over P_2O_5 in vacuo at room temperature to give 369 mg of powder (67.7% calculated from **6**). This compound does not have a clear melting point but slowly colorized above 150 °C: ^{1}H NMR (Me_2SO-d_6) δ 11.40 (br s, 1 H, NH), 8.44 (br s, 3 H, $NH_3^+Cl^-$), 7.94 (s, 1 H, H-6), 5.97 (t, 1 H, H-1', $J_{1',2'} = J_{1',2''} = 7.2$ Hz), 4.00 (m, 2 H, H-3',4'), 3.80 (m, 2 H, H-5',5''), 3.60 (br s, 1 H, 5'-OH), 2.66 (m, 1 H, H-2'), 2.00 (m, 1 H, H-2''), 1.81 (s, 3 H, 5-Me).

Anal. Calcd for $C_{10}H_{16}N_3O_4Cl\cdot0.5H_2O$: C, 41.89; H, 5.97; N, 14.66; Cl, 12.36. Found: C, 42.02; H, 5.67; N, 14.65; Cl, 12.07.

6,5'-Imino-5-deoxythymidine (18, R = H). A mixture of 5'-azido-5'-deoxythymidine[22] (100 mg) and LiN_3 (10 mg) in DMF (8 mL) was heated at reflux for 6 h, and then the solvent was removed in vacuo. **18** (R = H) was isolated by using preparative TLC (20 × 20 cm, CH_2Cl_2–EtOH 4:1) and crystallized from EtOH (64 mg, 71.5%): mp 226–227 °C dec; UV λ_{max} (H_2O) 291 nm (ϵ 18 400), λ_{max} (0.5 N HCl) 291 (ϵ 18 200), λ_{max} (0.5 N NaOH) 288 (ϵ 13 800); ^{1}H NMR (Me_2SO-d_6) δ 10.77 (br s, 1 H, NH), 6.80 (m, 1 H, H-1'), 6.08 (br d, bridgehead NH, spacing 6.4 Hz), 5.08 (d, 1 H, 3'-OH), 4.22 (m, 1 H, H-3'), 4.13 (s, 1 H, H-4'), 3.45 (m, 1 H, H-5' (this signal changed into a dd upon addition of D_2O), $J_{5',5''} = 13.9$, $J_{4',5'} = 2.4$ Hz), 2.97 (d, 1 H, H-5'', $J_{5',5''} = 13.9$ Hz), 2.50 (m, 2 H, H-2', H-2''), 1.71 (s, 3 H, 5-Me).

Anal. Calcd for $C_{10}H_{13}N_3O_4$: C, 50.21; H, 5.48; N, 17.56. Found: C, 50.03; H, 5.40; N, 17.36.

Treatment of 5'-*O*-tosylthymidine[23] (**16**) under similar conditions also afforded **18** (R = H).

6,5'-Imino-3'-*O*-acetyl-5'-deoxythymidine (18, R = Ac). **18** (R = H, 135 mg) was acetylated with Ac_2O (0.5 mL) in pyridine (5 mL) and crystallized from EtOH to give 55.5 mg (35%) of the acetate **18** (R = Ac): mp 273–275 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 10.84 (br s, 1 H, NH), 6.84 (m, 1 H, H-1'), 6.17 (br d, bridgehead NH, spacing 6.4 Hz), 5.15 (m, 1 H, H-3'), 4.36 (br s, 1 H, H-4'), 3.45–3.33 (m, 1 H, H-5', upon addition of D_2O, this signal became a dd, $J_{5',5''} = 13.4$, $J_{4',5'} = 2.5$ Hz), 3.03 (d, 1 H, H-5'', $J_{5',5''} = 13.4$ Hz), 2.35 (t, 2 H, H-2', H-2''), 2.04 (s, 3 H, OAc), 1.72 (s, 3 H, 5-Me).

Anal. Calcd for $C_{12}H_{15}N_3O_5$: C, 51.24; H, 5.38; N, 14.94. Found: C, 51.27; H, 5.33; N, 14.81.

Acknowledgment. We thank Dr. F. H. Field of the Mass Spectrometric Biotechnology Research Resource, Rockefeller University, for the mass spectrometry data and Mr. Marvin Olsen of this Institute for recording the ^{1}H NMR spectra. We are also indebted to Dr. J. H. Burchenal of this Institute for the preliminary tissue culture data.

