Tetrahedron Vol. 46, No. 15, pp. 5065-5076, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

TOTAL SYNTHESIS OF (-)-ISOAVENACIOLIDE AND (-)-ETHISOLIDE

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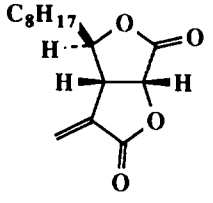
(*Received in USA* 29 *January* 1990)

Abstract: Natural isoavenaciolide and ethisolide were obtained from two bis-butyrolactone intermediates derived from a common bicyclic ester **8**, prepared from D-ribose.

The mold metabolites[1] avenaciolide **1**, isoavenaciolide **2a** and ethisolide **2b** possess the structurally interesting α-methylene-bis-butyrolactone skeleton and, in addition, avenaciolide and isoavenaciolide were found to exhibit antifungal and weak antibacterial activities[1]. Recently avenaciolide was also found to inhibit glutamate transport in rat liver mitochondria.[2] Their unique structures, along with their interesting biological activities, have attracted much synthetic attention. Numerous syntheses of avenaciolide have been reported;[3] however, relatively less attention has been directed towards the synthesis of isoavenaciolide[4] and ethisolide.[5] At the outset, since we also noted that D-ribose has never been used as a chiral starting material for the synthesis of these natural products, we decided to investigate this possibility. Herein, we present full details of our synthesis of (-)-isoavenaciolide and (-)-ethisolide.



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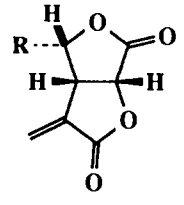
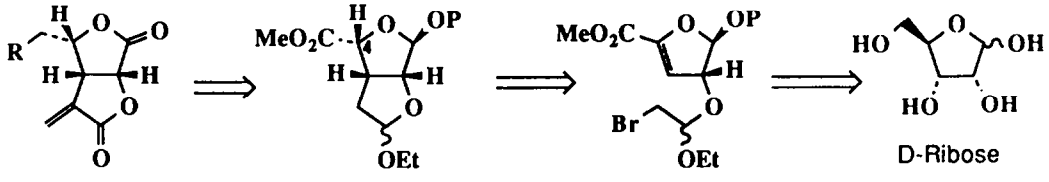


2a R= C_8H_{17}
2b R= C_2H_5

It was recognized that isoavenaciolide and ethisolide differ only in the C-4 substituent (isoavenaciolide numbering). Therefore, our plan was to prepare a key bicyclic intermediate such as **3**, which possesses a suitable functional group, such as an ester functionality, at C-4 that can be used for the introduction of the

Chart 1



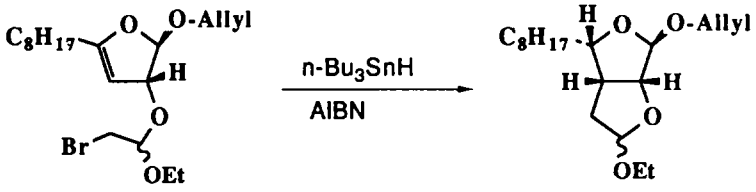
3
R= n-Heptyl or Methyl

4
P= $(CH_2)_2SiMe_3$

appropriate alkyl side-chain at later stages thus conferring flexibility in our synthesis. As shown in Chart I, compound **3** was to be prepared from **4** by free-radical carbocyclization. Compound **4** was, in turn, to be derived from D-ribose.

While our work was in progress, Dugger and McDonald reported[44] the synthesis of the bis-butyrolactone, required for the preparation of natural isoavenaciolide, from D-ribose. The key step in their synthesis involved the free radical cyclization of the mixed bromoacetal **A** to give the bicycle **B** (Scheme 1), and in this sense our work parallels their synthesis.

