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SYNTHESIS OF 2-ACYL-3,6-DIHYDROXY-2-CYCLOHEXEN-1-ONES

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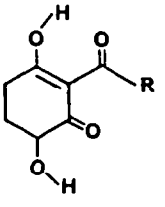
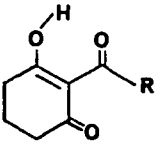
Abstract -- Two of the title compounds, recently identified as components of exudates produced by lace bug nymphs of the genus Corythucha, have been synthesized. 2-Acyl-3-hydroxy-2-cyclohexen-1-ones were converted to 3-alkyl-6,7-dihydro-1,2-benzisoxazol-4(5H)-ones which were hydroxylated at position 5, then reductively disassembled. Sodium borohydride and nickel chloride in DMF/THF containing 1-octene selectively reduced the isoxazole N-O bond without hydrogenating a side chain double bond.

As part of a continuing study of the chemistry of lace bug acetogenins[1-4], we recently reported[3] the identification of 3,6-dihydroxy-2-(1-oxo-10(E)-tetradecenyl)-2-cyclohexen-1-one (**1b**, R = 9(E)-$C_{13}H_{25}$) as the major component of a setal exudate produced by nymphs of the sycamore lace bug, Corythucha ciliata (Say), and have subsequently found that an analog with a saturated chain (**1a**, R = n-$C_{11}H_{23}$) is one of several related compounds secreted by the hawthorn lace bug, Corythuca cydoniae (Fitch).[4] We are aware of only two prior reports of this class of compounds as natural products: Mudd[5,6] identified a series of related compounds, with and without the 6-hydroxy groups (i.e., **1** and **2** with R = long chain alkyl or alkenyl), from mandibular gland secretions of Ephestia kuehniella larvae, and Kato, et al.[7] found an interesting variant with a phenyl group on the side chain (**1c**, R = $(CH_2)_{10}$-C_6H_5) in fruits of the South American trees Virola sebifera and V. elongata. The insect-derived materials described by Mudd were determined to have kairomonal activity (inducing ovipositional behavior in a parasite).[6] No syntheses of 2-acyl-3,6-dihydroxy-2-cyclohexen-1-ones have been reported.



1a—d

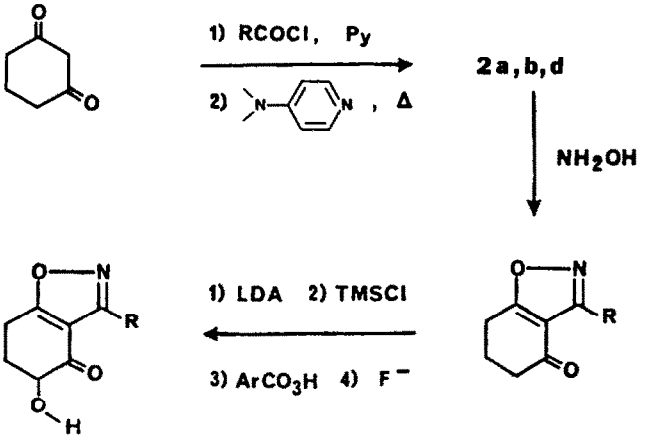


2a,b,d

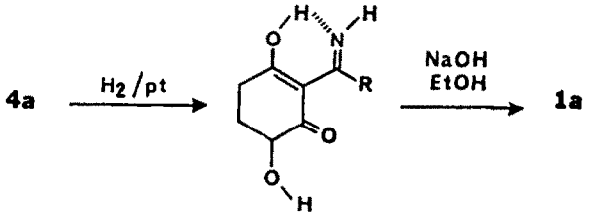
a. R = n-undecyl
b. R = (E)-9-tridecenyl
c. R = 10-phenyldecyl
d. R = (Z)-8-heptadecenyl

Mudd[8] described the preparation of several 2-acyl-3-hydroxy-2-cyclohexen-1-ones of type **2**, including the oleyl derivative **2d**, and since they are readily accessible in two steps from cyclohexane-1,3-dione and the appropriate acid chloride, RCOCl, **2a** seemed to be an attractive starting material for our initial target, the 6-hydroxy homolog **1a**. Because of its natural enolic nature, position 2 would be expected to be vulnerable to oxidation, and moreover, although positions 4 and 6 are equivalent, competition between those and the 2' position might be anticipated in a situation involving further enolization. Further, **1** is in the same oxidation state as a dihydroxyacetophenone, and Kato et al.[7] reported that dehydration/aromatization of **1c** to the corresponding 2,6-dihydroxy alkylphenone occurred readily. Thus, none of the standard procedures for introduction of a hydroxyl adjacent to a ketone seemed appropriate for **2a**.