Registry No. 1, 52450-18-7; 3, 42214-24-4; 5, 29706-84-1; 6, 66503-47-7; 7 (R = H), 73971-76-3; 7 (R = Ac), 73971-77-4; 8, 73971-78-5; 9, 73971-79-6; 9·HCl, 73971-80-9; 16, 7253-19-2; 17, 19316-85-9; 18 (R = H), 73971-81-0; 1-(3-azido-2,3-dideoxy-β-D-*threo*-pentofuranosyl)thymine, 73971-82-1; 18 (R = Ac), 73971-83-2.

(22) Horwitz, J. P.; Tomson, A. J.; Urbanski, J. A.; Chua, J. *J. Org. Chem.* **1962**, *27*, 3045.

(23) Reist, E. J.; Benitez, A.; Goodman, L. *J. Org. Chem.* **1964**, *29*, 554.

Total Synthesis of *dl*-3-Oxodiplophyllin and *dl*-Yomogin[1]

Drury Caine* and Gerard Hasenhuettl

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

Received February 25, 1980

The eudesman-8,12-olides *dl*-3-oxodiplophyllin (**1a**) and *dl*-yomogin (**1b**) have been totally synthesized. The enedione **2** was converted into the enedione ester **5** by formation of the enamine of the saturated ketone function, alkylation with ethyl bromoacetate, and hydrolysis. Reduction of **5** with K Selectride gave the 7β,8β-dihydro γ-lactone **3** steroselectively. Protection of the unsaturated carbonyl group in **3** by ketalization gave a mixture of double bond isomers. The γ-lactone functions of this mixture were converted into the corresponding α-methylene lactones by using the procedure of Grieco and Hiroi. Deketalization of this mixture gave *dl*-**1a**. Conversion of the ring A enone system of **1a** into the corresponding cross-conjugated dienone by oxidation with DDQ gave *dl*-**1b**.

A number of naturally occurring eudesman-8,12-olides having important biological properties[2] contain a 7β,8β cis-fused α-methylene lactone grouping. Total syntheses of *dl*-alantolactone,[3] *dl*-isoalantolactone,[4a,b] and *dl*-isotekelin,[4c] which are members of this class of compounds, have been reported. Herein we wish to report the total synthesis of *dl*-3-oxodiplophyllin (**1a**), which was isolated recently from the European liverwort *Chiloscyphus polyanthus* by Asakawa and co-workers,[5] and *dl*-yomogin (**1b**), which was isolated several years ago from *Artemisia princeps* Pamp by Geissman[6,7] (Chart I). A relay synthesis of yomogin from α-santonin has been published recently.[8]

The starting material for the syntheses of **1a** and **1b** was the known enedione **2**.[9] This compound was prepared by annelation of 2-methyl-4-(ethylenedioxy)cyclohexanone with ethyl vinyl ketone according to the procedure of Ross and Levine[10] followed by transketalization of the resulting octalone derivative with a catalytic amount of *p*-toluenesulfonic acid (PTSA) in acetone. The yield in the last step was significantly improved if the acid catalyst was neutralized before, rather than after,[9] the workup step. The conversion of the enedione **2** into the enone lactone **3** having a cis-fused 7β,8β-butanolide grouping was accomplished by the same general method as was used by Marshall, Cohen, and Hochstetler[3] for the synthesis of the corresponding 2-deoxy derivative. The saturated carbonyl group was selectively reacted with 1 equiv of pyrrolidine in benzene with the removal of water by azeotropic dis-

(1) This investigation was supported by Public Health Service Grant No. CA12193 from the National Cancer Institute.

(2) Rodriguez, E.; Towers, G. H. N.; Mitchell, J. C. *Phytochemistry* **1976**, *15*, 1573.

(3) Marshall, J. A.; Cohen, N.; Hochstetler, A. R. *J. Am. Chem. Soc.* **1966**, *88*, 3408.

(4) (a) Minato, H.; Horibe, I. *Chem. Commun.* **1965**, 531; *J. Chem. Soc. C* **1967**, 1575. (b) Miller, R. B.; Nash, R. D. *Tetrahedron* **1974**, *30*, 2961. (c) Miller, R. B.; Behare, E. S. *J. Am. Chem. Soc.* **1974**, *96*, 8102.

(5) (a) Asakawa, Y.; Toyota, M.; Takemoto, T.; Suire, C. *Phytochemistry* **1979**, *18*, 1007. (b) Naturally occurring 3-oxodiplophyllin is the enantiomer of structure **1a**.[5a] (c) Compound **1a** showed inhibitory activity toward germination and root elongation of rice husks.[5a] (d) The *ent*-3-deoxy derivative of **1a** exhibits activity against human epidermoid carcinoma (KB cell culture).[5c] (e) Ohta, Y.; Andersen, N. H.; Liu, C.-B. *Tetrahedron* **1977**, *33*, 617.

