of the polyene macrolide antibiotics.[9,10]

Registry No. 1, 69734-27-6; 2, 956-82-1; 3, 1931-63-1; 4, 953-29-7; 5, 834-33-3; 6, 71519-26-1; 7, 71519-27-2; 8, 71519-28-3; 9, 71519-29-4; 10, 71519-30-7; 11, 71519-31-8; 12, 71519-32-9; 13, 71519-33-0; 14, 71519-34-1; 15, 71519-35-2; 16, 64810-60-2; 17, 71519-36-3; 18, 71519-37-4; 19, 71519-38-5; (*E*)-20, 71519-39-6; (*Z*)-20, 71519-40-9; 21, 71519-41-0; 22, 31446-88-5; 23, 71519-42-1; 24, 71537-28-5; oleic acid, 112-80-1; oleic acid methyl ester, 112-62-9; 2-hydroxybutyraldehyde, 37428-67-4; dihydropyran, 110-87-2; *tert*-butyldiphenylsilyl chloride, 58479-61-1; dimethyl methylphosphonate lithium derivative, 34939-91-8.

(9) All new compounds exhibited satisfactory analytical and spectral data.

(10) This work was financially supported by Merck Sharp and Dohme and the University of Pennsylvania.

(11) Fellow of the Alfred P. Sloan Foundation, 1979–1981.

K. C. Nicolaou,*[11] S. P. Seitz
M. R. Pavia, N. A. Petasis
Department of Chemistry
University of Pennsylvania
Philadelphia, Pennsylvania 19104
Received July 9, 1979

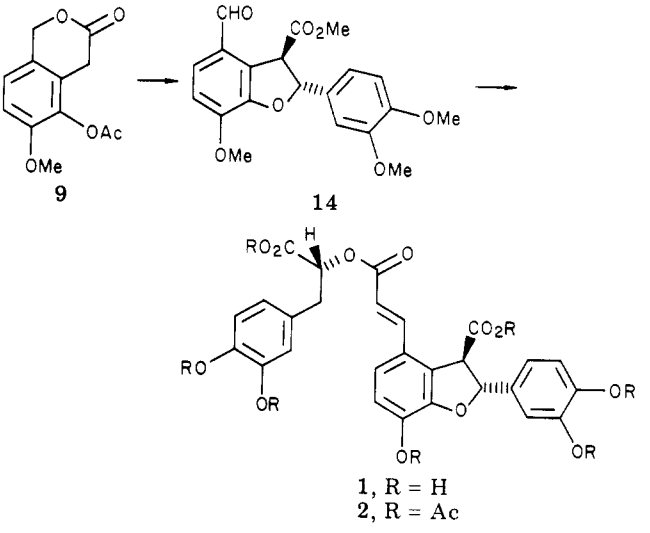
Total Synthesis of Heptamethyl Lithospermate

Summary: The total synthesis of *rac*-heptamethyl lithospermate (**2**) is described.

Sir: Extracts of several species of the genus *Lithospermum* have been shown to inactivate gonadotrophins.[1] They have proven capable of blocking the action of thyrotrophin and prolactin,[2] as well as LH, FSH, and TSH.[3] Lithospermic acid (**1**), the principal polyphenolic acid present in the roots of *Lithospermum ruderale* and *Lithospermum officinale*, has recently been isolated and characterized.[4,5] Out initial efforts toward developing a satisfactory synthetic access to **1** have resulted in the synthesis of the racemic permethylated derivative of lithospermic acid (**2**). The route described here involves three stages (Scheme I): (1) access to the 1,2,3,4 substitution pattern about the "central" aromatic ring; (2) conversion to the desired trans-substituted dihydrobenzofuran ring system; and (3) addition of the aryllactate/cinnamate side chain.

