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Synthesis of 2-Dodecanoyl-3,5-dihydroxy-2-cyclohexen-1-one

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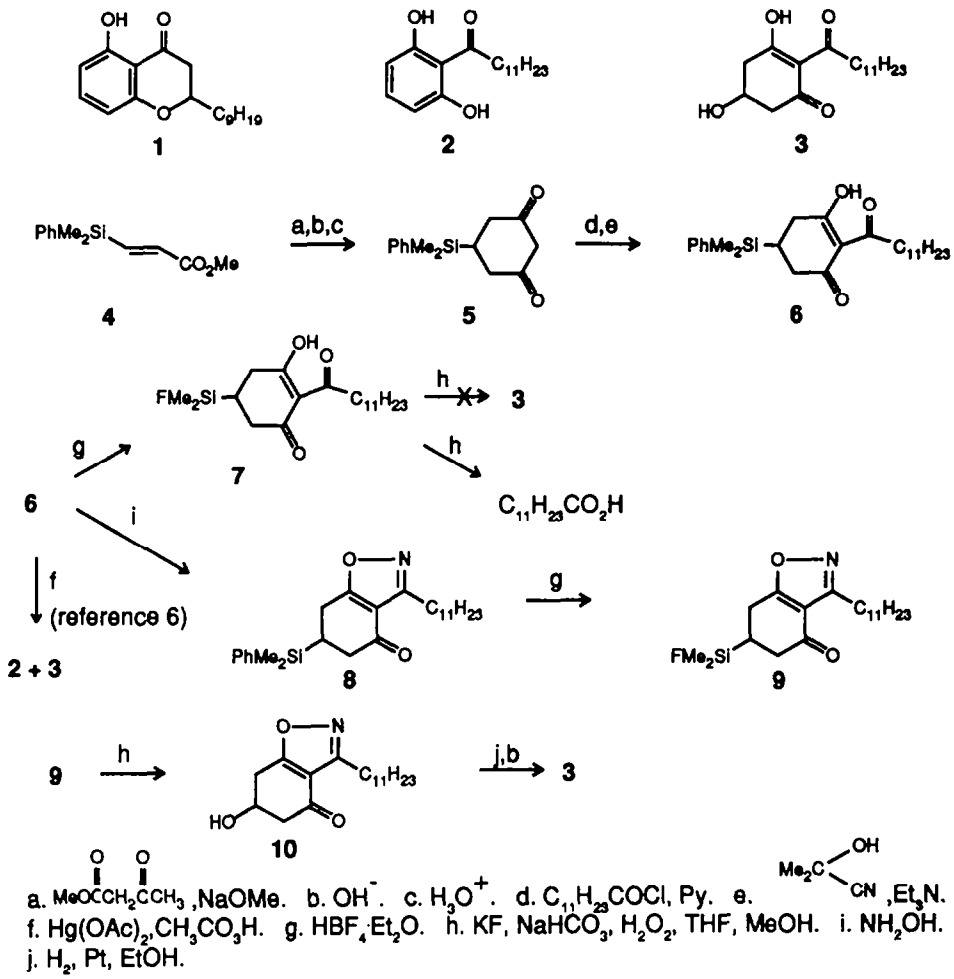
Abstract. 2-Dodecanoyl-3,5-dihydroxy-2-cyclohexen-1-one, identified from the setal exudate of immature andromeda lace bug nymphs, *Stephanitis takeyai*, was synthesized. Key steps involved construction of the cyclohexanedione ring containing a phenyldimethylsilyl substituent as a masked hydroxyl group, protection of the 1,3-dicarbonyl system as an isoxazole, oxidative desilylation, and reductive disassembly of the isoxazole.

For several years we have been interested in compounds secreted by lace bugs of the genus *Stephanitis*[1,2] and of the genus *Corythucha*[3,4]. From the latter we have identified 2-acyl-3,6-dihydroxycyclohex-2-en-1-ones[3,4], and have also recently reported the first synthesis of that novel class of compounds[5]. Continuing our investigations into the *Stephanitis* genus, we examined the andromeda lace bug, *S. takeyai*, and identified three major components of its exocrine secretion as the chromanone **1**, the 2,6-dihydroxyalkanophenone **2**, and the novel 2-dodecanoyl-3,5-dihydroxycyclohex-2-en-1-one **3**[6]. We here report a synthesis of **3**, undertaken to confirm the structural assignment and to provide sufficient material to evaluate its properties.