(6) Geissman, T. A. *J. Org. Chem.* **1966**, *31*, 2523.

(7) For a preliminary publication of this work, see: Caine, D.; Hasenhuettl, G. *Tetrahedron Lett.* **1975**, 743.

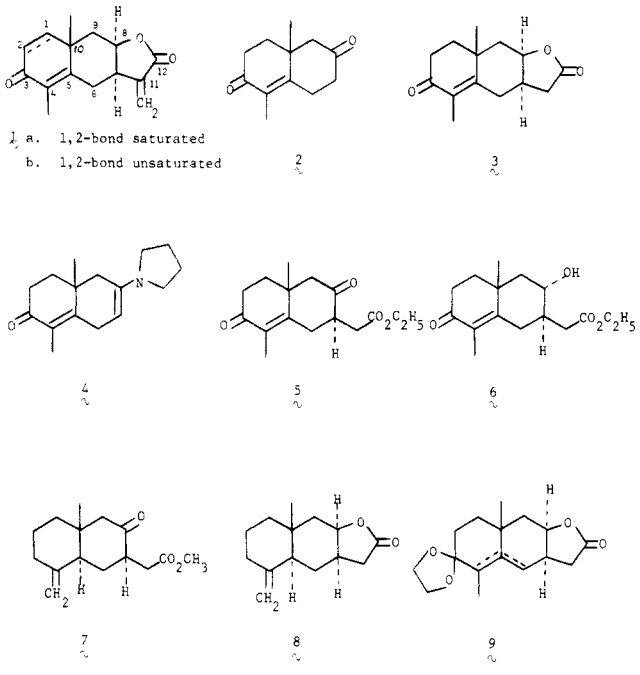
(8) Yamakawa, K.; Nishitani, K.; Yamamoto, A. *Chem. Lett.* **1976**, 177.

(9) Narang, S. A.; Dutta, P. C. *J. Chem. Soc.* **1960**, 2841.

(10) Ross, N. C.; Levine, R. *J. Org. Chem.* **1964**, *29*, 2341.

0022-3263/80/1945-3278$01.00/0

Chart I



tillation to give the enamine **4**. It was anticipated that formation of the enamine of the saturated carbonyl group would be favored kinetically. It was also felt that **4** might be more thermodynamically stable than the dienamine which would result from functionalization of the α,β-unsaturated carbonyl group because an interaction between the α-methyl group and the pyrrolidine ring methylene groups would exist in the latter substance. It may be worthwile to note that attempted conversion of the 4-normethyl derivative of **2** into the enamine corresponding to **4** was unsuccessful; only the starting material and polymeric material were recovered. Enamine **4** was not purified but was reacted in situ with ethyl bromoacetate to give the enedione ester **5** in 56% yield (based upon unrecovered starting material) from **2**.

The next step in the sequence required stereoselective reduction of the saturated carbonyl group in **5**. Marshall, Cohen, and Hochstetler[3] have shown previously that reduction of the 3-deoxy derivative of **5** with potassium borohydride in methanol occurred preferentially from the α side of the molecule to give an 8β-hydroxy derivative which cyclized spontaneously on workup to the corresponding cis lactone in 74% yield.

However, the reduction of **5** with potassium borohydride in methanol proved to be nonstereoselective and a ca. 1:1 mixture of the desired enone lactone **3** and another component, which on the basis of its spectroscopic properties (see Experimental Section) appeared to be the hydroxy ester **6**, were obtained. Surprisingly, we were unable to separate these two compounds by chromatographic methods, although the pure lactone **3** was isolated in ~25% yield by crystallization from ether. The ratio of **3** to **6** formed in the reduction reaction was determined directly by integration of the NMR spectrum of the mixture. It was felt that the stereoselectivity of the reduction in favor of **3** could be improved by using a bulkier reducing agent. Reduction of **5** with triisobutylaluminum[11] in benzene gave a mixture of **3** and **6** in a 7:3 ratio. However, as before, **3** could be isolated pure in only about 25% yield. Potassium tri-*sec*-butylborohydride (K Selectride, Aldrich Chemical Co.) proved to be the reagent of choice for the reduction. Upon treatment of **5** with 1.2 equiv of this reagent in tetrahydrofuran (THF) at −78 °C for 4 h, reduction of the saturated carbonyl group occurred almost exclusively from the α side of the molecule, and after workup and recrystallization of the crude product from diethyl ether, lactone **3** was obtained in 54% yield. In none of the runs with K Selectride was more than 5% of the hydroxy ester **6** present by integration of the NMR spectrum of the crude reduction product. Miller and Nash[4b] have recently carried out the conversion of the keto ester **7** to the cis γ-lactone **8** in high yield by using K Selectride as the reducing agent.

