 103.5–105 °C, 65% yield from **2**).

A sequence of reactions leading to a tricyclic substance amenable to introduction of the C_{14} methyl group was now

Scheme I[a]



[a] (a) LDA, THF (1 M), allyl bromide (1.1 equiv), −78 °C; (b) LDA, THF (1 M), diethyl fumarate, −78 °C; (c) NaH (5 equiv), $OC(OMe)_2$ (1 M), 0 °C, 30, min, DME (0.25 M), 22 °C, 1 h; (d) KHMDS (1 equiv), THF (0.5 M), −78 °C, CO_2, −78–0 °C, 3% HCl, −15 °C, CH_2N_2, CH_2Cl_2, −78 °C; (e) $NaBH_4$, MeOH (0.25 M), −20 °C; (f) $MeSO_2Cl$ (2 equiv), Et_3N (3 equiv), THF (0.2 M), 22 °C, 8; (g) collidine (1 M), 180 °C, 2 h; (h) diisobutylaluminum hydride (6 equiv), toluene (0.3 M), 0 °C, 6 N HCl; (i) MnO_2 (15 equiv), benzene (0.2 M), 22 °C, 4 h; (j) O_3, CH_2Cl_2 (0.25 M), pyridine (1.1 equiv), −78 °C, Me_2S; (k) MeOH (0.2 M), $CH(OMe)_3$ (5.0 equiv), HCl (0.2 equiv), 0 °C, 45 min; (l) Ph_3PCH_2Br (3 equiv), *n*-BuLi (3 equiv), THF (1 M), 0–40 °C; (m) $(Ph_3P)_3RhCl$ (0.1 equiv), benzene (0.1 M), H_2 (300 psi), 22 °C; (n) 10% H_2SO_4, acetone, H_2O, 40 °C, 12 h; (o) Jones, 22 °C, 3 h; (p) CH_2N_2, Et_2O, CH_2Cl_2, (q) MMC (20 equiv), 180 °C, 2 h, CH_2Cl_2, 3% HCl, −20 °C; (r) 30% CH_2O, Et_2NH, 40 °C.

† Dedicated to the memory of R. B. Woodward.

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commenced. Diisobutylaluminum hydride (5 equiv) reduction of **9** at 0 °C (acid workup), followed by manganese dioxide oxidation of the resulting allylic alcohol, gave the aldehyde-cyclopentenone **10** in 65% yield. Ozonolysis of this material (−78 °C 2 h) in methylene chloride containing pyridine (1.1 equiv) and workup with dimethyl sulfide provided the lactol **11** in 70% yield.[9] Treatment of the latter with methanol, trimethyl orthoformate, and acetyl chloride afforded the corresponding bis acetal which on reaction with methylene triphenylphosphorane in THF gave the diene **12**.[10] Lastly, reduction of the diene portion of **12** using tris(triphenylphosphine)chlororhodium in benzene (30 psi, H_2),[11] followed by acetal hydrolysis (acetone, H_2SO_4), Jones oxidation, and diazomethane treatment, afforded the lactone ester **13** (oil, 49% from **11**) as a 2:1 mixture of methyl group epimers at C_{14}—the β-methyl isomer predominating.[12]

The above mixture of epimers could not be readily separated by chromatrography and, therefore, was utilized as such for elaboration into the α-methylene lactone **14**. Several procedures for conversion of **13** into **14** were examined and by far the most convenient and efficient involved treatment of **13** with methoxymagnesium carbonate (20 equiv, 160 °C, 2 h), followed by reaction of the resulting lactone acid with 30% formalin solution containing diethylamine.[13] Vacuum filtration chromatography of the resulting mixture gave a 55% yield of the α-methylene lactone **14** (oil), determined by ^{1}H NMR spectroscopy to be exclusively the β-methyl isomer at C_{14}.[14]

Comparison of **14** with a sample of the α-methylene lactone (oil) kindly provided by Professor S. Danishefsky conclusively demonstrated these substances to be identical.[15] Since Danishefsky and co-workers have stereoselectively converted **14** into pentalenolactone (**1**) in good overall yield,[2a] our assemblage of **14** constitutes a total synthesis of this natural product. The preparation of **14** from 3-methoxy-2-methylcyclopentenone requires 19 steps and proceeds in an overall yield of 5.3%.

