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A SHORT SYNTHESIS OF ANCEPSENOLIDE

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ABSTRACT.—The synthesis of ancepsenolide (**1**) has been achieved using the alkylation of 5-methyl-3-(phenylthio)dihydro-2(3*H*)-furanone (**3**) with 12-bromododecanol to give 3-(12-hydroxydodecyl)-5-methyl-3-(phenylthio)-dihydro-2(3*H*)-furanone (**4**) as the key intermediate. The most efficient synthetic route gave ancepsenolide (**1**) from **3** in two steps by oxidation of the phenylthio moiety with sodium periodate followed by alkylation with 1,12-dibromododecane and thermal elimination of the phenylsulfinyl substituents.

During the past few years, several examples of cytotoxic linear C_{34} acetogenins containing a bistetrahydrofuran ring system have been reported (1-4). One characteristic feature of these naturally occurring acetogenins is the presence of a γ-methyl-γ-butyrolactone (5-methyl-2-furanone) moiety as either a butenolide or a butanolide linked to the bistetrahydrofuran system by a 13- or 14-carbon chain. As part of a synthetic approach to this class of acetogenins, it was desirable to alkylate γ-valerolactone with a functionalized 12-carbon chain to provide an intermediate, that could undergo further reaction at the chain terminus and be converted into either a butenolide or a butanolide. Alkylation of 5-methyl-3-(phenylthio)dihydro-2(3H)-furanone (**3**) with 12-bromododecanol formed **4** (Scheme 1), the desired key intermediate in this synthetic route. The structure of **4** suggested that it might also be a useful precursor for the synthesis of ancepsenolide (**1**), a bisbutenolide isolated from the gorgonians *Pterogorgia anceps* and *Pterogorgia guadalypensis* (5,6).

RESULTS AND DISCUSSION

The key feature of the synthesis of ancepsenolide (**1**) (Scheme 1) involves the alkylation of 5-methyl-3-(phenylthio)dihydro-2(3*H*)-furanone (**3**). The use of the phenylthio moiety not only activates the lactone ring for alkylation but also provides a suitable functional group for later elimination to form the double bond of the butenolide ring of ancepsenolide (**1**). Reaction of γ-valerolactone (**2**) with lithium diisopropylamide (LDA) in hexamethylphosphoramide (HMPA), followed by the addition of diphenyl disulfide resulted in a 52% yield of 5-methyl-3-(phenylthio)dihydro-2(3*H*)-furanone (**3**) as a mixture of diastereomers in an approximate ratio of 1:1 (7,8). Since the phenylthio moiety is eliminated in a later step, the diastereomers of **3** were not separated, and the mixture was used in the alkylation. This alkylation was most conveniently conducted by mixing **3** with five equivalents of 12-bromododecanol in HMPA followed by the addition of 6.2 equivalents of LDA at 0°, to give 3-(12-hydroxydodecyl)-5-methyl-3-(phenylthio)dihydro-2(3*H*)-furanone (**4**) in 70% yield. When only one equivalent of 12-bromododecanol was used, a significantly lower yield (50%) of **4** was obtained. In addition, if the reaction was conducted at a lower temperature (−78°), no alkylated product was obtained.

Bromination of **4** with carbon tetrabromide and tri-*n*-octyl phosphine followed by heating at 60° for 30 min gave 3-(12-bromododecyl)-5-methyl-3-(phenylthio)dihydro-2(3*H*)-furanone (**5**) in 47% yield (9). Although brominations of this type are normally carried out at room temperature or below, heat is required in this case for bromination to occur. Alternatively, **5** could be obtained directly from **3** in 71% yield by the alkyla-