The completion of the synthesis of *dl*-3-oxodiplophyllin required the conversion of enone lactone **3** into the corresponding α-methylene lactone. There is a plethora of methods available for accomplishing transformations of this type.[13] From among these the method of Grieco and Hiroi[14] appeared to be quite suitable. The enone function in **3** was protected by preparing the ethylene ketal derivative by using the conditions described by Green, Ourisson, and Muller.[15] In order to obtain a reasonably good yield, we found it necessary to run the reaction on a relatively small scale (<1 g) and to add a small amount of pyridine to the reaction mixture prior to workup. Examination of the NMR spectrum of the crude ketal indicated that partial isomerization of the double bond had occurred and that a ca. 1:1 mixture of the 4,5 and 5,6 double bond isomers (cf. **9**) was produced. Treatment of the ketal mixture with lithium diisopropylamide (LDA) in THF at −78 °C followed by reaction of the lactone enolates with dry, gaseous formaldehyde and acidification gave a mixture of hydroxymethyl derivatives of **9**. These compounds were converted via the corresponding mesylate derivatives into the corresponding α-methylene lactones which were deketalized to produce *dl*-3-oxodiplophyllin (**1a**). The UV, IR, and NMR spectra of **1a** were identical with those of the natural product.[5,16] Oxidation of **1a** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dioxane converted it into the cross-conjugated dienone *dl*-yomogin (**1b**). The UV, IR, NMR, and mass spectral properties of **1b** were identical with those of an authentic sample of natural yomogin.[6,17] The synthetic and natural materials also exhibited the same R_f values on TLC.

Experimental Section[18]

Preparation of Enedione 2. Anhydrous diethyl ether (300 mL) was added to a solution of 22.5 g (0.40 mol) of KOH in 75

(11) (a) Ashby, E. C.; Yu, S. H. *J. Org. Chem.* **1970**, *35*, 1034. (b) Ashby, E. C.; Heinsohn, G. E. *Ibid.* **1973**, *38*, 4232. (c) Haubenstock, H.; Davidson, E. B. *Ibid.* **1963**, *28*, 2772. (d) Winterfeldt, E. *Synthesis* **1975**, 617.

(12) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.

(13) For recent reviews, see: (a) Grieco, P. A. *Synthesis* **1975**, 67. (b) Gammill, R. B.; Wilson, C. A.; Bryson, T. A. *Synth. Commun.* **1975**, *5*, 245.

(14) Greico, P. A.; Hiroi, K. *J. Chem. Soc., Chem. Commun.* **1972**, 1317.

(15) (a) Green, A. E.; Muller, J. C.; Ourisson, G. *Tetrahedron Lett.* **1971**, 4147. (b) Muller, J. C., personal communication. We thank Dr. Muller for this information.

(16) We are grateful to Professor Asakawa for copies of these spectra. We believe that the reported[5a] value of 1.5 Hz for the coupling constants for the *exo*-methylene protons of **1a** should actually be 2.8 Hz.

(17) We are grateful to Professor T. A. Geissman for providing us with a generous sample of natural yomogin for comparison purposes.

(18) Melting and boiling points are uncorrected. Infrared spectra were determined by using a Perkin-Elmer Model 457 infrared spectrophotometer. Ultraviolet spectra were measured by using a Beckman Model 25 recording spectrophotometer using 1-cm matched quartz cells. NMR spectra were determined at 60 MHz with a Varian T-60 spectrometer. Signals are reported in parts per million (δ) downfield from internal tetramethylsilane. Mass spectra were obtained by using a Hitachi Perkin-Elmer RMU-7 or a Varian M-66 spectrometer. Microanalyses were obtained by Atlantic Microlabs Inc.