Compound **3** is the enol of a 2-acylcyclohexan-1,3-dione. We were unable to find literature precedent for a 5-hydroxycyclohexan-1,3-dione, with or without a 2-substituent. As a β-hydroxyketone, **3** would be expected to be subject to facile dehydration; whether the aromaticity gained in this case (**3** → **2**) would further promote the elimination of water was a subject of conjecture. In any event, we sought a synthetic pathway wherein the basic system would be constructed with the 5-position occupied by a group that was itself a poor leaving group but that could at an appropriate time be converted to, or replaced by, OH. Fleming and coworkers have recently described the use of the phenyldimethylsilyl group for this purpose; oxidative cleavage of the C-Si bond results in the overall replacement of $PhMe_2Si$ by OH[7-9].

Methyl (E)-3-(phenyldimethylsilyl)acrylate[10] (**4**, Scheme 1) reacted slowly but smoothly with methyl acetoacetate and sodium methoxide[11]. Successive treatment with OH^- and H_3O^+ achieved saponification and decarboxylation, respectively, without isolation of intermediates (insufficient water in the MeOH-H_2O medium during the latter step results in a considerable quantity of the methyl enol ether of **5**). The ^{1}H-NMR spectrum of **5** was complex when recorded in $CDCl_3$ (a mixture of keto and enol forms of a 5-arylcyclohexane-1,3-dione was observed by ^{1}H-NMR[12]), but was more easily interpretable when recorded in deuteropyridine (complete enolization). Enol esterification of **5** with dodecanoyl chloride proceeded smoothly, as did the CN^- catalyzed rearrangement[13] to give the 2-acyl derivative **6**.

Our initial attempts to oxidatively desilylate **6** to **3** with mercuric acetate and peracetic acid[7] had met with limited success: enough success to confirm the identity of **3** with the natural product, but too little to be synthetically useful[6]. In general, conditions vigorous enough to desilylate **6** also led to its oxidative degradation



Scheme 1

with side chain cleavage and generation of dodecanoic acid.

We therefore pursued the two step approach, **6**→**7**→**3** (Scheme 1). Fluoroboric acid etherate[8] converted **6** to the fluorodimethylsilane **7** which was a stable white solid. Attempted oxidative desilylations of **7** under a variety of conditions[14,15], however, were unsuccessful, with cleavage occurring and dodecanoic acid again being the only identifiable product.

Protection of the 1,3-dicarbonyl system as an isoxazole derivative had been useful during our synthesis of an isomer of **3**[5], and proved equally beneficial in the present case. One equivalent of hydroxylamine converted **6** to **8** which was converted to the fluorodimethylsily compound **9** with $HBF_4 \cdot Et_2O$. (Again we chose the two step (**8** → **9** → **10**) desilylation route over the one pot, $Hg(OAc)_2$/peracid procedure because of the mineral acid requirement of

the latter (7)). Mild F^--catalyzed oxidative desilylation[14] converted **9** to **10** at room temperature, and **10** was disassembled under conditions used previously[5] (brief catalytic hydrogenation followed by dilute NaOH) to provide **3** as a white solid. Compound **3** is reasonably stable at room temperature, and in fact is still detectable in samples of the crude natural products containing **1-3** that have been stored in a refrigerator for up to 2 years (although the relative concentrations of **2** and **3** seem to shift toward **2** with time). However, when the ^{1}H-NMR spectrum of **3** was rerecorded after 5 weeks in $CDCl_3$, more than 50% conversion to **2** had occurred, and some, but not complete, dehydration of **3** to **2** has occurred under most of the GLC conditions we have employed, so TLC and RP-HPLC have provided the most reliable assessments of purity. Similarly, the hydroxydihydrobenzisoxazolone **10** is a stable solid at room temperature, but reexamination of the $CDCl_3$ solution after 10 weeks revealed nearly complete dehydration and a ^{1}H-NMR spectrum identical to that of 4-hydroxy-3-undecyl-1,2-benzisoxazole[16].

EXPERIMENTAL

Melting points are uncorrected. Mass spectra were obtained from a Finnigan model 4510 gas chromatograph-mass spectrometer equipped with a 30 m x 0.32-mm id DB-1 (J&W Scientific) fused silica column. Electron ionization spectra were collected at 70 eV and a source block temperature of 150°. Ammonia chemical ionization spectra were obtained at a source temperature of 60° and a reagent gas pressure of 0.5 Torr. The ^{1}H-NMR spectra were obtained using a General Electric QE-300 NMR spectrometer. ^{1}H Chemical shift assignments were made by decoupling experiments and/or application of COSY. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Mention of a proprietary product does not imply endorsement by the U. S. Dept. of Agriculture.