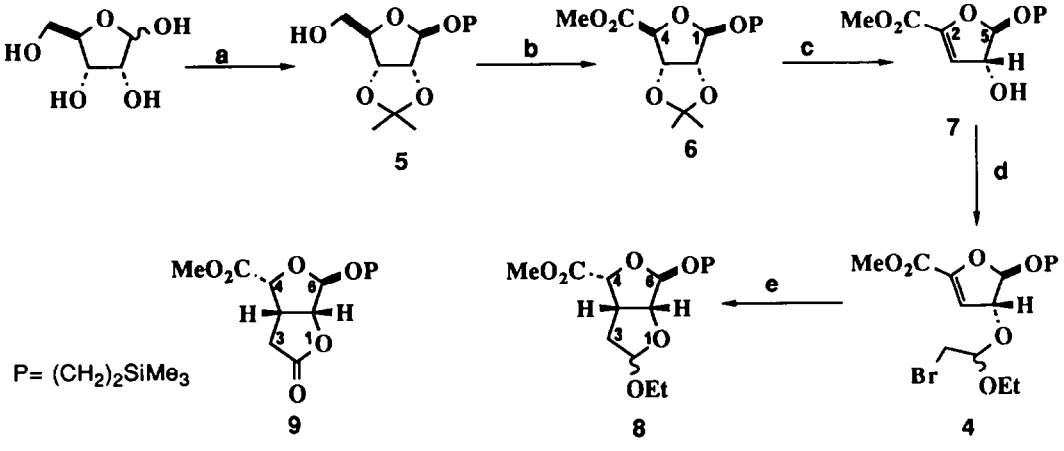
Scheme 1



A **B**

Our synthesis, as shown in Scheme 2, began with the preparation of the ribofuranoside **5**. It was found that this compound was best prepared by acid catalysed condensation of 2,3-O-isopropylidene-D-ribose[6] and 2-trimethylsilylethanol (TMSEtOH) (55% over two steps). The direct condensation of D-ribose with TMSEtOH in acetone resulted in lower yields of **5** (<30%). The formation of only the β-isomer

Scheme 2[a]



[a]Reagent: a; 1) Ref. 6; 2) TMSEtOH, TsOH, b; 1) $RuCl_3$, H_5IO_6, 2) CH_2N_2, c; NaOMe, MeOH, d; $brCH_2CH(Br)OEt$, Et_3N, -78°C, e; n-Bu_3SnH, AIBN.

can be attributed to the preferential attack of the TMSEtOH species on the incipient cis bicyclic oxonium ion, derived from 2,3-O-isopropylidene-D-ribose, from the sterically less hindered β-face. We chose the

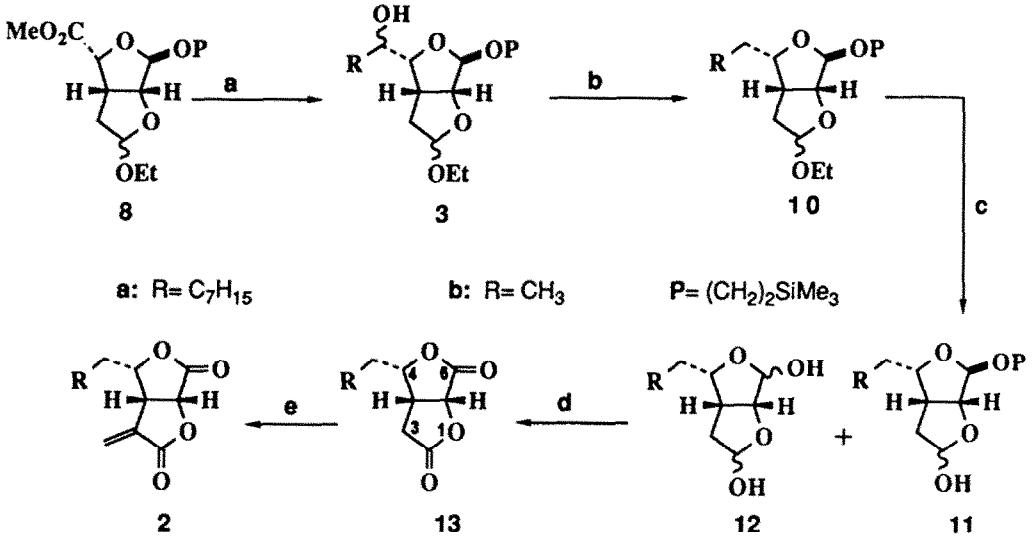
trimethylsilylethyl protecting group because our earlier attempts at the acid hydrolysis of the methoxy derivative (see **10**, R= OBn, P= Me) resulted only in the hydrolysis of the ethoxyl group implying that the incipient oxonium ion that is formed from hydrolysis of the methoxy unit is energetically unstable.[7] We reasoned that the removal of the trimethylsilylethyl group would be more favourable as it does not involve the formation of an unstable oxonium ion. Secondly, recent studies[8] have shown that the trimethylsilylethyl group can be readily removed under mild conditions.