Smith,[9] and Akhrem, et al.[10] established that 2-acetyl-3-hydroxy-2-cyclohexen-1-one reacted with hydroxylamine regioselectively to give only one of the two possible dihydrobenzisoxazoles, namely 3-methyl-6,7-dihydro-1,2-benzisoxazol-4(5H)-one. Reaction of **2a** with one equivalent of NH_2OH similarly provided a single isomer **3a**. In contrast to **2a**, **3a** has only one enolizable position (hydrogens on carbon α to the 5-position of isoxazoles--i.e. position 7 of **3a**--are sufficiently acidic to be removed by such bases as BuLi, $NaNH_2$, or LDA[11], but we expected them to be less acidic than those α to the carbonyl. As a result, ketone **3a** should be an acceptable substrate for the Rubottom hydroxylation procedure[12] and indeed the hydroxylated analog **4a** was obtained by that sequence.

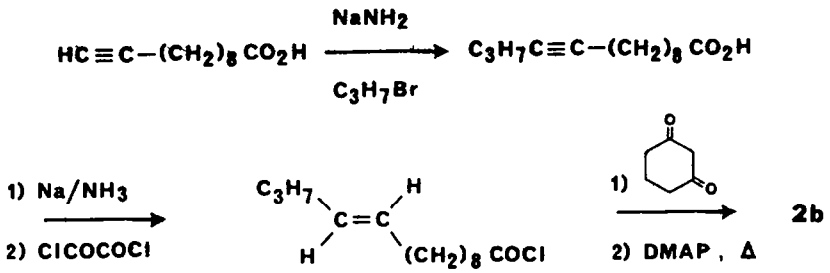


Catalytic hydrogenation has been almost universally used to disassemble isoxazoles, the initial products being enamino ketones which either undergo further transformations or are easily hydrolyzed to 1,3-dicarbonyl compounds with aqueous acid.[11,13] Catalytic hydrogenation (Pt, EtOH, 1 atm) of **4a** proceeded smoothly with uptake of one mole of H_2; the product **5a**, however, was surprisingly resistant to acid hydrolysis (aqueous HCl or oxalic acid) and this fact, plus spectral data (δ 12.13, enolic OH, UV spectrum similar to that of **1a** but shifted to longer wavelength), suggests the iminoenol structure **5a**. In contrast to its acid stability, **5a** was smoothly converted to **1a** with NaOH in aqueous ethanol. Compound **1a** was obtained as a crystalline solid and was identical by GLC and mass spectrometry to one of the minor components of the hawthorn lace bug secretion.



5a

A similar approach to the unsaturated homolog **1b** began with the preparation of **2b** as illustrated, a generally unexceptional series of reactions except that the low solubility of the ammonium salts in THF-NH_3 made the sodium/ammonia reduction of 10-tetradecynoic acid extremely difficult to carry to completion.



Consideration of the **2a**--->**1a** sequence suggests two potential problems in application of this sequence to the unsaturated analogs **2b**--->**1b**. The Rubottom hydroxylation procedure[12] employs m-chloroperoxybenzoic acid to introduce the oxygen via epoxidation of an enol trimethylsilyl ether, and the double bond in the side chain of **3b** would also be subject to epoxidation. However, it was expected that the enol-TMS ether would react more rapidly, and under the conditions employed (hexane, <0°, slight excess of oxidant) that was indeed the case, and **3b** was converted to **4b** without undue difficulty. The second problem, hydrogenation of the N-O bond of **4b** in the presence of the side chain C=C double bond, proved more challenging.

Isoxazole derivatives have proved extremely useful in organic syntheses, but in essentially all cases, catalytic hydrogenation has been employed for the generation/regeneration of 1,3-dicarbonyl compounds,[11,13] and we are unaware of cases wherein an exocyclic C=C has been preserved during reductive cleavage of an isoxazole. Trial catalytic hydrogenations (Pt or Ra-Ni) of **4b** were unpromising; the N-O and C=C were reduced at comparable rates. Examination of structure **4b** reveals that there are in fact a number of limitations with respect to potential reducing agents. Not only must the exocyclic C=C bond survive the reductant, but the keto and ketol functions have to be stable as well. Overreduction--i.e. of the C=NH of the initial product **5b** must also be avoided.

