(90 + b + g)), and 179 (M − (2 × 90 + c)). The interpretation of the spectrum of **9** was supported by the fragmentation pattern obtained in the mass spectrum of **11**. A shift upward by 9 or 18 mass units was found here for all ions interpreted to contain one or two trimethylsilyl ether groups, respectively.

Metabolite **4** of prostaglandin $F_{2\alpha}$ (**1**) corresponds to metabolite **3** formed from prostaglandin E_2[4] (**2**) and differs only in the functional group at C-5. These two metabolites can be visualized to be formed by dehydrogenation of the alcohol group at C-15, reduction of the Δ^{13} double bond,[2,4,10] two steps of β oxidation,[2,4,7] and ω oxidation.[4] Studies on the structures of the remaining urinary metabolites of prostaglandin $F_{2\alpha}$ in man are in progress in this laboratory.

Acknowledgment. This work was supported by grants from the Swedish Medical Research Council (Project No. 13X-217) and from Knut and Alice Wallenbergs Stiftelse.

(10) E. Änggård, K. Gréen, and B. Samuelsson, *J. Biol. Chem.*, 240, 1932 (1965).

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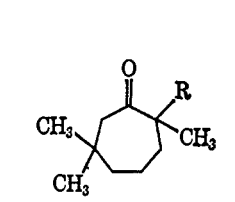
A Total Synthesis of Culmorin

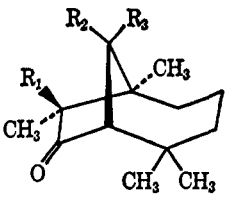
Sir:

The compact and rigid polycyclic ring systems associated with sesquiterpenes related to longifolene and longiborneol present a formidable challenge to total synthesis. The problems involved in rational construction of members of this family are typified by culmorin, a mold metabolite first isolated by Ashley, *et al.*, in 1937[1] and shown recently by Barton and Werstiuk in an elegant degradation study to possess structure **7**.[2] We report herein a rational total synthesis of culmorin which confirms the original structural assignment and which establishes a possible general synthetic pathway to related sesquiterpenes. The approach is based on construction of an intermediate bicyclo[4.2.1]nonane derivative appropriately substituted for introduction of remaining ring skeletal features and functionality.[3]

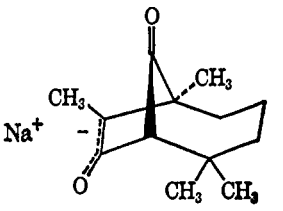
Treatment of tetrahydroeucarvone (**1a**)[4] with sodium hydride in glyme and alkylation of the resulting sodium enolate with 2-chloro-3-pentene[8] produced keto olefin



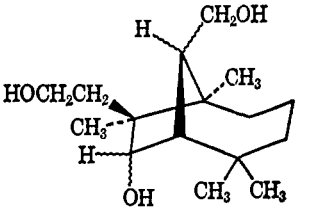
1a, R = H
b, R = CH(CH$_3$)CH=CHCH$_3$
c, R = CH(CH$_3$)CO$_2$C$_2$H$_5$



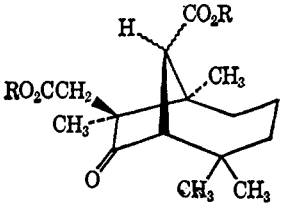
2a, R$_1$ = H; R$_2$, R$_3$ = =O
b, R$_1$ = H; R$_2$ = CH$_3$; R$_3$ = OH
c, R$_1$ = H; R$_2$, R$_3$ = =CH$_2$
d, R$_1$ = CH$_2$CO$_2$C$_2$H$_5$; R$_2$, R$_3$ = =CH$_2$



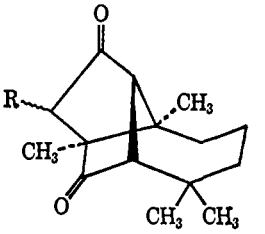
3



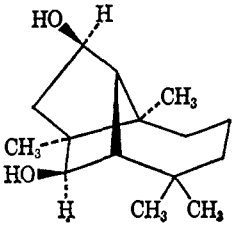
4



5a, R = H
b, R = CH$_3$



6a, R = CO$_2$C$_2$H$_5$
b, R = H



7

1b[9] [λ_{max}^{film} 3.31, 5.97, 10.35 (–CH=CH–), and 5.90 μ (CO), $\delta_{TMS}^{CCl_4}$ [10] 4.7–5.2(m, –C*H*=C*H*–)] in 86% yield as a mixture of epimers. Assignment of gross structure **1b** is based on results of an extensive study of base-catalyzed alkylation and acylation of tetrahydroeucarvone.[11] The latter investigation has established that substitution takes place exclusively at the α-methine position as shown by the appearance in the nmr spectra of a series of homogeneous substitution products of an AB quartet arising from methylene protons α to the ketone carbonyl group. The same type quartet appears in the spectrum of tetrahydroeucarvone. Lemieux–von Rudloff oxidation[12] of **1b** and conventional esterification (HCl–C_2H_5OH) of the resulting keto acid led to keto ester **1c** [λ_{max}^{film} 5.76 (ester CO) and 5.88 μ (ketone CO); $\delta_{TMS}^{CCl_4}$ 4.04 and 4.12 (overlapping quartets, –OC*H*$_2$CH$_3$, J = 7.2 cps)] as an epimeric

(1) J. N. Ashley, B. C. Hobbs, and H. Raistrick, *Biochem. J.*, 31, 385 (1937).