The alcohol **5** was efficiently oxidized with ruthenium(III) chloride-periodic acid[9] followed subsequently by ethereal diazomethane treatment to furnish the methyl ester **6** in 74%. The salient features of the ^{1}H n.m.r. of **6** are singlets at δ5.12 and 4.56 attributed to H-1 and H-4 (ribose numbering) indicating the lack of coupling (J <1 Hz) of these hydrogens to H-2 and H-3, respectively. This suggests that the dihedral angles between H-1/H-2 and H-3/H-4 are around 90°. Drieding molecular models show that this corresponds to a conformation in which the furanose ring in **6** adopts an envelope conformation where the four ring carbons are held coplanar to each other with the ring oxygen directed towards the endo side of the bicycle.

Sodium methoxide mediated β-elimination of **6** was best carried out at 37°C to provide the crystalline enol-ester **7** in 76% yield. Alkylation of the hydroxyl function of **7** with 1,2-dibromoethyl ethyl ether in the presence of triethylamine[11] yielded the bromo-ketal **4**. n-Tributyltin hydride (TBTH) mediated free-radical cyclization of **4** in refluxing degassed benzene proceeded efficiently to give the bicyclic ester **8** as a mixture of diastereoisomers resulting from the anomeric ethoxyl groups at C-2. The ratio of the α and β anomers was found to be 1.6:1 based on the integration of the H-2 double doublets centered at δ 5.08 and 5.15, respectively (isoavenaciolide numbering). The structure of **8** was further confirmed by selective acid hydrolysis of the C-2 ethoxyl group followed by Jones oxidation[12] to give the γ-lactone **9**. Its ^{13}C n.m.r. spectrum showed 11 lines and a ^{13}C DEPT[13] experiment permitted assignment of the resonances; the C-3 resonance occurred at δ 29.96. The protons in its ^{1}H n.m.r spectrum were fully assigned by double irridiation experiments; the characteristic signals are the doublets centered at δ4.75 (J=7.2 Hz) and 4.85 (J= 7.2 Hz) which are ascribed to H-4 and H-6a, the double doublets centered at δ2.30 (J= 14.4, 3.5 Hz) and 2.65 (J= 14.4, 8.9 Hz) which are due to H-3 (endo) and H-3 (exo), respectively, and the singlet at δ5.25 which is attributed to H-6. The large vicinal coupling constant of J= 7.2 Hz observed for H-4 indicates that it is cis to H-3a; the alternate trans arrangement would be expected to result in a vicinal coupling of J <1 Hz by analogy with the coupling results observed for H-4 in compound **6** (vide supra). Therefore, the C-4 carbomethoxy substituent occupies the endo position in **8** resulting from TBTH reduction from the less hindered β-face of the bicycle during the free-radical cyclization reaction. Similar examples of stereoselective reduction have previously been observed.[4a,11b]

Having obtained the requisite bicyclic-ester **8**, the stage was set for utilizing the ester function to introduce the C-4 side-chain. First, we addressed the synthesis of isoavenaciolide (Scheme 3). Reduction of the ester group with one equivalent of diisobutylaluminium hydride to the corresponding aldehyde followed, subsequently, by reaction with heptylmagnesium bromide generated the secondary alcohol **3a** as a mixture of diastereoisomers in an overall yield of 91%. The stereochemistry of the newly introduced center at C-7 was of no consequence because the hydroxyl group was removed in the next step, and we planned to

Scheme 3[b]



[b]Reagent: a; 1) DiBAH, -78°C; 2) $C_7H_{15}MgBr$ or MeMgBr, -10°C, b; 1) PhOC(S)Cl, DMAP; 2) n-Bu_3SnH, AIBN, c; dioxane - 0.5% H_2SO_4 (5:2), d) CrO_3, H_2SO_4, H_2O, e; Ref. 3l.

achieve this by employing free-radical deoxygenation technology. The secondary alcohol was first converted to the phenylthiocarbonate[14] by treatment with phenoxythiocarbonyl chloride in the presence of 4-N,N-dimethylaminopyridine (DMAP). This alcohol was, unexpectedly, quite hindered and required seven mole equivalents of DMAP for efficient esterification; use of lesser amounts (e.g. 2 mole equivalents) of DMAP resulted in incomplete conversion to product. Reduction of the phenylthiocarbonate **3a** with TBTH then gave the deoxy compound **10a** in 96.7% yield.