5-(Phenyldimethylsilyl)-cyclohexane-1,3-dione **5**. Methyl acetoacetate (0.31 mol) was dissolved in a solution of sodium methoxide (from 7.7 g Na, 0.33 mol) in methanol (250 mL), then 52 g of methyl (E)-3-(phenyldimethylsilyl)propenoate **4**[10] (85% by GLC, ∴ *ca.* 0.20 mol) was added and the solution was heated at reflux under N_2 28 h. After cooling, a solution of KOH (60 g) in H_2O (200 mL) was added and the resulting solution was boiled 1.5 h, then again cooled, and concentrated HCl (125 mL) was added dropwise. A distillation head was attached, and the white mixture was boiled 1.5 h while *ca.* 150 mL of MeOH was removed. The remaining mixture was partitioned between ether and water to afford 58.4 g of a crude ether-soluble oil; this was determined by GLC-mass spectrometry and ^{1}H-NMR to be a mixture of **5** and its methyl enol ether. The entire mixture was therefore refluxed 3.5 h in 5% aqueous oxalic acid, then cooled, and **5** was collected as a white solid. Recrystallization from hexane plus benzene gave 26.9 g (55%) **5**, mp 119-120°C. Processing the combined filtrates, flash chromatography and recrystallization gave an additional 4.1 g pure **5**. ^{1}H-NMR (C_5D_5N): 0.30 (6H,s,CH_3Si), 1.70 (1H,m,H-5), 2.3-2.7 (4H,m,H-4 and H-6), 5.85 (1H,s,H-2), 7.4-7.8 (5H,m,phenyl). IR(KBr) 3446(br), 2953, 2935, 2887, 1573, 1531, 1448, 1410, 1347, 1302, 1248, 1213, 1155, 836 cm^{-1}. Mass spectrum: m/z (%): 246 (M^+, 7), 218(10), 203(6), 168(6), 161(6), 155(6), 142(13), 137(11), 136(14), 135(100), 127(29), 121(6), 119(6), 107(10), 105(13), 91(6), 75(10). Anal. Calcd for $C_{14}H_{18}O_2Si$: C, 68.24; H, 7.36. Found: C, 68.11; H, 7.34.

3-Hydroxy-2-(1-oxododecyl)-5-(phenyldimethylsilyl)-cyclohex-2-en-1-one 6. A solution of 5 (1.35 g, 5.5 mmol) in CH_2Cl_2 (10 mL) and pyridine (0.5 mL) was treated dropwise with a solution of dodecanoyl chloride (1.27 g, 5.8 mmol) in CH_2Cl_2 (4 mL). After stirring at room temperature 1.5 h, the mixture was partitioned between ice-water and hexane, and the hexane phase was washed with cold dilute HCl, H_2O, and 2N Na_2CO_3. The solvent was dried and concentrated, leaving 2.35 g (100%) of the enol ester that was not characterized, but was rather dissolved in MeCN (25 mL) containing Et_3N (3 mL) and acetone cyanohydrin (50 µL). The solution was allowed to remain at room temperature overnight, then was partitioned between hexane and cold, dilute HCl. The hexane phase was rinsed with water, dried ($MgSO_4$) and concentrated to give 2.21 g (94%) of 6 as a clear oil that consisted of a single component as determined by GLC. A portion was purified by flash chromatography (5% EtOAc in hexane) for spectra and analysis. ^{1}H-NMR ($CDCl_3$): 0.35 (6H,s,CH_3Si), 0.88 (3H,t,J=7,CH_3), 1.25 (methylene envelope), 1.59 (3H,m,H-5 and H-3'), 2.22 (1H,t,J=14, H-4 ax or H-6 ax), 2.4-2.6 (3H,m,remaining H-4 and H-6), 2.96 (2H,dt,J=7.2 and 1.8, H-2'), 7.37-7.46 (5H,m,phenyl), 18.25 (1H,s,enolic OH). IR(CS_2): 3069, 3051, 2953, 2923, 2853, 1666, 1408, 1319, 1301, 1249, 1158, 1144, 1114, 1084, 846, 830, 821, 776, 735, 701. Mass spectrum, m/z (%): 428(M^+, 5), 337(14), 223(22), 210(12), 197(16), 137(15), 136(15), 135(100), 75(12), 69(11), 57(11), 55(12). Anal. Calcd for $C_{26}H_{40}O_3Si$: C, 72.84; H, 9.41; Found: C, 72.98; H, 9.45.