mL of absolute ethanol, and the mixture was cooled to 0–5 °C under nitrogen in an ice–salt bath. 2-Methyl-4-(ethylenedioxy)cyclohexanone[19] (85 g, 0.5 mol) was added dropwise with stirring over a 15-min period, and the mixture was stirred for 45 min. A solution of 33.6 g (0.40 mol) of ethyl vinyl ketone in 250 mL of anhydrous ether was added dropwise with stirring over a 1-h period while the temperature was maintained at 0–5 °C. The mixture was allowed to warm to room temperature and stirred for 1 h. It was then poured onto 1000 g of ice, and the layers were separated. The aqueous layer was extracted with three 100-mL portions of ether, and the combined ether extracts were dried over anhydrous Na_2SO_4. The ether was removed in vacuo and the residue distilled to yield a forerun of the starting cyclohexanone derivative [bp 68–70 °C (0.5 mm)] and 61 g (65%) of 6,6-(ethylenedioxy)-1,10-dimethyl-1(9)-octalin-2-one, bp 136–138 °C (0.25 mm) [lit.[9] 140–142 °C (0.3 mm)].

A solution of 50 g (0.21 mol) of the above octalone in 800 mL of acetone containing 0.5 g of PTSA was heated at reflux under nitrogen for 18 h. The mixture was cooled to room temperature, and 3.0 g of solid $NaHCO_3$ was added. The solvent was removed under reduced pressure and the residue partitioned between 200 mL of benzene and 200 mL of water. The organic phase was separated and washed with three 100-mL portions of 5% aqueous $NaHCO_3$ and one 100-mL portion of water. The organic solution was dried over anhydrous $MgSO_4$ and the solvent removed in vacuo to give 30.5 g (75%) of **2**: mp 98–99 °C (lit.[9] 103–104 °C); UV (95% C_2H_5OH) 244 nm (ϵ 11 800); IR ($CHCl_3$) 1710 (saturated C=O), 1665 (α,β-unsaturated C=O), 1620 cm^{-1} (conjugated C=C); NMR (CCl_4) δ 1.24 (s, 3 H, angular CH_3), 1.75 (s, 3 H, vinyl methyl).

Preparation of Enedione Ester 5. A solution of 78.0 g (0.41 mol) of octalindione **2** in 1000 mL of benzene containing 40.0 g (0.45 mol) of freshly distilled pyrrolidine was heated at reflux under nitrogen in an apparatus fitted with a Dean–Stark trap for 16 h. At this point approximately 1 equiv of water had collected in the trap. The mixture was cooled to room temperature, and 83.5 g (0.5 mol) of ethyl bromoacetate was added slowly. The mixture was then heated at reflux for 36 h under nitrogen. A solution of 100 mL of 1% aqueous acetic acid was then added, and the mixture was stirred and heated at reflux for 1 h. The mixture was cooled to room temperature, and the phases were separated. The organic phase was washed with three 250-mL portions of 10% hydrochloric acid and one 100-mL portion of water. The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo. The unreacted portion of the starting material **2** was removed by triturating the residue with 100 mL of cold ether followed by filtration. The ether was removed from the filtrate in vacuo and the residue distilled to yield 19.0 g (56%, based upon unrecovered starting material) of the enedione ester **5**: bp 190–196 °C (0.2 mm); UV (95% C_2H_5OH) 241 nm (ϵ 12 000); IR (thin film) 1730 (saturated ester C=O), 1720 (saturated C=O), 1665 (α,β-unsaturated C=O), 1615 cm^{-1} (conjugated C=C); NMR (CCl_4) δ 1.21 (s, 3 H, angular CH_3), 1.21 (t, J = 7 Hz, 3 H, $OCH_2\mathbf{CH_3}$), 1.78 (s, 3 H, vinyl CH_3), 4.08 (q, J = 7.0 Hz, 2 H, $\mathbf{OCH_2}CH_3$); mass spectrum (70 eV), m/e (relative intensity) 278.1561 (14; EMC (exact mass calculated) = 278.1517), 232 (30), 190 (30), 58 (100), 43 (100), 15 (66).

Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.06; H, 7.91. Found: C, 68.83; H, 8.02.