When the bis-ketal **10a** was refluxed in a mixture of aqueous sulfuric acid and dioxane the bis-lactol[3e] **12a** and mono-lactol **11a** were formed in a ratio of 3:1. We found it best to stop the hydrolysis after 3h because prolonged heating to effect complete hydrolysis resulted in some decomposition of the desired bis-lactol product. Compound **11a** was rehydrolysed to give **12a**, as a waxy compound, in a final yield of 78%. Jones oxidation[12] of **12a** yielded the bis-butyrolactone **13a**,[3e,4d] which is the key intermediate in previous synthesis[4d,e] of isoavenaciolide. α-Methylenation of **13a** using the procedure of Parker and Johnson[3l], provided (-)-isoavenaciolide **2a**.

In a similar manner, the preparation of (-)-ethisolide entailed the reduction of **7** with diisobutylaluminium hydride, reaction of the corresponding aldehyde with ethereal methylmagnesium bromide to give the secondary alcohol **3b**, deoxygenation of the secondary alcohol, acid hydrolysis (**12b**:**11b**, 2:1, final yield 78%) and then Jones oxidation[12] to give the crystalline bis-lactone **13b**. The structure of **13b** was fully substantiated by its ^1H n.m.r (including ^1H 2D COSY n.m.r.) and ^{13}C n.m.r. (8 lines). Subjection of **13b** to α-methylenation[3l] yielded synthetic (-)-ethisolide **2b**.

In summary, the total synthesis of natural isoavenaciolide and ethisolide have been described from a common bicyclic intermediate which is, in turn, conveniently prepared from D-ribose.

EXPERIMENTAL

General: Melting points were determined on a Kofler melting point apparatus and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 1600FT infrared spectrophotometer. N.m.r. spectra were obtained on a Bruker WH 200 at the University of Alberta and Bruker QNP 200 at the University of Regina: Chemical shifts are reported in parts per million (δ) relative to the appropriate reference signals. ^{1}H n.m.r. (200 MHz) were recorded in deuteriochloroform ($CDCl_3$) using tetramethylsilane (δ_H 0.0) or residual chloroform (δ_H 7.24) as reference; multiplicities of signals are given as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and coupling constants are given in Hertz. Proton assignments were based on homonuclear decoupling experiments. ^{13}C n.m.r and ^{13}C DEPT-135 (50.32 MHz) were recorded in $CDCl_3$ using the $CDCl_3$ signal at δ 77.0 as reference. The notation (-) is used to indicate inverted signals[15] in the DEPT experiments. Microanalyses were performed at the Microanalytical Department, University of Alberta and at Guelph Chemical Laboratories, Guelph, Ontario, Canada. Low resolution electron impact (70 eV) and chemical ionization (NH_3 as reactant gas) mass spectra were recorded at the Universities of Alberta and Saskatchewan on MS-12 spectrometers. Optical rotations were measured on a Perkin-Elmer 141 polarimeter (Na_D= 589 nm) at the University of Alberta. Reaction progress was monitored by thin layer chromatography on Merck silica gel 60_{F254} precoated (0.25 mm) on aluminium backed sheets. Petroleum ether used is the fraction with bp. 35-60°C. Chromatographic purification means flash chromatography[15] performed on Merck silica gel 60 (230-400 mesh). Air and moisture sensitive reactions were conducted under a static pressure of argon. Dichloromethane, benzene and acetonitrile were dried by distillation from calcium hydride, and methanol was dried by distillation from magnesium methoxide.