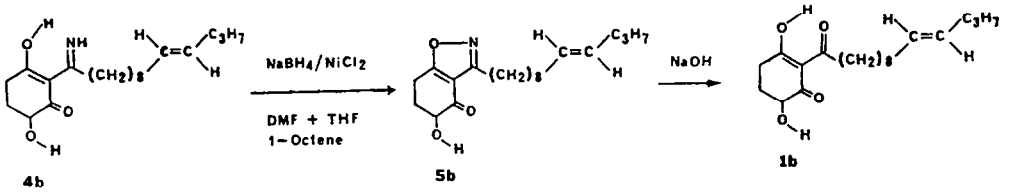
Brown and Ahuja[14] reported that reaction of nickel salts with sodium borohydride in aqueous ethanol generated H_2 and provided a black solid with useful catalytic properties comparable in some respects to Raney nickel. We are unaware of any reported reductions of isoxazoles with this reagent, although we have recently learned that Annunziata, et al.[15] used $NiCl_2 \cdot 6H_2O$ and $NaBH_4$ or $Zn(BH_4)_2$ to reduce some toluenesulfinyl substituted 4,5-dihydroisoxazoles. In these latter cases, the N-O bond was reductively cleaved, as was the toluenesulfinyl group, but the C=N double bond was also reduced so that the final products were 3-aminoalcohols.

We found that the N-O bond of **4b** was very rapidly cleaved by addition of $NaBH_4$ to solutions of **4b** containing $NiCl_2$ in either aqueous EtOH or DMF. However, the stoichiometry of the reduction was difficult to establish (excess $NaBH_4$ had to be used) and conditions were difficult to reproduce. Some preliminary small scale reactions were promising in that complete conversion of **4b** to **5b** was achieved with no reduction of the C=C double bond (or other functional groups), but so simple an alteration as doubling the amounts of all reactants could lead to incomplete reduction. Larger excesses of $NaBH_4$ rapidly reduced the C=C double bond. (In contrast to the Annunziata, et al.[15] results, reduction of the C=N double bond did not seem to be a problem.) It was evident that reduction of the N-O was more rapid than hydrogenation of the C=C, but fully reliable selectivity remained elusive.

In the original work[14] with this reducing agent, it was observed that 1-octene was reduced much more rapidly than the disubstituted olefins examined. Reasoning that the rate of reduction of 1-octene might be intermediate between those of the N-O and C=C bonds of **4b**, we reacted **4b** with $NiCl_2/NaBH_4$ in DMF in the presence of excess 1-octene. A substantial excess of $NaBH_4$ was added quickly, then after 5-10 sec, the reaction was quenched. Under these conditions, clean reduction of **4b** to **5b** was achieved with virtually no reduction of the side chain double bond. It was then found that tetrahydrofuran (initially added to improve the

solubility of 1-octene in $NiCl_2 \cdot 6H_2O$-saturated DMF) also improved the selectivity of this reduction, and the most convenient conditions found for reproducibly complete reaction without overreduction included THF as a cosolvent. Its function remains undefined as does the relationship of this reduction to these reported in the literature. Much of the work to date has focused on the catalytic properties of the black solid that precipitates after combination of solutions of $NaBH_4$ and $NiCl_2$; under our conditions this solid separated approximately 10 seconds after combination of the reactants. By that time, however, reduction of the isoxazole N-O bond was usually complete, so evidently heterogeneous catalysis was not involved.

Iminodiketone **5b** was converted with NaOH in EtOH to dl-**1b**, indistinguishable by GLC, MS, and ^{1}H-NMR from the natural product isolated from sycamore lace bugs[3].



Using a completely parallel series of reactions beginning with oleic acid and cyclohexane-1,3-dione, but without characterization of intermediates, we also synthesized 3,6-dihydroxy-2-[1-oxo-9-(Z)-octadecenyl]-cyclohex-2-en-1-one **1d**. This material was identical to a sample isolated from Ephestia kuehniella.[5,6] In this case too, no reduction of the side chain double bond was observed during the moderated $NaBH_4/NiCl_2$ reduction.

To date, we have made no attempt to control the absolute configuration at position 6 of **1a** or **1b**. That stereochemistry has not been determined in any of the natural products (the lace bug-derived compounds are extremely difficult to obtain in quantity, the nymphs themselves weighing only a few hundred micrograms, and as yet we have no bioassay to distinguish between the isomers). The position is technically an enolizable one, but we have no information concerning the rate or ease of racemization.