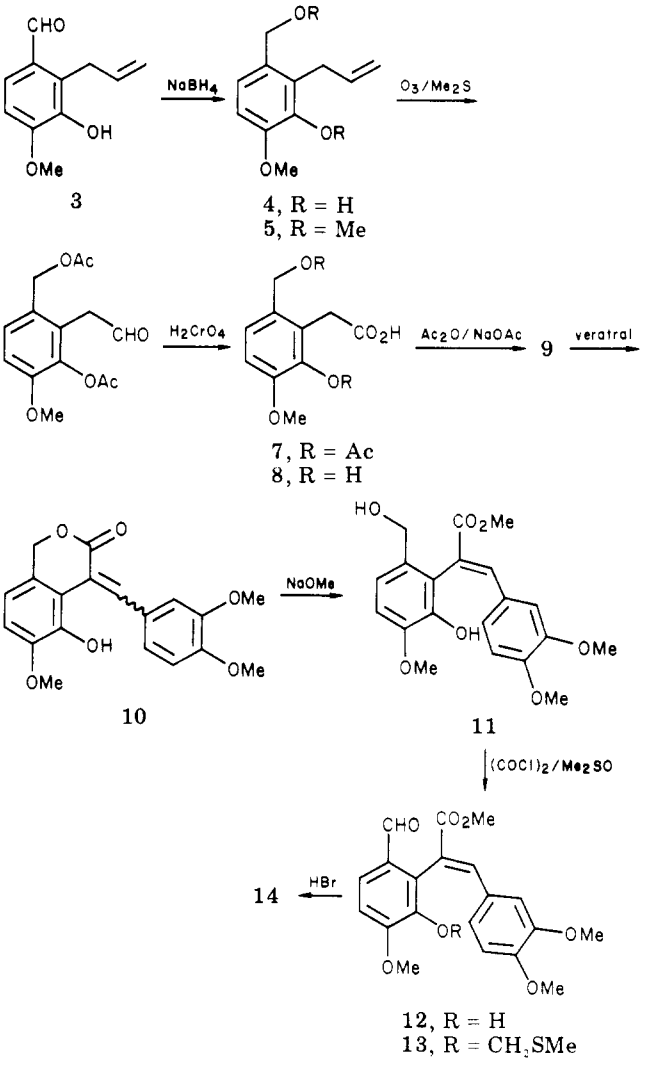
Our entry into the required 1,2,3,4 substitution pattern was found in the synthesis of the benzopyranone **9**. To this end (Scheme II), isovanillin was converted into 2-allylisovanillin (**3**) via the published procedure[6] involving Claisen rearrangement of *O*-allylisovanillin. Sodium borohydride reduction of **3** afforded the crystalline alcohol **4** in 90% yield: mp 85–86 °C; ^{1}H NMR ($CDCl_3$) δ 1.6 (br s, 1 H), 3.53 (dt, J = 2 and 6 Hz, 2 H), 3.88 (s, 3 H), 4.60 (s, 2 H), 4.7–5.2 (m, 2 H), 5.77 (br s, 1 H), 5.6–6.4 (m, 1 H), 6.70 (d, J = 8 Hz, 1 H), 6.88 (d, J = 8 Hz, 1 H); MS

Scheme I



1, R = H
2, R = Ac

Scheme II



12, R = H
13, R = CH_2SMe

m/e 194.096 (M^+). The diol **4** was protected as the diacetate **5** (90%) by treatment with acetic anhydride and triethylamine in refluxing THF. Ozonolysis of **5**, followed by reduction with dimethyl sulfide, afforded the aldehyde **6** in 76% yield: mp 71–73 °C; ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3 H), 2.30 (s, 3 H), 3.65 (d, J = 2 Hz, 2 H), 3.83 (s, 3 H), 5.07 (s, 2 H), 6.93 (d, J = 9 Hz, 1 H), 7.30 (d, J = 9 Hz, 1 H), 9.48 (t, J = 2 Hz, 1 H); IR 1770, 1745 cm^{-1}; MS m/e

(1) (a) E. M. Cranston, *J. Pharm. Exp. Ther.*, **83**, 130 (1945); (b) E. R. Plunkett and R. L. Noble, *Endocrin.*, **49**, 1 (1951); (c) E. M. Cranston and G. A. Robinson, *Proc. Soc. Exp. Biol. Med.*, **70**, 66 (1949); (d) W. R. Breneman, M. Carmack, D. E. Overack, R. O. Creek, and R. Shaw, *Endocrin.*, **67**, 583 (1960).

(2) (a) F. Kemper and A. Loeser, *Acta Endocrin.*, **29**, 525 (1958); (b) R. L. Noble, E. R. Plunkett, and R. C. B. Graham, *J. Endocrin.*, **10**, 212 (1954).

(3) (a) F. J. Zeller, W. R. Breneman, and M. Carmack, *Poul. Sci.*, **37**, 455 (1958); (b) W. R. Breneman, F. J. Zeller, M. Carmack and C. J. Kelley, *Gen. Comp. Endocrin.*, **28**, 24 (1976).