(2) (a) D. H. R. Barton and N. H. Werstiuk, *Chem. Commun.*, 30 (1967); (b) D. H. R. Barton and N. H. Werstiuk, *J. Chem. Soc., C*, 148 (1968).

(3) A pioneering achievement in total synthesis in this family of natural products was the recent preparation of longifolene: E. J. Corey, M. Ohno, R. B. Mitra, and P. A. Vatakencherry, *J. Am. Chem. Soc.*, 86, 478 (1964).

(4) Tetrahydroeucarvone is conveniently prepared by catalytic hydrogenation of eucarvone,[5] which in turn is available from carvone.[6] Carvone has been synthesized previously by several routes.[7]

(5) (a) O. Wallach, *Ann.*, 381, 51 (1911); (b) Y. Naves and P. Ardizio, *Helv. Chim. Acta*, 32, 329 (1949).

(6) (a) A. Baeyer, *Chem. Ber.*, 27, 810 (1894); (b) E. J. Corey and H. J. Burke, *J. Am. Chem. Soc.*, 78, 174 (1956).

(7) For reviews of early synthetic work, see: (a) J. L. Simenson, "The Terpenes," Vol. I, 2nd ed, Cambridge University Press, London, 1953; (b) P. de Mayo in "The Chemistry of Natural Products," Vol. II, K. W. Bentley, Ed., Interscience Publishers, Inc., New York, N. Y., 1959.

(8) J. Baudrenghien, *Bull. Sci. Acad. Roy. Belg.*, 15, 53 (1929); *Chem. Abstr.*, 23, 4196 (1929).

(9) (a) Compositional analyses of all new substances reported herein, including epimeric mixtures, were consistent with assigned structures. (b) Synthetic intermediates described in this report are all racemic. The configurational series depicted is that of natural culmorin.[2]

(10) Unless indicated otherwise, all nmr spectra were recorded at 60 Mcps.

(11) B. W. Roberts and S. C. Welch, unpublished results.

(12) (a) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, 33, 1701, 1710 (1955); (b) E. von Rudloff, *ibid.*, 33, 1714 (1955).

mixture in an over-all yield of 26% from **1b**. Direct alkylation of tetrahydroeucarvone with ethyl α-bromopropionate afforded in 30% yield a similar epimeric mixture of **1c**, albeit in 90% purity (vpc), and for convenience this slightly impure but more directly accessible material was used in the next stage.

Generation of the requisite bicyclo[4.2.1]nonane intermediate was accomplished by base-catalyzed intramolecular acylation of keto ester **1c** under carefully defined conditions. Treatment of a 1% (w/v) solution of the latter substance in glyme with 3 molar equiv of sodium hydride and one drop of ethanol for 14 hr at 75° under nitrogen and subsequent quenching of the reaction with acetic acid in ether at 0° produced in 65% yield a single diketone [mp 88–89°; $\lambda_{max}^{CHCl_3}$ 5.70 and 5.81 μ (CO); $\delta_{TMS}^{CCl_4}$ (100 Mcps) 1.10 (d, CH_3CHCO–, J = 7.5 cps[13]), 2.10 (d, –$COCHCO$–, J = 1.7 cps[13]), and 2.28 (quartet of doublets, CH_3CHCO–, J = 1.7, 7.5 cps[13])] to which we have assigned structure **2a** with an *endo*-methyl group on the following basis. The penultimate product of cyclization is probably sodium enolate **3** rather than the alternate bridgehead enolate since significant conjugative stabilization in the latter would require a high degree of ring strain and probably lead to a violation of recently redefined limitations of Bredt's rule.[14,15] Furthermore, a molecular model of the bicyclo[4.2.1]nonane ring system reveals that approach to the five-membered ring should be strongly directed to the face opposite the four-carbon bridge due to steric interference by the latter. On this basis stereoisomer **2a** is envisaged to arise *via* stereospecific kinetically controlled *exo* protonation of enolate **3** during work-up. This same argument rationalizes the high stereoselectivity observed in reactions described below which also involve attack on the five-membered ring of a bicyclo[4.2.1]nonane.

