Synthesis of Squamostanal-A

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The first synthesis of squamostanal-A (1), separated as a degradation product of tetrahydrofuranic acetogenin, is described. Iodide 7, which corresponds to the latent aldehyde moiety of 1, was prepared through a 2-step sequence from 13-[tetrahydropyranyl-2-yl]oxi]-2-tridecyne-1-ol (5). The NaHMDS-based coupling reaction of 7 with γ-lactone 8 gave compound 9, which by a 3-step sequence, was converted to 1.

Key words: annonaceous acetogenins; oxidative cleavage

Annonaceous acetogenins have attracted much attention due to their unique structural features and wide range of biological activities.1-5) Most of this class of compounds found in the literature possess one or more tetrahydropyranyl rings, along with an unsaturated γ-lactone unit on C-35 or C-37 long-carbon chains. In addition to this major class of acetogenins, there is a minor group of compounds that can be assumed to be degradation products formed from precursor acetogenins; e.g., squamostan-A (1),6) muricatacin (2),7) and acerin (3).8) Squamostan-A (1) was isolated from Annona squamosa L. (Annonaceae) by Y. Fujimoto and co-workers in 1994. It can be assumed that squamostan-A (1) was formed via the oxidative degradation of such tetrahydrofuranic acetogenins as squamocin (4)9) that co-existed in A. squamosa. Squamostan-A (1) is not only an oxidative degradation product, but it would also be an important intermediate in synthetic studies of tetrahydrofuranic acetogenins. As part of our continuing synthetic studies on annonaceous acetogenins, we describe in this paper the first synthesis of squamostan-A (1).

Firstly, alkynyl alcohol 5, prepared through a 3-step sequence from 1,10-decanediol,10) was hydrogenated with a catalyst of 5% palladium on charcoal to give saturated alcohol 6. This alcohol 6 was then treated with iodine, imidazole (ImH), and triphenylphosphine (PPh₃) to give 7, which was subjected to alkylation with the sodium enolate of γ-lactone 8 to afford compound 9 in a 52% yield.11) Removal of the tetrahydrofuranyl (THF) group of 9 with p-toluene sulfonic acid (p-TsOH) afforded 10. Oxidation of 10 with m-chloroperbenzoic acid (m-CPBA) and subsequent thermal elimination afforded compound 11. Oxidation of 11 with Dess-Martin periodinane12) gave (+)-squamostan-A (1). Its melting point and optical rotation value were 66-68°C and +21.1° (c = 0.65, CHCl₃), respectively. The ¹H-NMR and mass spectral data for synthetic 1 were in good agreement with those reported for natural 1.6,8)

Experimental
All melting point (mp) data are uncorrected. Optical rotation was measured with a JASCO DIP-4 spectrometer, and IR spectra were taken with a JASCO IR-810 infrared spectrometer. ¹H-NMR spectra were measured with a JEOL GSX-270 (270 MHz) spectrometer, and Mass spectra were recorded by JEOL JMS-DX 300 and DX-303 instruments.

13-[1H-Tetrahydropyran-2-yl]oxi]-2-tridecyne (7). To a solution of alkynyl alcohol 5 (560 mg, 1.89 mmol) in EtOH (5 ml) was added 5% Pd-C (50 mg) at room temperature, and the suspension was vigorously stirred in a hydrogen atmosphere. After being stirred for 1 h, the reaction mixture was filtered through a Celite pad and concentrated in vacuo. Silica gel column chromatography of the residue (hexane: AcOEt = 6:1) gave saturated alcohol 6 (535 mg, 1.60 mmol, 85%) as a colorless oil. IR (film) νmax cm⁻¹: 3420 (OH), 2920, 2850, 1460, 1200, 1030; ¹H-NMR (CDCl₃) δ: 1.20-1.90 (29H, m), 3.38 (1H, m), 3.90 (1H, m), 3.64 (2H, t, J = 6.6 Hz, CH₂); 6.78 (OH), 3.75 (1H, m), 3.88 (1H, m), 4.57 (1H, m, O-CH₂); HR-EIIMS m/z (M⁺ - 1H): calc. for C₁₄H₂₃O₂: 238.1900; found: 238.1917.

13-Iodo-13-[1H-tetrahydropyran-2-yl]oxi]-2-tridecane (8). To a suspension of alcohol 6 (150 mg, 0.498 mmol) in benzene (5 ml) were added imidazole (85 mg, 1.25 mmol) and then PPh₃ (328 mg, 1.25 mmol) at room temperature. After stirring for 5 min, iodine (254 mg, 1.00 mmol) was added at the same temperature, stirring being continued for 30 min. The mixture was quenched with saturated aqueous Na₂SO₃ and extracted with benzene, the organic layer being washed with saturated aqueous NaHCO₃, dried over MgSO₄, and concentrated in vacuo. Silica gel column chromatography of the residue (benzene: AcOEt = 10:1) gave iodide 7 (154 mg, 0.374 mmol, 75%) as a colorless oil. IR (film) νmax cm⁻¹: 2920, 2850, 1460, 1200, 1030; ¹H-NMR (CDCl₃) δ: 1.20-1.90 (29H, m), 3.19 (2H, t, J = 6.6 Hz, CH₂), 4.19 (1H, CH₂), 4.57 (1H, O-CH₂).
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\[ J = 7.1 \text{ Hz, CH}_3 \text{ CH}_2 \text{ I}, 3.38 \text{ (1H, m), 3.50 (1H, m), 3.75 (1H, m), 3.88 (1H, m), 4.57 (1H, m, } O-CH_2-O \text{; HREIMS m/z: } M^+ - \text{H} \text{; calculated for C}_9H_9O_2 \text{, 409.1684; found, 409.1580.} \]