Preparation of the Enone Lactone 3 by Reduction of the Enedione Ester 5. a. with Potassium Borohydride. A solution of 0.25 g (0.005 mol) of KBH_4 in 100 mL of anhydrous methanol was added dropwise over 30 min with stirring under nitrogen to a solution of 5.0 g (0.018 mol) of **5** at 5 °C. The mixture was stirred for 30 min at 5 °C and for 14 h at room temperature. The solvent was removed under reduced pressure, and the residue was partitioned between 50 mL of benzene and 50 mL of water. The organic layer was separated and washed with three 25-mL portions of a saturated solution of NaCl and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to give 2.5 g of a mixture containing the enone lactone **3** and what appeared from its spectral properties (see below) to be the hydroxy ester **6**. Crystallization of the residue from diethyl ether yielded 1.0 g (25%) of the enone lactone **3**: mp 115–117 °C; UV (95% C_2H_5OH) 243 mm (ϵ 10 300); IR ($CHCl_3$) 1775 (γ-lactone), 1663 (α,β-unsaturated C=O), 1620 cm^{-1} (conjugated C=C); NMR ($CDCl_3$) δ 1.30 (s, 3 H, angular CH_3), 1.78 (s, 3 H, vinyl CH_3), 4.63 (m, 1 H, >CHO); mass spectrum (70 eV), m/e (relative intensity) 234.1266 (100; EMC = 234.1241), 219 (66), 216 (58), 206 (61), 192 (87), 175 (69), 174 (69), 133 (86), 132 (61), 131 (72), 119 (56), 107 (55), 91 (52).

Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.79; H, 7.69. Found: C, 71.67; H, 7.75.

The solvent was removed from the mother liquor obtained above. The NMR spectrum of the residue in addition to the absorptions for **3** showed absorptions at δ 1.09 (s, angular CH_3), 1.16 (t, J = 7 Hz, $OCH_2\mathbf{CH_3}$), ~3.70 (br m, CHOH), and 4.20 (q, J = 7 Hz, $\mathbf{OCH_2}CH_3$). By integration of the quartet at δ 4.20 and the vinyl methyl signal at δ 1.78 for both **3** and **6** and the absorptions at δ 1.30 for **3** and at δ 1.09 for **6**, the **3**:**6** ratio in the crude reduction product was found to be ~1:1. Hydroxy ester **6** could not be obtained pure by column chromatography of the mixture on silica gel or alumina or by preparative TLC using 0.25-mm silica gel plates.

B. With Triisobutylaluminum. To a solution of 0.5 g (1.8 mmol) of the enedione ester **5** in 50 mL of dry benzene was added 1.8 mL of 1.11 M triisobutylaluminum in benzene under nitrogen at room temperature. The mixture was heated at reflux for 36 h. It was then cooled to room temperature, filtered, and washed with three 25-mL portions of 5% hydrochloric acid and one 25-mL portion of water. The organic phase was then dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo to give 0.4 g of residue. Integration of the NMR spectrum of this material revealed that it was a ca. 7:3 mixture of **3** and **6**. Lactone **3**, 100 mg (25%), was obtained by recrystallization of the residue from ether.

c. With Potassium Tri-*sec*-butylborohydride. A solution of 51 mL of 25.8 mmol of K Selectride (potassium tri-*sec*-butylborohydride, 0.5 M solution in THF, Aldrich Chemical Co.) was added dropwise with stirring over 30 min to a solution of 6.0 g (22.0 mmol) of enedione ester **5** in 150 mL of anhydrous THF at −78 °C under nitrogen. A deep purple color appeared soon after the addition was started. The solution was stirred at −78 °C for 4 h, and 18 mL of a 3 N solution of KOH was added with vigorous stirring. The mixture was exposed to the atmosphere and stirred for 4 h at room temperature. It was then poured into 80 mL of 3 N hydrochloric acid and stirred for 1 h. The volume of the mixture was reduced to about 100 mL in vacuo and the remaining material extracted with three 50-mL portions of benzene. The combined organic extracts were washed with three 25-mL portions of saturated NaCl and dried over anhydrous $MgSO_4$. Removal of the solvent gave 4.7 g of crude product whose NMR spectrum indicated that it contained less then 5% of hydroxy ester **6**. Recrystallization of this material from anhydrous ether gave 2.7 g (54%) of the enone lactone **3**.

Preparation of DL-3-Oxodiplophyllin (1a). A solution of g (4.3 mmol) of the enone lactone **3**, 10.3 g (0.166 mol) of ethylene glycol, and 30 mg of PTSA in 100 mL of dry benzene was heated at reflux at 14 h. The water which was produced in the reaction was collected in a Dean–Stark trap containing anhydrous K_2CO_3. The solution was cooled to room temperature, and 2 mL of pyridine and 4 g of $NaHCO_3$ were added. The benzene solution was then washed consecutively with 50 mL each of water, 5% aqueous $NaHCO_3$, and 10% aqueous NaCl. The organic phase was dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo to yield 1.1 g (90%) of a cream-colored solid which was a 1:1 mixture of the 4,5 and 5,6 double bond isomers of the ketal **9**: mp 162–169 °C; IR 1770 cm^{-1} (γ-lactone); NMR ($CDCl_3$) δ 5.13 (br s, $^1/_2$ H, vinyl H), 3.94 (s, 4 H, OCH_2CH_2O), 1.64 (s, 1.5 H, vinyl CH_3), 0.80 and 0.88 (s, 3 H, angular CH_3's); mass spectrum (70 eV), m/e 278.1504 (EMC = 278.1512).