5-(Fluorodimethylsilyl)-3-hydroxy-2-(1-oxododecyl)-cyclohex-2-en-1-one 7. A solution of 6 (119 mg) in CH_2Cl_2 (1 mL) was treated at room temperature with 1 mL of 85% $HBF_4 \cdot Et_2O$. A dark amber color developed. After 4 h the mixture was partitioned between hexane and ice-H_2O; drying and evaporation of the solvent gave 107 mg of a white solid that was recrystallized from 80% EtOH to give 85 mg (82%) of 7, mp 51.5-52°C. ^{1}H-NMR ($CDCl_3$): 0.30 (6H,d,J=7.5, CH_3Si), 0.87 (3H,t,J=7, CH_3), 1.27 (methylene envelope), 1.47-1.70 (3H,m,H-5 and H-3'), 2.37 (1H,dd,J=16.5 and 13.8, H-4 ax or H-6 ax), 2.5-2.75 (3H,m, remaining H-4 and H-6), 3.02 (2H,t,J=7.5, H-2'), 18.32 (1H,s,enolic OH). IR(KBr) 3426(br), 2924, 2855, 1667, 1650, 1570, 1501, 1466, 1430, 1258, 857, 792. Mass spectrum, m/z (%): 370(M^+, 16), 244(25), 243(100), 231(12), 230(81), 215(48), 187(10), 126(23), 121(14), 79(13), 77(55), 69(21), 57(15), 55(28). Anal. Calcd for $C_{20}H_{35}FO_3Si$: C, 64.82; H, 9.52. Found: C, 65.01; H, 9.51.

6-(Phenyldimethylsilyl)-3-undecyl-6,7-dihydro-1,2-benzisoxazol-4(5H)-one 8. A solution of 6 (430 mg, 1 mmol) in C_6H_6 (5 mL) at room temperature was treated with a methanol solution of hydroxylamine (from 87 mg $NH_2OH \cdot HCl$ (1.2 mmol) and KOH (82 mg, 1.24 mmol). After stirring 16 h, the solution was diluted with hexane, rinsed with dil. HCl, H_2O, and aq. $NaHCO_3$, dried, and concentrated to give 0.43 g (100%) of a pale oil. Flash chromatography (5% EtOAc in hexane) gave 0.35 g of 8 as a colorless oil. ^{1}H-NMR ($CDCl_3$): 0.40 (6H,s,CH_3Si), 0.87 (3H,t,J=6.9, CH_3), 1.24 (methylene envelope), 1.53-1.62 (2H,m,H-2'), 1.62-1.73 (1H,tt,H-6), 2.26 (1H,dd,J=16.5 and 13.8, H-5 ax), 2.51 (1H,dd,J=16.8 and 3.6, H-5 eq), 2.70 (1H,dd,J=17.7 and 12.6, H-7 ax), 2.81 (2H,t,J=7.8,H-1'), 2.94 (1H,dd,J=17.7 and 4.8, H-7 eq), 7.41 (5H,m,phenyl-H). IR(CS_2) 3069, 2954, 2925, 2852, 1691, 1410, 1376, 1341, 1299, 1254, 1155, 1146, 1114, 1073, 1053, 984, 887, 863, 832, 817, 775, 735, 701. Mass spectrum, m/z (%): 425(M^+, 14), 313(12), 298(14), 285(10), 137(10), 136(17), 135(100), 57(10), 55(13). Anal. Calcd for $C_{26}H_{39}NO_2Si$: C, 73.36, H, 9.24. Found: C, 73.28, H, 9.27.