(3RS,5S)-3,4,13'-[3-Hydrazinothiocarbonyl]-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (9). To an ice-cooled solution of 3-glyc one 8 (270 mg, 1.30 mmol) in THF (5 ml) was added sodium bis(trimethylsilyl)amide (3.5 M) solution in THF (1.3 ml). After the mixture had been stirred at 0 ºC for 30 min, iodide 7 (265 mg, 0.645 mmol) in HMPPA (2 ml) was added, and the whole was allowed to warm to room temperature. The reaction mixture was then poured into saturated aqueous NH_4Cl and extracted with diethyl ether. Drying over MgSO_4 and subsequent evaporating gave crude 9, which was chromatographed over silica gel (hexane:AcOEt = 6:1) to give compound 9 (164 mg, 0.334 mmol, 52%), as a colorless oil. IR (film, cm\(^{-1}\)) 3025, 2920, 2850, 1700 (O = C = O), 1460, 1180 (O = C = O), 1130, 740, 690; \( ^1H \) NMR (CDCl_3, \( \delta \)) 1.10 2.00 (3H, m, CH(H)CH(O)COCH_3), 3.38 (1H, m, 3.50 (1H, m), 3.75 (1H, m, 4.40 4.64 (1H, m, CH_2CH(O)COCH_3), 5.47 (1H, m, O-CH_2-O), 7.36 (3H, m, aromatic-H), 7.54 (2H, m, aromatic-H); HREIMS m/z: (M^+): calculated for C_22H_20O_6S, 490.3171; found, 490.3092.

(3RS,5S)-3,4,13'-Hydroxytridecyl]-5-methyl-3-(phenylsulfanyl)tetrahydrofuran-2-one (10). To a cold solution of compound 9 (164 mg, 0.334 mmol) in MeOH (2 ml) was added p-TsOH (10 mg) at 0 ºC. After being stirred at room temperature for 3 h, the reaction mixture was quenched with saturated aqueous NaHCO_3 (2 ml), and MeOH was evaporated. The organic layers were combined, washed with brine, dried over MgSO_4 and concentrated in vacuo. Silica gel column chromatography of the residue (hexane:AcOEt = 3:1) gave hydroxy lactone 10 (102 mg, 0.250 mmol, 75%) as a colorless oil. IR (film, cm\(^{-1}\)) 3400 (OH), 3050, 2920, 2850, 1760 (O = C = O), 1460, 1440, 1340, 1180 (O = C = O), 740, 690; \( ^1H \) NMR (CDCl_3, \( \delta \)) 2.00 (29H, m), 2.28 2.57 (1H, m, CH(H)CH(O)COCH_3), 3.46 (2H, t, J = 6.6 Hz, CH_2CH(OH), 4.40 4.64 (1H, m, CH_2CH(O)COCH_3), 5.37 (3H, m, aromatic-H), 7.55 (2H, m, aromatic-H); HREIMS m/z: (M^+ - 2H): calculated for C_22H_20O_6S, 460.2542; found, 460.2534.

(5S)-3,4,13'-Hydroxytridecyl]-5-methyl-2,5-dihydrofuran-2-one (11). To a solution of hydroxy lactone 10 (40 mg, 0.098 mmol) in MeOH (2 ml) was added m-CBPA (34 mg, 0.196 mmol) at 0 ºC. After the mixture had been stirred at this temperature for 15 min, filtration afforded a yellow solid, which was used in the next step without further purification. The solid was dissolved in toluene (10 ml), and the solution was refluxed for 1 h. After completing the reaction, evaporation gave crude 11 (26 mg, 0.088 mmol, 90%), which upon recrystallization (hexane) gave pure \( z \)-unsaturated lactone 11 as a white solid, mp 62 63°C; \( [\alpha]_D^25 \) +17.3 (c = 0.63, CHCl_3); IR (KBr) \( \nu_{max} \) cm\(^{-1}\): 3300 (OH), 3070, 2920, 2850, 1740 (C = C = O), 1465, 1440, 1320, 1200, 1070, 1030, 880, 720; \( ^1H \) NMR (CDCl_3, \( \delta \)) 1.20 1.40 (19H, m), 1.41 (3H, d, J = 6.6 Hz, CH(O)COCH_3), 0.80 1.80 (4H, m, CH_3CH_2CH(OH), 2.27 (2H, t, J = 7.7 Hz, CH_2CH(OH), 3.64 (2H, t, J = 6.6 Hz, CH_2COCH_3), 5.00 (1H, dq, J = 1.7, 6.8 Hz, CH(O)COCH_3), 6.99 (1H, dq, J = 1.7 Hz, C = CH(O)COCH_3), 7.00 (1H, d, J = 1.7 Hz, C = CH(O)COCH_3); HREIMS m/z: (M^+): calculated for C_{14}H_{22}O_4, 296.2351; found, 296.2322.

References