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 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. UV spectra were recorded on ca. 1.3 x 10^{-3} M ethanolic solutions. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. 10-Tetradecynoic acid, prepared from 11-undecynoic acid[17] by treatment with $LiNH_2$ in liq. NH_3 followed by 1-bromopropane[18], was a low-melting solid that was not characterized except for electron impact and chemical ionization mass spectra of its methyl ester: EI, m/z (%): 207 (1.5), M^+-CH_3O; 96 (31); 95 (18); 82 (100), 81 (62); 79 (22); 67 (88); 55 (55); CI (NH_3): 273 (64), $M^+ + N_2H_7^+$; 256 (100), $M + NH_4^+$.

Sodium/ammonia reduction proceeded very slowly: a solution of 14.68 g of the 10-tetradecynoic acid in 125 mL THF was added slowly to a solution of 5.8 g Na in 500 mL NH_3 (formation of the ammonium salt occurred as the solution left the addition funnel); at several hr intervals 3.5 g portions of Na and a little more THF were added and the mixture allowed to stand overnight. Solid NH_4Cl (100 g) was added, and after the NH_3 had evaporated, ice and dil. HCl were added and the product partitioned into Et_2O. After drying and removal of solvent, 14.8 g of an oil was obtained that consisted of 32% unreduced 10-tetradecynoic acid and 68% of the desired (E)-10-tetradecenoic acid. The entire procedure was repeated on this mixture with small portions of Na, and occasionally additional NH_3, being added over two days; the product was now a 90:10 mixture of (E)-10-tetradecenoic acid and unreduced 10-tetradecynoic acid and was used as such for the subsequent step. Mass spectra of the methyl ester of (E)-10-tetradecenoic acid ($C_{15}H_{28}O_2$, 240): EI m/z (%): 240 (3), M^+, 208 (7), 166 (9), 124 (10), 110 (11), 98 (18), 97 (26), 96 (22), 87 (27), 84 (23), 83 (23), 81 (19), 74 (43), 69 (38), 55 (100). CI (NH_3): 275 (100), $M + N_2H_7^+$, 258 (90), $M + NH_4^+$.

2-Acyl-3-hydroxycyclohex-2-en-1-ones **2a** and **2b** were prepared by the method of Mudd[9]: 2-(1-oxodecyl)-3-hydroxycyclohex-2-en-1-one **2** was an oil that solidified just below room temperature: UV (EtOH) 232 (8500), 272 (10,800). ^{1}H-NMR (C_6D_6): 0.91 (3H, t, J = 7.3 Hz, CH_3), 1.10 (1H, p, J = 9.1 Hz, H-5), 1.26 (methylene envelope), 1.74 (1H, p, J = 8.2 Hz, H-5) 1.92 and 2.01, (4H, dt, J = 7.2, and 2), 3.17 (2H, t, J = 8.5, H-2'), 18.69 (1H, s, H-bonded enolic OH). Mass spectrum: m/z (%): 294 (11, M^+); 168 (12); 167 (100); 154 (58); 139 (41); 126

(13); 69 (24); 55 (37). Anal. Found: C, 73.65: H, 10.70. Calcd. for $C_{18}H_{30}O_3$: C, 73.43; H, 10.27.

2-(1-Oxo-10-(E)-tetradecenyl)-3-hydroxycyclohex-2-en-1-one **2b** was initially contaminated with several per cent of the corresponding acetylenic analog as a result of the incomplete Na/NH_3 reduction, but most of the impurity was removed during flash chromatography on silica gel (92.5:7.5 hexane:EtOAc): **2b** was an oil at room temperature but solidified upon refrigeration: UV (EtOH) 232 (9800) and 273 (10,200). ^{1}H-NMR (C_6D_6): 0.89 (3H, t, J = 8.2 Hz, CH_3), 1.10 (1H, p, J = 7Hz, 5-H), 1.2-1.4 (methylene envelope), 1.72 (1H, p, J = 8Hz, 5-H); 1.92 and 2.00, (4+H, dt as in **2a** but with allylic H's superimposed on lower-field portion of signal), 3.16 (2H, t, J = 8.3, H-2'); 5.46 (2H, 5 poorly resolved peaks, olefinic); 18.69 (1H, s, H-bonded enolic OH). Mass spectrum: m/z (%): 320 (3, M^+); 167 (100); 154 (75); 139 (60); 126 (13); 69 (35); 55 (79).