6-(Fluorodimethylsilyl)-3-undecyl-6,7-dihydro-1,2-benzisoxazol-4(5H)-one 9. A solution of **8** (4.25 g) in CH_2Cl_2 (40 mL) was treated with 85% $HBF_4 \cdot Et_2O$ (85%, 15 mL). The solution was stirred under N_2 24 h, then was concentrated *in vacuo*, and the residue was partitioned between ice water and hexane. The hexane phase was washed well with H_2O and 1 M Na_2CO_3, then was dried and concentrated to give 3.50 g (95%) of **9** as a pale oil (essentially pure by GLC). A small portion was purified by flash chromatography (5% EtOAc in hexane) to give a colorless oil. ^{1}H-NMR ($CDCl_3$: 0.33 (3H,d,J=7.2,CH_3Si), 0.34 (3H,d,J=7.2,CH_3Si), 0.87 (3H,t,J=6.9, CH_3), 1.25 (methylene envelope), 1.32 (sh), 1.63-1.83 (3H,m,H-2′ and H-6), 2.39 (1H,dd,J=16.8 and 13.8, H-5ax), 2.57 (1H,dd,J=16.8 and 3.6, H-5eq), 2.85 (2H,t,J=7.8,H-1′), 2.88 (1H,dd,J=17.7 and 17.7, H-7ax), 3.07 (1H,dd,J=17.7 and 4.8, H-7eq). IR (CS_2) 2954, 2923, 2853, 1691, 1412, 1375, 1345, 1261, 1054, 985, 894, 881, 854, 836, 798, 788. Anal. Calcd for $C_{20}H_{34}FNO_2Si$: C, 65.35; H, 9.32. Found: C, 65.21; H, 9.43.

6-Hydroxy-3-undecyl-6,7-dihydro-1,2-benzisoxazol-4(5H)-one 10. To a solution of **9** (2.93 g) in 30 mL 1:1 MeOH-THF was added KF (4.2 g) and $NaHCO_3$ (5.2 g). The mixture was stirred and cooled and slowly treated with 30% H_2O_2 (27 mL). The ice bath was removed and the mixture was stirred overnight at room temperature, then was diluted with water and extracted with Et_2O. The ether solution was washed well with H_2O, then with brine, and finally dried and concentrated to give 2.65 g of a colorless oil which was dissolved in boiling hexane. The hot solution was filtered and chilled whereupon **10** separated as a white solid (1.38 g, 56%), mp 60-61.5°C. ^{1}H-NMR ($CDCl_3$): 0.88 (3H,t,J=7.2), 1.25 (methylene envelope), 1.31 (sh,H-3′ ?), 1.70, (2H,m,H-2′), 1.88 (1H,s,OH?), 2.75 (2H, skewed t, H-5), 2.85 (2H,t,J=7.5, H-1′), 3.11 (1H,dd,J=17.4 and 4.5, H-7ax), 3.27 (1H,dd,J=17.4 and 4.5, H-7 eq), 4.66 (1H,m,H-6). IR(CS_2) 3606, 2954, 2923, 2853, 1694, 1412, 1063, 1021. Mass spectrum, m/e (%) 307(1.7, M^+), 250(6), 236(11), 222(13), 209(10), 208(18), 195(13), 194(17), 180(43), 167(66), 154(100), 136(26), 69(19), 68(10), 57(19), 56(100), 55(37). Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51. Found: C, 70.37; H, 9.44.

3,5-Dihydroxy-2-(1-oxododecyl)-cyclohex-2-en-1-one 3. A solution of **10** (1.23 g) in 95% EtOH (40 mL) containing PtO_2 (56 mg) was hydrogenated at 1 atm. for 20 min, then was filtered through a pad of Celite. The filtrate, which contained 3,5-dihydroxy-2-(1-iminododecyl)-cyclohex-2-en-1-one (mass spectrum m/e (%) 309(21, M^+), 292(14), 210(23), 182(100), 169(55), 164(29), 128(25), 97(25), 96(33), 83(21), 69(14), 55(26)) was treated with a solution of NaOH (0.52 g) in H_2O (15 mL). After 1.25 h at room temperature the solution was neutralized with aqueous NH_4Cl plus a little HOAc and extracted 3X with Et_2O. The ether solution was washed well with water, then with brine, and finally was dried and concentrated to give 1.29 g of an oil that crystallized. Recrystallization from hexane gave 0.95 g (77%) of **3** as a white solid, mp 55-56°C. ^{1}H-NMR ($CDCl_3$) 0.88(3H, t, J = 6.9), 1.26(methylene envelope), 1.61 (2H,m,H-3′), 2.6-2.95 (4H,m,H-4 and H-6), 3.02 (2H,t,J=7.8, H-2′), 4.36 (1H,m,H-5), 18.36 (1H,s,enolic OH). IR(CS_2) 3608, 3456(br), 2953, 2923, 2853, 1673, 1061, 857, 721 cm^{-1}. Mass spectrum, m/z (%) 310(14, M^+), 292(6), 184(25), 183(100), 171(11), 170(64), 165(34), 155(28), 137(24), 134(10), 129(24), 128(11), 126(19), 111(17), 98(12), 97(15), 85(13), 84(11), 71(15), 69(58), 57(20), 55(47). Anal. Calcd for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 70.04; H, 9.78.

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