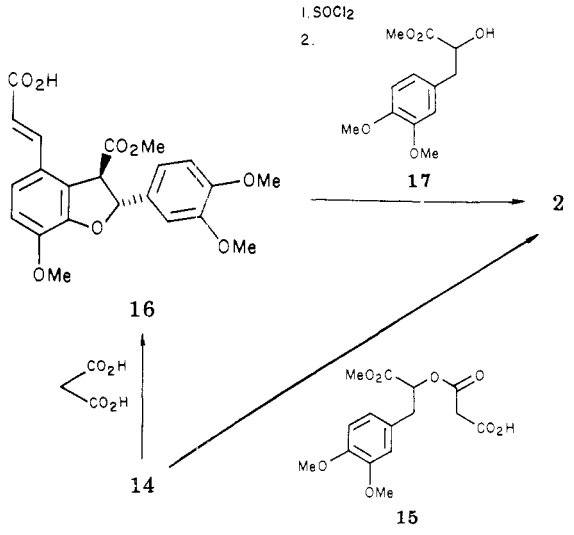
(4) C. J. Kelley, J. R. Mahajan, L. C. Brooks, L. A. Neubert, W. R. Breneman, and M. Carmack, *J. Org. Chem.*, **40**, 1804 (1975).

(5) H. Wagner, D. Wittman, and W. Schaffer, *Tetrahedron Lett.*, 547 (1975).

(6) F. Caesar and A. Mondon, *Chem. Ber.*, **101**, 990 (1968).

0022-3263/79/1944-4013$01.00/0 © 1979 American Chemical Society

Scheme III



280 (M^+). Jones' oxidation of **6** yielded the acid **7** (82%): mp 105 °C dec; ^1H NMR ($CDCl_3$) δ 2.03 (s, 3 H), 2.32 (s, 3 H), 3.72 (s, 2 H), 3.87 (s, 3 H), 5.15 (s, 2 H), 6.93 (d, J = 9 Hz, 1 H), 7.32 (d, J = 9 Hz, 1 H), 9.12 (br s, 1 H); IR 1755, 1730, 1710 cm^{-1}; MS m/e 296.093 (M^+). Removal of the acetates on **7** to obtain the diol acid **8** was accomplished in quantitative yield by treatment with methanolic sodium methoxide at 0 °C. Reaction of **8** with sodium acetate in refluxing acetic anhydride afforded a 78% yield of the desired benzopyranone **9**: mp 134–136 °C; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3 H), 3.54 (s, 2 H), 3.79 (s, 3 H), 5.23 (s, 2 H), 6.84 (d, J = 9 Hz, 1 H), 7.04 (d, J = 9 Hz, 1 H); IR 1745, 1735 cm^{-1}; MS m/e 236.069 (M^+). None of the isomeric benzofuranone, which would have resulted from lactonization of the acid with the phenolic oxygen, could be detected in the reaction mixture.

With a satisfactory synthesis of **9** in hand, we turned to the elaboration of **9** into the required dihydrobenzofuran ring system **14**. Piperidinium benzoate catalyzed condensation[7] of **9** with veratral afforded the aldol product **10** as a mixture of double bond isomers. Opening of the lactone ring in **10** was effected by heating with an excess of methanolic sodium methoxide, yielding the alcohol ester **11** (62%) as the E isomer exclusively: ^1H NMR ($CDCl_3$) δ 1.99 (br s, 1 H), 3.36 (s, 3 H), 3.73 (s, 3 H), 3.76 (s, 3 H), 3.83 (s, 3 H), 4.24 (d, J = 12 Hz, 1 H), 4.38 (d, J = 12 Hz, 1 H), 5.75 (br s, 1 H), 6.44 (d, J = 2 Hz, 1 H), 6.66 (d, J = 8.5 Hz, 1 H), 6.79 (dd, J = 2 and 8.5 Hz, 1 H), 6.88 (d, J = 8.5 Hz, 1 H), 6.99 (d, J = 8.5 Hz, 1 H), 7.86 (s, 1 H); IR 1703 cm^{-1}. Oxidation of the alcohol ester **11** with PCC[8] resulted in low yields of the desired E aldehyde **12**; however, oxidation using Me_2SO/oxallyl chloride[9] afforded a 78% yield of **12** accompanied by 14% of the methyl thiomethyl ether (**13**). The structure of **12** was supported by its ^1H NMR [($CDCl_3$) δ 3.39 (s, 3 H), 3.70 (s, 3 H), 3.76 (s, 3 H), 3.90 (s, 3 H), 5.95 (s, 1 H), 6.40 (d, J = 2 Hz, 1 H), 6.64 (d, J = 9 Hz, 1 H), 6.74 (dd, J = 2 and 9 Hz, 1 H), 6.94 (d, J = 8.5 Hz, 1 H), 7.57 (d, J = 8.5 Hz, 1 H), 7.97 (s, 1 H), 9.79 (s, 1 H)], IR (1705, 1690 cm^{-1}), and MS[m/e 372.122 (M^+)]. Cyclization of **12** with HBr in benzene/chloroform afforded a 67% yield of the *trans*-dihydrobenzofuran aldehyde **14**: ^1H NMR ($CDCl_3$) δ 3.74 (s, 3 H), 3.83 (s, 6 H), 3.94 (s, 3 H), 4.66 (d, J = 7 Hz, 1 H), 5.81 (d, J = 7 Hz, 1 H), 6.78 (d, J = 8.5 Hz, 1 H), 6.87 (d, J = 2 Hz, 1 H), 6.91 (dd, J = 2 and 8 Hz, 1 H), 6.94 (d, J = 8 Hz, 1 H), 7.38 (d, J = 8.5 Hz, 1 H), 9.75 (s, 1 H); IR 1730, 1680 cm^{-1}; MS m/e 372 (M^+). The trans stereochemistry was suggested by a lack of shielding of the 3-carbomethoxyl group by the 2-aryl substituent, which would be expected for *cis*-**14**.[10] Confirmation of the trans stereochemistry rests on the conversion of **14** to **2**.