To a solution of 0.0064 mol of LDA [prepared from 1 mL of diisopropylamine and 2.7 mL (0.0052 mol) of phenyllithium (in benzene)] in 200 mL of THF containing 30 mg of 2,2′-bipyridyl at −78°C under nitrogen was added dropwise with stirring 60 mL of a solution of 1.2 g of ketal lactone **9** in 10 mL of anhydrous THF. The solution was stirred for 30 min at −78 °C and allowed to warm to −20 °C. Gaseous formaldehyde, which was obtained by immersing a pyrolysis apparatus containing paraformaldehyde

(19) Lukes, R. M.; Poos, G. I.; Sarett, L. H. *J. Am. Chem. Soc.* **1952**, *74*, 1401.

in an oil bath preheated to 160 °C, was passed through the solution in a stream of nitrogen for 5 min. The color of the solution changed from brownish red to bright yellow during this period. Water (2 mL) was then added, the mixture was allowed to warm to room temperature, and the solvent was removed under reduced pressure. The residue was partitioned between 100 mL of ether and 50 mL of water, and the ether solution was washed with three 25-mL portions of saturated NaCl and dried over $MgSO_4$. Removal of the solvent in vacuo gave 1.1 g (85%) of the hydroxymethyl derivatives of **9**: IR ($CHCl_3$) 3450 (OH), 1757 cm^{-1} (H-bonded γ-lactone).

To a solution of 1 g (3.2 mmol) of the hydroxymethyl derivatives of **9** in 25 mL of dry pyridine at 0 °C was added 0.7 g (6 mmol) of methanesulfonyl chloride with stirring under nitrogen. The mixture was then heated at reflux for 6 h. The pyridine was removed under reduced pressure and the residue partitioned between 50 mL of ether and 25 mL of water. The ether solution was washed with three 25-mL portions of saturated NaCl and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo gave 0.69 g (74%) of the α-methylene derivatives of **9** as a dark oil: IR (thin film) 1761 (conjugated γ-lactone), 1622 cm^{-1} (conjugated C=C); NMR ($CDCl_3$) δ 6.14 and 5.61 (2 d, J = 2.0 Hz, 1 H each, $=CH_2$), 5.11 (m, 0.5 H, vinyl H), 4.70 (m, 1 H, >CHO), 3.86 (s, 4 H, OCH_2CH_2O), 1.15 (s, 3 H, angular CH_3's).

A solution of 0.54 g (1.8 mol) of the α-methylene derivatives of **9** in 75 mL of dry acetone containing 50 mg of PTSA was heated at reflux under nitrogen for 12 h. The solution was cooled to room temperature, 0.5 g of solid $NaHCO_3$ was added, and the acetone was removed under reduced pressure. The residue was partitioned between ether and water and worked up in the usual way. The crude product was then chromatographed on a column containing 20 g of Florisil. Elution with 30–50% $CHCl_3$/benzene gave 200 mg (45%) of *dl*-3-oxodiplophyllin (**1a**): mp 168–169 °C; UV (95% C_2H_5OH) 246 nm (ε 14 500); IR ($CHCl_3$) 1764 (α,β-unsaturated γ-lactone C=O), 1660 (α,β-unsaturated (C=O), 1625 cm^{-1} (conjugated C=C); NMR δ 1.25 (s, 3 H, angular CH_3), 1.83 (br s, 3 H, vinyl CH_3), 4.64 (m, 1 H, >CHO), 6.40 and 5.78 (2 d, J = 2.8 Hz, 1 H each, $=CH_2$; mass spectrum (70 eV), m/e (relative intensity) 246.1245 (100; EMC = 246.1255); 204 (68), 108 (60), 93 (42), 91 (61), 79 (45), 77 (44), 53 (50), 41 (47). These spectral properties were in close agreement with those reported by Asakawa and co-workers[5,16] for natural 3-oxodiployphyllin.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.03; H, 7.36.