3-Undecyl-6,7-dihydro-1,2-benzisoxazol-4(5H)-one **3a**. A solution of NH_2OH was prepared by combining warm methanol solutions of NH_2OH·HCl (0.36 g, 5.2 mmol in 2 mL) and KOH (.34 g, 5 mmol, in 1.5 mL); after filtration, the solution was added to a solution of **2a** (1.47 g, 5 mmol) in benzene (15 mL). After stirring overnight at room temperature, ether and water were added, and the organic phase was washed with 1N NaOH, H_2O, and sat. NaCl, then was dried over Na_2SO_4 and concentrated to give 1.30 g (89%) of **3a** as a pale yellow oil that gave essentially a single peak by GLC. Flash chromatography (9:1 hexane:EtOAc) gave 0.99 g as a nearly colorless oil: UV (EtOH): 201 (6400) and 227 (7200). ^{1}H-NMR (C_6D_6): 0.91 (3H, t, J = 7.3 Hz, CH_3, 1.1-1.5 (methylene), 1.8-2.1 (4H, m, 5-H and 7-H), 3.01 (2H, t, J = 7.9 Hz, H-1'). Mass spectrum: m/z (%): 291 (1.5, M^+); 290 (1.5); 234 (8); 220 (9); 206 (11); 192 (20); 179 (11); 178 (21); 164 (37); 151 (37); 138 (100); 69 (11); 57 (13); 55 (36). Anal. Found: C, 73.78; H, 10.06, Calcd. for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03.

3-[(E)-9-tridecenyl]6,7-dihydro-1,2-benzisoxazol-4(5H)-one **3b**, similarly prepared from **2b**, was an oil at room temperature: UV (EtOH) 201 (7800) and 227 (7600). ^{1}H-NMR (C_6D_6): 0.88 (3H, t, J = 8Hz, CH_3), 1.2-1.5 (methylene), 1.75-1.95 (4H, m, allylic), 1.95-2.1 (4H, m, 5-H, and 7-H) 2.88 (2H, t, J = 8.5 Hz, H-1'), 5.46 (2H, m, olefinic). Mass spectrum: m/z (%): 317 (2.5, M^+); 316 (2.5); 274 (10); 246 (13); 232 (14); 220 (10); 206 (17); 192 (20); 190 (12); 178 (16); 166 (35); 164 (46); 153 (25); 151 (26); 138 (46); 125 (12); 81 (18); 69 (20); 67 (32); 55 (100). Anal. Found: C, 76.15; H, 9.93. Calcd. for $C_{20}H_{31}NO_2$: C, 75.66; H, 9.84.

5-Hydroxy-3-undecyl-6,7-dihydro-1,2-benzisoxazol-4(5H)-one **4a**. A solution of 8.73 g (30 mmol) of **3a** in 100 mL dry THF was stirred and cooled under N_2 with a dry ice-MeOH bath, then 33 mL of a ca. 1 M solution of freshly prepared lithium diisopropylamide was slowly added. An amber solution developed that became red near the end of the LDA addition (dianion formation?). The solution was allowed to slowly warm to ca -30°, then 15 mL of chlorotrimethylsilane was added. After 15 min the solvent was stripped in vacuo and replaced with hexane; filtration gave a clear yellow solution that was again concentrated, reconstituted with hexane, and refiltered. The filtrate was added dropwise to a stirred, cold (ice/MeOH) mixture of m-chloroperoxybenzoic acid (7.7 g, ca. 38 mmol) and hexane (500 mL). After stirring in the cold 0.5 h, the mixture was filtered and the filtrate concentrated in vacuo; the residue was taken up in pentane, the solution filtered and concentrated, and the residue was treated with 5 g of Et_3N·HF and 75 mL CH_2Cl_2. After stirring overnight the solvent was stripped and the residue was partitioned between ether and aq. $NaHCO_3$, the ether solution was washed with H_2O, dil. HCl, $NaHCO_3$ and brine, then was dried and concentrated to give 8.71 g of a dark oil. Flash chromatgraphy (in 2 batches) with 25% EtOAc in hexane yielded a total of 5.46 g (59%) of **4a** as an oil that solidified. Recrystallization from EtOH-H_2O gave 4.79 g of a white solid, mp. 55°. UV (EtOH) 201 (7400) and 229 (7300). ^{1}H-NMR (C_6D_6), 0.91 (3H, t, J = 7.1 Hz, CH_3); 1.2-1.5 (methylene): 1.75-2.1 (2H, m, 7-H), 2.89 (2H, t, 1'-H) 3.58-3.7 (2H, dd + s, 5-H + O-H). Mass spectrum: m/z (%): 307 (1.6, M^+); 306 (1.5); 250 (11); 208 (15); 195 (11); 194 (15); 180 (38); 177 (10); 167 (64); 164 (11); 154 (89); 136 (54); 97 (20); 69 (41); 55 (100). Anal. Found: C, 70.70; H, 9.93. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51.