Elaboration of **14** into heptamethyl lithospermate can be realized via two related methods (Scheme III). Knoevenagel condensation of **14** with the malonic acid monoester **15** (obtained in 70% yield from methyl 3,4-dimethoxyphenyllactate (**17**)[11] and Meldrum's acid[12]) afforded heptamethyl lithospermate (**2**) in modest yield. A more efficient procedure involves condensation of **14** with malonic acid resulting in the cinnamic acid **16** (75%). Acid chloride formation using thionyl chloride in benzene, followed by treatment with **17**, afforded **2** and its diastereomer in 50% yield: ^1H NMR ($CDCl_3$) δ 3.04–3.14 (m, 2 H), 3.69 (br s, 6 H), 3.79 (s, 3 H), 3.83 (br s, 9 H), 3.89 (s, 3 H), 4.41 (d, J = 5 Hz, 1 H), 5.25 (m, 1 H), 5.97 (d, J = 5 Hz, 1 H), 6.25 (dd, diastereomers, J = 2 and 16 Hz, 1 H), 6.66–6.89 (m, 7 H), 7.15 (dd, diastereomers, J = 3.5 and 8.5 Hz, 1 H), 7.68 (dd, diastereomers, J = 3 and 16 Hz, 1 H); IR (CCl_4) 1748, 1725, 1615, 1265, 1160, 1030, 980 cm^{-1}; MS m/e 636.219 (M^+, 12), 414 (43), 337 (65), 223 (23), 222 (100), 191 (17), 181 (57), 163 (13), 151 (90). The spectral data agree with those obtained by Wagner[5] on optically active heptamethyl lithospermate obtained by methylation of extracts of *Lithospermum officinale*.

Thus, an efficient route to the lithospermic acid system from readily available starting materials has been realized. Application of this general route toward the synthesis of lithospermic acid (**1**) is in progress, and will be reported in due course.[13]

Acknowledgment. This work was supported by Public Health Service Grant 1-R01-GM24856-01 and Biomedical Research Support Grant PHS S05 RR 7031. R.A.R. gratefully acknowledges fellowship support by the Lubrizol Corporation.

(7) C. F. H. Allen and F. W. Spangler, "Organic Synthesis", Collect. Vol. 3, Wiley, New York, 1955, p 377.
(8) E. J. Corey and J. W. Suggs, *Tetrahedron Lett.*, 2647 (1975).
(9) K. Omura and D. Swern, *Tetrahedron*, 34, 1651 (1978).
(10) S. P. Pappas, B. C. Pappas, and J. E. Blackwell, Jr., *J. Org. Chem.*, 32, 3066 (1967).
(11) E. A. Flexman, Ph.D. Dissertation, Indiana University, 1966.
(12) H. Junek, E. Ziegler, U. Herzog, and H. Kroboth, *Synthesis*, 332 (1976).
(13) ^1H NMR spectra were recorded on Varian T60-A and HR 220 spectrometers. Mass spectra were obtained at 70 eV on a Varian MAT CH-7, CEC 21-110, or a Hewlett-Packard 5992A GC/mass spectrometer. Infrared spectra were measured in $CHCl_3$ on a Perkin-Elmer Model 467 spectrophotometer. Compounds **2**, **4**, **7**, **9**, and **12** gave satisfactory high-resolution mass spectral and/or combustion analytical data, which were submitted for review.

Richard M. Jacobson,* Richard A. Raths
Department of Chemistry, Indiana University
Bloomington, Indiana 47405
Received June 4, 1979

Stereospecific Total Synthesis of (±)-Isocomene (Berkheyaradulene)

Summary: The unusual triquinane sesquiterpene **2** has been synthesized in eight steps from bicyclic enone **3** through utilization of three separate organometallic addition reactions suitably interspersed between hydrolytic and oxidative steps.

0022-3263/79/1944-4014$01.00/0 © 1979 American Chemical Society