***dl*-Yomogin (1b).** A solution of 160 mg (0.65 mmol) of the α-methylene lactone **1a** in 30 mL of dry dioxane (freshly distilled from sodium metal) containing 160 mg (0.71 mmol) of DDQ was heated at reflux with stirring under nitrogen for 18 h. The mixture was cooled to room temperature and filtered, and the solvent was removed in vacuo. The residue was dissolved in 50 mL of benzene, and the solution was extracted with four 25-mL portions of 1% aqueous NaOH and one 25-mL portion of water. The organic phase was dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure. The residue was recrystallized from diethyl ether to give 100 mg (62%) of *dl*-yomogin (mp 170–172 °C) with IR, NMR, and mass spectral properties identical with those of an authentic sample.[6,17] The synthetic and natural material also showed identical R_f values on TLC in ether, chloroform, and benzene.

Registry No. (±)-**1a**, 56393-93-2; (±)-**1b**, 56393-94-3; (±)-**2**, 56393-88-5; (±)-**3**, 56393-91-0; (±)-**5**, 73986-30-8; (±)-**6**, 73986-31-9; **9** (4,5-ene), 56393-92-1; (±)-**9** (5,6-ene), 56393-95-4; **9** (hydroxymethyl derivative), 73986-39-7; **9** (α-methylene derivative), 56396-20-4; (±)-2-methyl-4-(ethylenedioxy)cyclohexanone, 54316-77-7; ethyl vinyl ketone, 1629-58-9; 6,6-(ethylenedioxy)-1,10-dimethyl-1(9)-octalin-2-one, 13944-80-4; ethyl bromoacetate, 105-36-2.

Stereospecific Total Synthesis of the Potent Synthetic Pyrethroid NRDC 182[1]

Charles E. Hatch III* and Jonathan S. Baum

Agricultural Chemicals Research Group, FMC Corporation, Princeton, New Jersey 08540

Toshiyuki Takashima and Kiyosi Kondo

Sagami Chemical Research Center, Sagamihara, Kanagawa 229, Japan

Received February 1, 1980

A highly stereospecific synthesis of (1*R*,3*R*)-*cis*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid was devised which allowed for a total synthesis of the potent synthetic pyrethroid insecticide (*S*)-cyano-(3-phenoxyphenyl)methyl (1*R*,3*R*)-*cis*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate (NRDC 182). Asymmetric reduction of 1,1,1-trichloromesityl oxide with an LAH–ephedrine complex produced (2*R*)-1,1,1-trichloro-2-hydroxy-4-methylpent-3-ene which was transformed to a diazoacetate ester via the corresponding diazoacetoacetate. Copper-catalyzed thermal decomposition of the diazoacetate resulted in internal carbenoid cyclization onto the olefin in nearly quantitative stereoselectivity. The resultant bicyclic lactone was ring opened via a Boord-type reaction to give the requisite cyclopropane acid which was esterified with racemic 3-phenoxybenzaldehyde cyanohydrin followed by crystallization and epimerization of the mother liquor to produce NRDC 182.

Since the discovery in the early seventies of the photostable and highly active synthetic pyrethroid permethrin, **1a** (Table I), by Elliott et al.,[2] synthetic pyrethroids have emerged as a new and important class of agricultural insecticides. They combine both low mammalian toxicity and biodegradibility with high activity against a large number of insect types, including the important Lepidoptera cotton pests.

Subsequent to Elliott's initial report, a number of even more active materials have been found, including decamethrin[4] (**1b**) and its dichloro analogue NRDC 182 (**1c**). While esters **1b** and **1c** are both highly potent insecticides, **1c** offers the advantage of being more stable chemically and significantly less toxic to mammals. Our recent in-

(1) (a) Presented in part at the 177th National Meeting of the American Chemical Society, Honolulu, Hawaii, Apr 1979, No. PEST 103 (C. Hatch). (b) For a communication on earlier related work see: K. Kondo, T. Takashima, and D. Tunemoto, *Chem. Lett.*, 1185 (1979).

(2) M. Elliott, A. Farnham, N. Janes, R. Needham, D. Pulman, and J. Stevenson, *Nature (London)*, **246**, 169 (1973).

(3) Average topical data against several Lepidopterous insects relative to permethrin.

(4) M. Elliott, A. Farnham, N. Janes, R. Needham, and D. Pulman, *Nature (London)*, **248**, 710 (1974).

0022-3263/80/1945-3281$01.00/0