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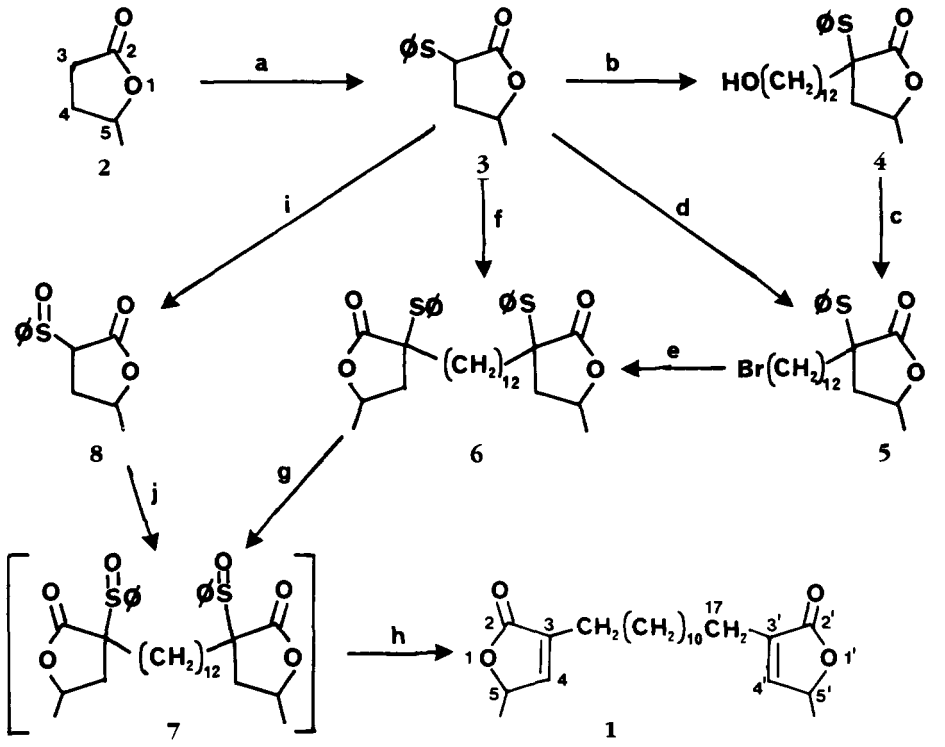

SCHEME 1.

a. LDA, $C_6H_5SSC_6H_5$, HMPA, −25°; **b**. LDA (6.2 equiv.), $HO(CH_2)_{12}Br$ (5.0 equiv.), HMPA, 0°; **c**. CBr_4, $(C_8H_{17})_3P$, 60°, 30 min; **d**. LDA, $Br(CH_2)_{12}Br$ (5.0 equiv.), HMPA, 0°; **e**.. LDA, **3**, HMPA, 0°; **f**. LDA, $Br(CH_2)_{12}Br$ (0.5 equiv.), HMPA, 0°; **g**. $NaIO_4$ (5.0 equiv.), MeOH, H_2O; **h**. $CH_3C_6H_5$, 120°; **i**. $NaIO_4$ (2.4 equiv.), MeOH, H_2O; **j**. LDA, $Br(CH_2)_{12}Br$ (0.5 equiv.), HMPA, 0°.

tion of **3** with five equivalents of 1,12-dibromododecane in the presence of LDA. Alkylation of the lithium enolate of **3**, prepared from the reaction of **3** and LDA, with **5** then gave **6**, the precursor to ancepsenolide (**1**), in 33% yield. A more efficient approach to **6** was the simultaneous alkylation of two equivalents of **3** with one equivalent of 1,12-dibromododecane. This procedure gave 3-{12-[5-methyl-3-(phenylthio)-dihydro-2(3H)-furanone-3-yl]dodecyl}-5-methyl-3-(phenylthio)-dihydro-2(3H)-furanone (**6**) directly in 61% yield.

Oxidation (7,8) of **6** with sodium periodate, followed immediately by thermolysis in refluxing toluene, yields ancepsenolide (**1**) (60%), presumably via **7**. However, incomplete oxidation of **6** was observed even when a large excess of sodium periodate was used, and the yield could not be increased above 60%. To determine if the problem with this oxidation was limited to **6**, the oxidation of **3** with sodium periodate was examined. In this case, however, the quantitative oxidation of **3**, to yield 5-methyl-3-(phenylsulfinyl)-dihydro-2(3*H*)-furanone (**8**), occurs when 2.4 equivalents of sodium periodate are used. If less than 2.4 equivalents are used, incomplete oxidation is again observed.