Trimethylsilylethyl 2,3-O-isopropylidene-D-ribofuranoside (5). 2,3-O-Isopropylidene-D-ribose[6] (2.71g, 14.3 mmol) and 2-trimethylsilylethanol (2.03g, 17.2 mmol) were dissolved in dry CH_2Cl_2 (40 mL) under argon. Anhydrous $MgSO_4$ (3.44g, 28.7 mmol) and p-$TSO_3H.H_2O$ (0.55g, 2.9 mmol) were added and the mixture was stirred at R.T. for 18h. Then saturated aq. $NaHCO_3$ (20 mL) was added to the reaction mixture, the CH_2Cl_2 layer was separated and washed with water (20 mL). The combined aqueous phases were extracted with CH_2Cl_2 (20 mL), the combined organic layers were dried (Na_2SO_4), filtered and concentrated to give an oil. Chromatographic purification (1:8 ethyl acetate-petroleum ether) yielded a clear homogenous oil (2.54g, 60%; 55% over two steps from 2,3-O-isopropylidene-D-ribose). $\nu_{max.}$ (neat): 3200-3575, 2951, 1457, 1416, 1381 and 1372 cm^{-1}. δ_H: 0.00 (s, 9H, $SiMe_3$), 0.80-1.00 (m, 2H, CH_2Si), 1.30 (s, 3H, Me), 1.49 (s, 3H, Me), 3.45-3.95 (m, 5H, OCH_2, H-4, H-5), 4.38 (bt, 1H, J= 2.7 Hz, OH), 4.56 (d, 1H, J= 5.6 Hz, H-3), 4.83 (d, 1H, J= 5.6 Hz, H-2) and 5.05 (s, 1H, H-1). δ_C: -1.53, 18.01(-), 24.82, 26.27, 63.95, 65.92(-), 81.50, 86.00, 88.21, 108.13 and 111.94. CIMS m/z : 308 (M + NH_4), 275 (M - CH_3) and 262 (M - CO).

Methyl Trimethylsilylethyl-2,3-O-isopropylidene-β-D-ribofuranosiduronate (6). The alcohol (3.48g, 12.0

mmol) was dissolved in a mixture of carbon tetrachloride (30 mL) and acetonitrile (30 mL). An aqueous solution of ruthenium trichloride trihydrate (40 mL, 0.30 mmol, 2.2 mol%, from a stock aqueous solution of $RuCl_3.3H_2O$; 1.9mg/mL) was added and the mixture vigorously stirred at R.T. Periodic acid (10,0g, 43.4 mmol) was added portionwise over a period of 1h. Stirring was continued for an additional 6h. Ethylene glycol (1 mL) was added to destroy unreacted oxidants; the mixture was stirred for 30 min and then CH_2Cl_2 (50 mL) was added. The aqueous phase was separated and backextracted with CH_2Cl_2 (2x20 mL). The combined organic extracts were washed with 10% aq. sodium thiosulfate (2x20 mL), water and then dried (Na_2SO_4). The filtered solution was concentrated, the residual acid was taken into ether (30 mL), cooled to 0°C in an ice-bath and treated with excess ethereal diazomethane. After 2h at 0°C, glacial acetic acid was carefully added, and the mixture washed with water (2x20 mL), saturated aq. $NaHCO_3$ (4x20 mL) and dried (Na_2SO_4). The filtered solution was concentrated and purified by chromatography (1:9 ethyl acetate-petroleum ether) to give the ester as a pale yellow oil (2.28 g, 73.6%). ν_{max} (neat): 2950, 2900, 1763 and 1740 cm^{-1}. δ_H: 0.00 (s, 9H, Me_3Si), 0.65-1.0 (m, 2H, CH_2Si), 1.25 (s, 3H, Me), 1.45 (s, 3H, Me), 3.35-3.55 (m, 1H, C*H*CH_2Si), 4.54 (t, 1H, J= 6.6 Hz, H-3), 4.56 (bs, 1H, H-4), 5.12 (s, 1H, H-1) and 5.25 (d, 1H, J= 6.6 Hz, H-2). δ_C: -1.48, 17.88(-), 24.94, 28.30, 52.15, 65.14(-), 82.05, 83.32, 84.43, 107.35, 112.58 and 170.52. Anal. Calcd for $C_{14}H_{26}O_6Si$: C, 52.80; H, 8.24. Found: C, 53.00; H, 8.15.