Completion of the tricyclic ring system of culmorin was effected by construction and Dieckmann cyclization of keto diester **5b**. Addition of methyllithium in ether to diketone **2a** afforded in 84% yield a single ketol, **2b** [mp 130–131°; $\lambda_{max}^{CHCl_3}$ 2.77, 2.86 (OH), and 5.82 μ (CO)], which on treatment with thionyl chloride in pyridine underwent dehydration to olefinic ketone **2c** [$\lambda_{max}^{CHCl_3}$ 5.80 (CO) and 6.07 μ (C=CH_2); $\delta_{TMS}^{CCl_4}$ 4.90 and 5.08 (broad singlets, C=CH_2)] in 58% yield after separation by preparative vpc. Treatment of the latter with sodium hydride in glyme and alkylation of the resulting sodium enolate with ethyl bromoacetate produced a single olefinic keto ester, **2d** (82%) [$\lambda_{max}^{CHCl_3}$ 5.77 (ester and ketone CO) and 6.06 μ (C=CH_2); $\delta_{TMS}^{CCl_4}$ 2.07 (br s, –CH_2CO_2–), 2.39 (br s, –$COCHC$=CH_2), 3.98 (q, –OCH_2CH_3, J = 7.0 cps), and 5.05 and 5.12 (broad singlets, C=CH_2)]. Structures **2b** and **2d** have been assigned to the ketol and olefinic keto ester, respectively, in line with the steric argument presented above for formation of diketone **2a**.[16] Hydroboration of **2d** with concurrent reduction of carbonyl functionality yielded triol **4** [mp 170–172°; λ_{max}^{KBr} 2.97 μ (v br, OH)], which was oxidized with ruthenium tetroxide–sodium periodate[17] to keto diacid **5a** [mp 237–242°; λ_{max}^{KBr} 5.86 and 5.75 μ (CO); $\delta_{TMS}^{C_5D_5N}$ 12.13 (br s, –CO_2H)]. Esterification of the latter with diazomethane then produced the desired keto diester **5b** [$\lambda_{max}^{CCl_4}$ 5.74 μ (ester and ketone CO)] in an over-all yield of 58% from **2d**. The physical properties of triol **4** and keto diacid **5a** made unambiguous analysis for stereochemical composition difficult. However, the methoxyl proton absorption in the nmr spectrum of keto diester **5b** in the range δ 3.5–3.9 revealed the presence of a minor stereoisomer which was probably carried through from the triol stage.[19]

Finally, Dieckmann cyclization ($NaOC_2H_5$–C_2H_5OH) converted keto diester **5b** to diketo ester **6a** (43%) [mp 120–122.5°, $\lambda_{max}^{CHCl_3}$ 5.69, 5.73, and 5.81 μ (ester and ketone CO); $\delta_{TMS}^{CDCl_3}$ 2.14 (s), 2.83 (br s), 3.23 (d, J = 1 cps) (–$COCHCHCOCHCO_2C_2H_5$), and 4.12 (q, –OCH_2–CH_3, J = 7.0 cps)], which on hydrolysis–decarboxylation (aqueous HCl–HOAc) afforded in 73% yield *dl*-culmorin diketone, **6b** [mp 117–118.5°], the solution infrared, nmr, and mass spectra of which were identical in detail with those of material prepared from authentic culmorin.[2] Since the diketone has previously been converted to culmorin,[2] the preparation of racemic **6b** completes the synthesis.

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(13) These coupling constants were obtained by first-order analysis and may be apparent values.

(14) (a) J. A. Marshall and H. Faubl, *J. Am. Chem. Soc.*, **89**, 5965 (1967); (b) J. R. Wiseman, *ibid.*, **89**, 5966 (1967).

(15) There is experimental evidence to support this supposition. Thus, bicyclo[4.2.1]nonan-9-one and the homologous bicyclo[5.2.1]-decan-10-one are nonenolizable and enolizable ketones, respectively: C. D. Gutsche and T. D. Smith, *J. Am. Chem. Soc.*, **82**, 4067 (1960).

(16) *exo* carboethoxymethylation of olefinic ketone **2c** is essential for the synthesis, and ultimate obtention of culmorin diketone (**6b**) confirms the course of alkylation.

(17) This oxidation was effected by a highly efficient modification developed in our laboratory of the catalytic method:[18] S. K. Ladisch and J. P. Greenberg, to be published.

(18) R. Pappo and A. Becker, *Bull. Res. Council Israel*, **5A**, 300 (1956).

(19) Since the one-carbon bridge is an epimerizable center in **5b**, stereochemical integrity at this stage is not vital to completion of the synthesis.

(20) National Science Foundation Summer Fellow, 1965; National Science Foundation Trainee, 1965–1967; National Institutes of Health Predoctoral Fellow, 1967–1968.

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Structure of the Spiramycins (Foromacidines) and Their Relationship with the Leucomycins and Carbomycins (Magnamycins)

Sir:

Paul and Tchelitcheff, following a series of reports,[1] proposed[1f] structures Ia–c for the spiramycins[1g] I–III,

(1) (a) R. Paul and S. Tchelitheff, *Bull. Soc. Chim. France*, 443 (1957); (b) *ibid.*, 724 (1957); (c) *ibid.*, 1059 (1957); (d) *ibid.*, 150 (1960); (e) *ibid.*, 189 (1965); (f) *ibid.*, 650 (1965); (g) S. Pinnert-Sindico, L. Ninet, J. Preud'Homme, and C. Cosar, *Antibiot. Ann.*, 724 (1954); (h) R. Corbaz, L. Ettlinger, E. Gaumann, W. Keller-Schierlein, E. Kyturz, L. Neipp, V. Prelog, A. Wettstein, and H. Zahaer, *Helv. Chim. Acta*, **39**, 304 (1956).