The nonequivalence of the H-2' hydrogens, clearly displayed in the ^{1}H-NMR spectra of **1a** and **1b**, was not observed with the H-1' signals in the spectra of **4a** or **4b**. For that reason the spectrum of **4a** was recorded in $CDCl_3$; although a number of solvent-induced chemical shifts were observed relative to the C_6D_6 spectrum, the signal for the H-1' hydrogens was still observed as a fairly clean triplet, J = 8.3 Hz at δ 2.85 ppm (2.89 in C_6D_6).

5-Hydroxy-3-[(E)-9-tridecenyl]-6,7-dihydro-1,2-benzisoxazol-4(5H)-one **4b** was prepared in the same way from **3b**, m.p. (EtOH-H_2O) 40-41°, UV (EtOH) 202 (8700) and 229 (7400) ^{1}H-NMR (C_6D_6): 0.89 (3H, t, J = 8 Hz, CH_3), 1.2-1.5 (methylene), 1.75-1.95 (2H, m, 7-H), 1.95-2.1 (4H, m, allylic), 2.88 (2H, t, J = 8.5 Hz, 1'= H), 3.58-3.64 (2H, dd + s, 5-H + O-H), 5.46 (2H, m, olefinic). Mass spectrum: m/z (%): 333 (6, M^+); 180 (16); 167 (18); 136 (18); 82 (10); 81 (18); 69 (29); 68 (12); 67 (29); 57 (16); 55 (100). Anal. Found: C, 72.20; H, 9.90. Calcd. for $C_{20}H_{31}NO_3$: C, 72.03; H, 9.37.

3,6-Dihydroxy-2-[1-iminododecyl]-cyclohex-2-en-1-one (**5a**). A sample of **4a** was hydrogenated (1 atm., PtO_2) for 0.5 h in 95% EtOH; after filtration and concentration, the product was recrystallized from hexane then again from EtOH-H_2O, m.p. 81-83°. UV (EtOH): 249 (15,200) and 289 (15,400). ^{1}H-NMR (C_6D_6): .93 (3H, t, CH_3), 1.2-1.5 (methylene), 1.5-1.65 (m), 1.95-2.05 (m), 2.1-2.25 (m), 2.35-2.5 (m), 2.55-2.7 (m), 3.9-3.95 (1H, m, CH-OH), 4.37 and 4.66 (total of 1H, ca. 1:3, respectively, O-H?), 5.04 (1H, br. s., NH), 11.44 and 12.14 (total of 1H, br. s., ca 1:3, respectively, enolic OH). Addition of a small amount of pyridine to the solution resulted in essentially no change in the spectrum; however, when it was rerun in C_6D_6 containing 0.2% trifluoroacetic acid, the pair of sharp singlets at 4.37 and 4.66 ppm disappeared and were replaced by a broad singlet at 3.45 ppm, the 11.44 and 12.14 ppm pair of peaks were replaced by a broad singlet at 12.03 with a shoulder at 11.87, and a general simplification, in terms of multiplicity, was observed for most of the other signals. Mass spectrum: m/z (%): 309 (33, M^+), 252 (11); 210 (27); 182 (100); 169 (28); 164 (11); 152 (14); 141 (28); 139 (35); 138

(29); 136 (15); 124 (10); 112 (22); 110 (17); 97 (18); 96 (30); 84 (70); 83 (53); 69 (23); 57 (27); 55 (54). Anal. Found: C, 69.73; H, 10.16. Calcd. for $C_{18}H_{31}NO_3$: C, 69.86; H, 10.10.