Methyl (4R, 5R)-4-hydroxy-5-trimethylsilylethoxy-4,5-dihydro-2-furancarboxylate (7). A solution of NaOMe in MeOH was prepared by dissolving Na metal (1.0g, 32.06 mmol) in dry MeOH (75 mL) at 0°C under nitrogen. This solution was then warmed in an oil bath at 40°C. A solution of the ester **6** (4.39g, 10.6 mmol) in dry MeOH (5 mL) was added dropwise via cannula (plus additional 5 mL dry MeOH rinse) to the NaOMe solution under nitrogen. After 24h, the reaction mixture was cooled to 0°C in an ice-bath. Concentrated HCl acid (3.5 mL) was carefully added to neutralize the solution and a light brown mixture resulted. The mixture was concentrated on the evaporator to about 15 mL. Ethyl acetate (60 mL) was added followed by water (20 mL). The aqueous layer was separated and reextracted with ethyl acetate (2x30 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated to give a yellow oil. Chromatographic purification (1:2 ethyl acetate-petroleum ether) gave a pale yellow oil (2.73g, 75.9%) which slowly crystallized. mp (ether-petroleum ether): 45-47°C. $[\alpha]_D^{28}$ -253.5° (c. 1.89, $CHCl_3$). ν_{max} (nujol): 3231-3569, 1732 and 1632 cm^{-1}. δ_H: 0.00 (s, 9H, Me_3Si), 0.85-1.05 (m, 2H), 2.90-3.30 (bs, OH), 3.60-3.75 (m, 2H), 3.80 (s, 3H, OMe), 4.70 ('t', 1H, J= 2.4, 1.2 Hz, H-4), 5.39 (d, 1H, J= 1.2 Hz, H-5) and 6.02 (d, 1H, J= 2.4 Hz, H-3). δ_C: -1.46, 17.93(-), 52.39, 67.91(-), 78.86, 111.23, 111.59, 149.98 and 160.10. Anal Calcd. for $C_{11}H_{20}O_5Si$: C, 50.74; H, 7.75. Found: C, 50.32, H, 7.38.

(4R, 5R)-4-[2'-Bromo-1'(α:β)-ethoxyethoxy]-5-trimethylsilylethoxy-4,5-dihydro-2-furancarboxylate (4). A 1M solution of 1,2-dibromoethyl ethyl ether was prepared: Ethyl vinyl ether (6.04 mL) was dissolved in dry CH_2Cl_2 (60 mL) and cooled to -78°C, under N_2. Bromine (3.07 mL) was added dropwise to the solution and the mixture was stirred at -78°C for 20 min. and then warmed slowly to R.T.

A CH_2Cl_2 solution of 1,2-dibromoethyl ethyl ether (45 mL, 44.83 mmol) was cooled to -78°C, under N_2, and a solution of the enol-ether 7 (2.05g, 10.19 mmol) and dry Et_3N (7.2 mL, 51.96 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise via cannula (with additional 5 mL dry CH_2Cl_2 rinse). After addition was complete, the reaction mixture was stirred at -78°C for 30 min and at R.T. for 18h. The mixture was cooled to 0°C in an ice-bath and saturated aq. $NaHCO_3$ (20 mL) was added. The CH_2Cl_2 layer was separated and the aqueous layer was reextracted with CH_2Cl_2 (2x20 mL). The combined organic layers were washed with water, dried (Na_2SO_4), filtered and concentrated to give an oil. Flash chromatographic purification (1:6 ethyl acetate-petroleum ether) gave a colorless oil (3.60g, 86%). ν_{max} (neat): 1637.8 and 1737 cm^{-1}. δ_H: 0.0 (s, 9H, Me_3Si), 0.85-1.0 (m, 2H, CH_2Si), 1.22 (t, 3H, J= 6.6 Hz, Me), 3.33 (d, 2H, J= 6.2 Hz, CH_2Br), 3.50-3.75 (m, 3H, OCH_2, $CHCH_2Si$), 3.80 (s, 3H, OMe), 4.70-4.85 (m, 2H, CHOEt, H-2), 5.49 and 5.50 (s, H-1), 5.97 and 5.99 (d, J= 2.8 Hz, H-3).