In an attempt to surmount the problem of incomplete oxidation of **6** and to take advantage of the quantitative oxidation of **3**, **8** was alkylated with 0.5 equivalents of 1,12-dibromododecane in the presence of LDA, followed immediately by thermolysis in refluxing toluene. Ancepsenolide (**1**) was obtained in 40% yield. In this case, the low yield of ancepsenolide (**1**) results from incomplete bisalkylation, not incomplete thermolysis of **7**. This conclusion is supported by the identification of 3-(12-

bromododecyl)-5-methyl-3-(phenylsulfinyl)dihydro-2(3*H*)-furanone, resulting from monoalkylation, and β-angelic lactone, resulting from thermal elimination of the phenylsulfoxide moiety of **8**, in the reaction mixture.

In each case, the synthetic ancepsenolide (**1**) was compared by tlc retention time and spectral comparisons with an authentic sample and was found to be identical. Although the yields were not finally optimized, the shortest route (**2**→**3**→**8**→**1**) provided the best overall yield (20.8%) of ancepsenolide (**1**), and has the potential to provide sufficient material and derivatives for further work.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Infrared spectra were recorded on a Perkin-Elmer 735B spectrophotometer. ^{1}H- and ^{13}C-nmr spectra were recorded on Varian XL-300 or Bruker WP80 spectrometers with TMS as the internal standard. Radial chromatography was conducted with a Harrison Research Model 7924 chromatotron using a 4-mm plate with silica gel 60 GF 254 (EM Labs) as the adsorbent. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected.

5-METHYL-3-(PHENYLTHIO)DIHYDRO-2(3*H*)-FURANONE (**3**).—To a solution of 0.11 mol of LDA in 140 ml THF-hexane (1:1) at −78° was added 10.0 g (0.10 mol) of γ-valerolactone (**2**) in 50 ml of THF and 19 ml of HMPA. The solution ws stirred for 15 min at −78°, then warmed to −25°, followed by addition of 24.0 g (0.11 mol) of diphenyl disulfide in 50 ml of THF. This mixture was stirred at −25° for 1 h followed by 6 h at room temperature. The solution was diluted with 300 ml of Et_2O and quenched with saturated NH_4Cl. The organic layer was washed with saturated NH_4Cl, saturated $NaHCO_3$,H_2O, dried over concentrated $MgSO_4$, and concentrated. The liquid residue was purified by flash chromatography on silica gel eluted with 10% EtOAc/hexane followed by 30% EtOAc/hexane to yield 10.9 g **3** (52%) (oil); ir (film) ν max 1770 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 7.68-7.23 (m, 5H, C_6H_5), 4.80-4.25 (m, 1H, H-5), 4.22-3.75 (m, 1H, H-3), 3.00-1.50 (m, 2H, H-4), 1.37, 1.34 (2d, J=6.7 Hz, 3H, 5-CH_3).

3-(12-HYDROXYDODECYL)-5-METHYL-3-(PHENYLTHIO)DIHYDRO-2(3*H*)-FURANONE (**4**).—To a mixture containing 100 mg (0.48 mmol) of **3** and 640 mg (2.4 mmol) of 12-bromododecanol in 2 ml of HMPA chilled to 0° was added a solution of 3 mmol LDA in 2 ml of HMPA-hexane (1:9). This mixture was stirred at 0° for 45 min, then diluted with Et_2O and quenched with saturated NH_4Cl. The organic layer was washed with saturated NH_4Cl, H_2O, dried over anhydrous $MgSO_4$, and concentrated. The liquid residue was purified by radial ptlc (20% EtOAc/hexane) to yield 130 mg **4** (70%) (oil); ir (film) ν max 3350, 1755 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 7.72-7.27 (m, 5H, C_6H_5), 4.75-4.25 (m, 1H, H-5), 3.78-3.52 (m, 2H, H-17), 2.67-1.13 (m, 28H, OH, H-6-16, H-4, 5-CH_3); ms *m/z* 392 (M^+). *Anal.* calcd. for $C_{23}H_{36}O_3S$: C, 70.36, H, 9.24, S, 8.17. Found: C, 70.23, H, 9.17, S, 7.92.