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References and Notes

(1) (a) D. G. Martin, G. Slomp, S. Mizsak, D. J. Duchamp, and C. G. Chidester, *Tetrahedron Lett.*, 4901 (1970); (b) S. Takeuchi, Y. Ogawa, and H. Yonehara, *ibid.*, 2737 (1969); (c) S. Takeuchi, J. Uzawa, H. Seto, and H. Yonehara, *ibid.*, 2943 (1977); (d) H. Seto, T. Sasaki, H. Yonehara, and J. Uzawa, *ibid.*, 923 (1978).
(2) (a) S. Danishefsky, M. Hirama, K. Gombatz, T. Harayama, E. Berman, and P. Schuda, *J. Am. Chem. Soc.*, **100**, 6536 (1978); (b) F. Plavac and C. H. Heathcock, *Tetrahedron Lett.*, 2115 (1979), have recently described yet another interesting potential route to this natural product.
(3) The numbering for pentalenolactone used in this text follows that given in ref 1a.
(4) A detailed preparation of this compound has been described by M. L. Quesada, R. H. Schlessinger, and W. H. Parsons, *J. Org. Chem.*, **43**, 3968 (1978).
(5) For an account of similar alkylation procedures, see ref 4. Compound **3**, as well as all other substances described herein, has been fully characterized.
(6) Since **4** is a 1:1 mixture of epimers and since the bicyclic product **2** is formed in >50% yield, it seems clear that epimerization is occurring at C_5 during the course of reaction—when epimerization of C_5 occurs (before or after cyclization) is not known with certainty by us. Reaction sequences for which an overall yield is reported normally were carried out using crude intermediates—only the final product of a given sequence was purified.
(7) The transformation **2** → **7** was accomplished by (a) sodium borohydride reduction of the cyclopentanone residue and protection of the resulting secondary alcohol residue with chloromethylmethyl ether; (b) ozonolysis of the allyl moiety, followed by reductive workup (sodium borohydride) and subsequent acidification to yield the lactone.
(8) Deprotonation of **2** in the kinetic manner affords the enolate derived by abstraction of the angular methine proton at C_8. This differing course of deprotonation (kinetic vs. thermodynamic) was demonstrated by alkylation experiments. The source of this phenomenon may well lie in the considerable strain experienced by the kinetic enolate and caused by sp^2 hybridization of five of the eight carbon atoms present in the pentalene skeleton of **2**.
(9) Pyridine is critical to the success of this reaction. For a leading reference concerning the effect of pyridine on ozonolysis reactions of this type, see G. Slomp and J. L. Johnson, *J. Am. Chem. Soc.*, **80**, 915 (1958).
(10) Reaction of either the lactone–acid or the lactone–ester analogues of **11** with this Wittig reagent was not successful. Undoubtedly, these results are due to the acidity of the C_8 methine hydrogen—hence the conversion of **11** into its bis acetal derivative.
(11) J. W. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc. A*, 1711 (1966).
(12) This ratio was readily determined by ^{1}H NMR examination of the doublets representing the two methyl epimers—the β isomer exhibiting a chemical shift and coupling constant essentially identical with those of C_{14} methyl group of the natural product. Danishefsky reports[2a] completely stereoselective reduction of an A-ring diene system possessing a carbonyl group at C_{11}, a single bond between C_6 and C_7, as well as a β-oriented carbomethoxy group attached to C_6. It is our feeling that the hindering effect of this C_6 carbomethoxy group may well enhance the stereoselectivity of this reduction.
(13) For a detailed description of this highly useful methylenation sequence, see W. H. Parker and F. J. Johnson, *J. Org. Chem.*, **38**, 2489 (1973).
(14) The authors claim no credit for this clearly fortuitous experimental event—the origin of which is yet obscure.
(15) We thank Professor Danishefsky for generous samples of both the α-metheylene lactone **14** and methyl pentalenolactonate, as well as for stimulating discussion during the course of this work.

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Additions and Corrections

Three-Electron Oxidations. VIII. Direct Evidence for the Synchronous Character of Three-Electron Oxidations [*J. Am. Chem. Soc.*, **96**, 6802 (1974)]; **Three-Electron Oxidations. IX. Chromic Acid Oxidation of Glycolic Acid** [*Ibid.*, **97**, 1444 (1975)]; **Three-Electron Oxidations. X. Cooxidation of Isopropyl Alcohol and Glycolic Acid** [*Ibid.*, **97**, 3762 (1975)]. By FARIZA HASAN and JAN ROČEK,* Department of Chemistry, University of Illinois at Chicago Circle, Chicago, Illinois 60680.

One of the original authors (J.R.) and S. Ramesh were unsuccesful in attempts to reproduce the synthesis of glycolic-d_2 acid, $HOCD_2CO_2H$, described in the original publications. Glycolic-d_2 acid prepared by two other methods gave considerably lower deuterium isotope effects than originally reported. We are therefore forced to conclude that the unusually high values for deuterium isotope effects reported in Tables I, V, and IV, respectively, of the original set of publications were in error. Results of a full reinvestigation of the chromic acid oxidation of glycolic acid and its cooxidation with isopropyl alcohol will be reported as soon as completed.

Hydrogen Atom Exchange between Nitroxides and Hydroxylamines [*J. Am. Chem. Soc.*, **101**, 3592 (1979)]. By MARTIN A. SCHWARTZ, J. WALLACE PARCE, and HARDEN M. MCCONNELL,* Stauffer Laboratory for Physical Chemistry, Stanford University, Stanford, California 94305.

In the first sentence in the Experimental Section, 2-Methyl-2-nitro-5-pentanone should be replaced by 2-