3-6-Dihydroxy-2-[1-oxododecyl]-cyclohex-2-en-1-one **1a**. A sample of **4a** (0.37 g) was hydrogenated and the crude product, after filtration, was treated with 2.5 mL 1N NaOH. After 3 h at room temperature a few drops of HOAc were added and the product was partitioned between water and 1:1 Et_2O-hexane. The organic phase was washed with H_2O, aq. $NaHCO_3$, and brine, then was dried and concentrated to give 0.31 g of a tan oil that crystallized on standing. Recrystallization from EtOH-H_2O gave a white solid, mp 51-53°. UV (EtOH), 233 (10,700) and 273 (11,900). ^{1}H-NMR (C_6D_6): 0.92 (3H, t, J = 7 Hz, CH_3), 1.2-1.45 (methylene), 1.6-1.8 and 1.8-2.0 (3-4 H, m, H-4 and H-5?), 2.85-3.0 and 3.0-3.15 (2 H, dddd, H-2'), 3.54 (1 H, dd, J = 14 and 5.3 Hz, H-6), 18.51 (1 H, s, enolic OH). Mass spectrum: m/z (%): 310 (29, M^+); 266 (13, $M^+-C_2H_4$); 183 (100); 168 (17); 165 (17); 153 (24); 142 (19); 140 (35); 139 (26); 137 (18); 126 (27); 85 (33); 84 (26); 69 (44); 57 (64); 55 (82). Anal. Found: C, 69.37; H, 10.29. Calcd. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74.

3,6-Dihydroxy-2-[1-oxo-10-(E)-tetradecenyl]-cyclohex-2-en-1-one **1b**. The following conditions gave reproducible results in several runs over a greater than 10-fold scale change. Excess $NiCl_2$ $6H_2O$ was allowed to stand in DMF overnight; filtration gave a bright green solution that was employed as the primary reaction solvent. A solution of **4b** (166 mg) in 13 mL of this solution, diluted with THF (6.5 mL) and 1-octene (130 µL), was stirred at room temperature and treated with 0.8 mL of ca 1 M $NaBH_4$ in DMF. After 10 sec (just as a black color and H_2-evolution began to develop), the reaction was quickly quenched with excess ice plus conc. NH_4Cl. A little dilute HCl was added and the mixture was extracted well with 1:1 ether-hexane, then the organic phase was washed with H_2O, dil aq. NH_3, dil HCl, and aq. $NaHCO_3$, then was dried (Na_2SO_4) and concentrated to provide 168 mg of a tan residue. GLC analysis indicated a 95:5 mixture of **5b** and unreacted **4b**, respectively, with none of the product from side chain reduction (which elutes slightly later than **5b**). Except for its mass spectrum, which was analogous to that of **5a**, **5b** was not characterized but rather was converted directly to **1b**. Mass spectrum (ei) of **5b**: m/z (%) 355 (100, M^+), 278 (8), 252 (12), 210 (12), 182 (72), 169 (22), 164 (12), 152 (12), 141 (23), 139 (21), 138 (18), 136 (15), 112 (15), 112 (15), 96 (22), 84 (44), 83 (31), 69 (20), 67 (15), 55 (51).

To the crude **5b** was added 25 mL 95% EtOH and 5 mL 1N NaOH; after 1.5 h at room temperature the solution was worked up and the product passed through a small portion of silica gel in 3:1 hexane:ether. Evaporation of the filtrate gave a pale oil (116 mg) that crystallized upon standing and provided a single peak by glc whose retention time was identical to that of the previously isolated lace bug component.[3] Recrystallization from wet ethanol gave a white solid, mp 41-42°: UV (EtOH) 233 (9750) and 272 (11,500). ^{1}H-NMR (C_6D_6): 0.89 (3 H, t, J = 8.1 Hz, CH_3), 1.2-1.45 (methylene), 1.65 (1 H, m, 5-H), 1.7-2.1 (complex, 4-H + allylic), 2.85-3.0 and 3.0-3.15 (2 H, dddd, H-2') 3.53 (1 H, dd, J = 5 and 14 Hz, 6-H) 4.13 (1 H, s, OH), 5.47 (2 H, m, olefinic), 18.50 (1 H, s,, enolic OH). Mass spectrum: m/z (%): 336 (83 M^+); 183 (45); 170 (15); 168 (34); 165 (15); 155 (13); 154 (10); 153 (14); 142 (14); 140 (16); 139 (12); 137 (20); 126 (26); 85 (23); 69 (44); 67 (21); 55 (100). Anal. Found: C, 71.53; H, 9.89. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59.

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