3-(12-BROMODODECYL)-5-METHYL-3-(PHENYLTHIO)DIHYDRO-2(3*H*)-FURANONE (**5**).—*Method 1.*—To a solution of **4** (100 mg, 0.26 mmol) and CBr_4 (170 mg, 0.51 mmol) in 0.4 ml of Et_2O at room temperature was added 190 mg (0.51 mmol) of tri-*n*-octyl phosphine in 0.4 ml Et_2O. The solution was stirred for 15 min at room temperature followed by evaporation of the solvent under reduced pressure. The resulting liquid was heated to 60° for 30 min. The liquid was purified by column chromatography on neutral alumina eluted with 10% EtOAc/hexane to yield 55 mg **5** (47%) (oil); ir (neat) ν max 1760 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 7.65-7.25 (m, 5H, C_6H_5), 4.75-4.25 (m, 1H, H-5), 3.40 (t, J=7 Hz, 2H, H-17), 2.65-1.07 (m, 27H, H-6-16, H-4, 5-CH_3), ms *m/z* 456 (M^++1). *Anal.* calcd. for $C_{23}H_{35}BrO_2S$: C, 60.66, H, 7.75, Br, 17.54, S, 7.03. Found: C, 60.96, H, 7.96, Br, 17.33, S, 7.08.

Method 2.—To a solution of 2.6 mmol of LDA in 2.2 ml HMPA-hexane (1:3) at 0° was added 500 mg (2.4 mmol) of **3** in 1 ml of HMPA. The solution was stirred for 15 min at 0° and then added to a mixture of 1,12-dibromododecane (4.0 g, 12 mmol) in HMPA at 0°. The mixture was stirred at 0° for 2 h, then diluted with Et_2O and quenched with saturated NH_4Cl. The organic layer was washed with saturated NH_4Cl, H_2O, dried over anhydrous $MgSO_4$, and concentrated. The semisolid material was purified by flash chromatography on silica gel eluted with 10% EtOAc/hexane followed by radial ptlc (10% EtOAc/hexane) to yield 775 mg **5** (71%) (oil), identical to **5** prepared by Method 1.

3-{12-[5-METHYL-3-(PHENYLTHIO)DIHYDRO-2(3*H*)-FURANONE-3-YL-]DODECYL}-5-METHYL-3-(PHENYLTHIO)DIHYDRO-2(3*H*)-FURANONE (**6**).—*Method 1.*—To a solution of LDA (0.6 mmol) in 0.6 ml of HMPA-hexane (1:2) at 0° was added 115 mg (0.55 mmol) of **3** in 0.3 ml of HMPA. The mixture was stirred at 0° for 15 min, then added to a solution of **5** (250 mg, 0.55 mmol) in 0.2 ml of HMPA at 0°. The solution was stirred at 0° for 1 h, followed by 3 h at room temperature. The solution was diluted with Et_2O

and quenched with saturated NH_4Cl. The organic layer was washed with saturated NH_4Cl, H_2O, dried over anhydrous $MgSO_4$, and concentrated. The resulting liquid was purified by radial ptlc (10% EtOAc/hexane) to yield 105 mg **6** (32%) (oil); ir (film) ν max 1769 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.63-7.20 (m, 10H, C_6H_5), 4.75-4.25 (m, 2H, H-5, H-5'), 2.62-1.00 (m, 34H, H-6-17, H-4, H-4', 5-CH_3, 5'-CH_3); ms *m/z* 582 (M^+). *Anal.* calcd. for $C_{34}H_{46}O_4S_2$: C, 70.06, H, 7.96, S, 11.20. Found: C, 69.99, H, 8.03, S, 11.14.

Method 2.—To a solution of LDA (2.6 mmol) in 2.2 ml of HMPA-hexane (1:3) at 0° was added 500 mg (2.4 mmol) of **3** in 1 ml of HMPA. The solution was stirred for 15 min at 0°, followed by the addition of 400 mg (1.2 mmol) of 1,12-dibromododecane in 2.5 ml of HMPA. The mixture was stirred at 0° for 1 h, followed by 2 h at room temperature. The solution was diluted with Et_2O and quenched with saturated NH_4Cl. The organic layer was washed with saturated NH_4Cl, H_2O, dried over anhydrous $MgSO_4$, and concentrated. The resulting liquid was purified by radial ptlc (20% EtOAc/hexane) to yield 430 mg **6** (61%) (oil), identical to the **6** prepared by Method 1.

5-METHYL-3-(PHENYLSULFINYL)DIHYDRO-2(3*H*)-FURANONE (**8**).—To a solution of 100 mg (0.48 mmol) of **3** in 4 ml of MeOH at 0° was added 247 mg (1.15 mmol) of $NaIO_4$ in 2 ml of H_2O. The solution was stirred for 5 min at 0° followed by 24 h at room temperature. The mixture was filtered, and the solvent was evaporated under reduced pressure. The residue was dissolved in Et_2O, dried over anhydrous $MgSO_4$, and concentrated to yield 104 mg (100%) of **8** as a semisolid material; ir (film) ν max 1750, 1055 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.87-7.42 (m, 5H, C_6H_5), 5.12-3.50 (m, 2H, H-3, H-5), 3.12-1.12 (m, 5H, H-4, 5-CH_3).

ANCEPSENOLIDE (**1**).—*Method 1.*—To a solution of **6** (150 mg, 0.26 mmol) in 5 ml of MeOH at 0° was added 388 mg (1.79 mmol) of $NaIO_4$ in 3 ml of H_2O. The solution was stirred at 0° for 10 min, then at room temperature for 27 h. The mixture was filtered, and the solvent was evaporated under reduced pressure. The residue was dissolved in Et_2O, dried over anhydrous $MgSO_4$, and concentrated to yield 180 mg of a semisolid material. This material was dissolved in 10 ml of toluene and heated at reflux for 45 min. The solvent was evaporated under reduced pressure to yield a semisolid material which was crystallized from $CHCl_3$/hexane to yield 56 mg **1** (60%), mp 90-92° [lit (5,6) 90.5-92°]; ^{13}C nmr ($CDCl_3$) 174.0 (C-2, C-2'), 148.9 (C-3, C-3'), 134.3 (C-4, C-4'), 77.2 (C-5, C-5'), 29.6, 29.5, 29.4, 29.3, 29.2, 27.4, 25.2 (C-6-17), 19.2 (5-CH_3, 5'-CH_3).

Method 2.—To a solution of 0.35 ml (2.46 mmol) of diisopropylamine in 0.5 ml of HMPA under nitrogen and at 0° was added 1.54 ml (2.46 mmol) of 1.6 M *n*-butyllithium in hexane. The solution was stirred at 0° for 15 min. To the solution of LDA was added 500 mg (2.23 mmol) of **8** in 1 ml of HMPA. The solution was stirred at 0° for 15 min followed by the addition of 370 mg (1.12 mmol) of 1,12-dibromododecane in 2.5 ml of HMPA. The resulting solution was stirred at 0° for 3 h followed by 1 h at room temperature. The solution was diluted with Et_2O and quenched with saturated NH_4Cl. The organic layer was washed with saturated NH_4Cl, H_2O, dried over anhydrous $MgSO_4$, and concentrated to give 474 mg of an oil. The oil was dissolved in 15 ml of toluene and heated at reflux for 1.5 h. Evaporation of the solvent under reduced pressure yielded a semisolid residue which was crystallized from $CHCl_3$/hexane to give 160 mg **1** (39%), identical with the **1** prepared from Method 1.

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