Trimethylsilyl Methyl-3-C-(2-ethanal)-β-L-lyxofuranuronate-2,3-[2'(α:β)-ethoxy]-tetrahydrofuran (8). The bromoacetal 4 (373.9 mg, 0.9097 mmol) was dissolved in dry degassed benzene (12 mL) under N_2, and the solution was refluxed. A solution of n-Bu_3SnH (366 uL, 1.364 mmol) and AIBN (30 mg, 0.1819 mmol) in dry degassed benzene (34 mL) was added dropwise by syringe infusion pump to the refluxing solution over a period of 3h. After this time, the mixture was refluxed for another 1h. The cooled reaction mixture was concentrated, the residue was taken into ether (30 mL) and aqueous 10% KF solution was added. The mixture was stirred for 1h at R.T. The ethereal layer was carefully separated from the aqueous phase, the aqueous phase extracted once with ether (10 mL) and the combined ethereal layers were dried ($MgSO_4$), filtered and concentrated. Chromatographic purification, initially using 1:9 and then 1:5 ethyl acetate-petroleum ether, gave a diastereoisomeric mixture of the bicyclic ester (285.1 mg, 94.4%). ν_{max} (neat): 1765 and 1725 cm^{-1}. δ_H: 0.00 (s, 9H, Me_3Si), 0.80-0.95 (m, 2H), 1.15 and 1.18 (t, J= 7.2 Hz, Me), 1.60-2.20 (m, 2H, CH_2), 3.10-3.95 (m, 5H), 4.51 d, 1H, J= 6.8 Hz, H-4), 4.72 (d, 1H, J= 7.5 Hz, H-6a), 5.08 and 5.15 (dd, 1H, J= 4.6, 1.7 Hz, H-2), 5.12 and 5.16 (s, 1H, H-6). Anal. Calcd for $C_{15}H_{28}O_6Si$: C, 54.18; H, 8.49. Found: C, 54.21; H, 8.67.

For further structural confirmation, a sample of the bicyclic ester 8 (40 mg) was hydrolysed in aqueous 60% CF_3CO_2H - dioxane (1:1) at 60°C for 3h followed subsequently by Jones oxidation of the hemiacetal to provide the γ-lactone 9 (26.0 mg, 70%). mp. 76-78°C. $[\alpha]_D^{28}$ -67.95° (c. 1.89, $CHCl_3$). ν_{max} (CH_2Cl_2): 1790 and 1760 cm^{-1}. δ_H: 0.00 (s, 9H, Me_3Si), 0.70-0.95 (m, 2H, CH_2Si), 2.30 (dd, 1H, J= 14.4, 3.5 Hz, H-3), 2.65 (dd, 1H, J= 14.4, 8.9 Hz, H-3'), 3.35-3.60 (m, 2H, H-3a, $CHCH_2Si$), 3.62-3.74 (m, 1H, $CHCH_2Si$), 3.80 (s, 3H, OMe), 4.75 (d, 1H, J= 7.20 Hz, H-4), 4.85 (d, 1H, J= 7.20 Hz, H-6a) and 5.25 (s, 1H, H-6). δ_C: -1.41, 17.85(-), 29.96(-), 39.64, 52.52, 65.65(-), 78.17, 85.94, 105.42, 189.12 and 174.50. CIMS m/z: 320 (M + NH_4).

Diisobutylaluminium Hydride Reduction of Bicyclic-Ester (8) and Reaction with Heptyl or Methylmagnesium Bromide. Compound 8 (139.6 mg, 0.4204 mmol) was dissolved in dry toluene (5 mL), under argon and the solution was cooled to -78°C. Diisobutylaluminium hydride (0.441 mL. 0.4414 mmol,

1M in toluene) was added dropwise to the ester solution at -78°C. The reaction mixture was stirred at -78°C for 4h. Saturated aqueous NH_4Cl (2 mL) was added at -78°C, the cooling bath removed and the reaction mixture allowed to warm slowly to R.T. Anhydrous Na_2SO_4 was added and the mixture stirred for 30 min, filtered and the residue washed with ether (2x10 mL). The filtrate was concentrated on the evaporator to give the aldehyde (119.5 mg). The aldehyde was used in the next step without further purification. ν_{max} (neat): 1733.9 cm^{-1}. δ_H: 0.00 (s, 9H, Me_3Si), 0.80-0.95 (m, 2H, CH_2Si), 1.12 and 1.16 (t, 3H, J= 6.6 Hz, Me), 1.60-2.10 (m, 2H, H-3), 3.10-3.95 (m, 5H, H-3a, CH_2CH_2Si, OCH_2), 4.40 and 4.45 (bd, 1H, J= 7.6 Hz, H-4), 4.52 and 4.59 (d, 1H, J= 7.3 Hz, H-6a), 4.97-5.20 (m, 1H, H-2), 5.12 and 5.18 (s, 1H, H-6), 9.67 (d, J= 2.5 Hz) and 9.72 (bs) (1H, CHO).

(a) Reaction of Aldehyde with Heptylmagnesium Bromide. Heptylmagnesium bromide was prepared by the reaction of heptyl bromide (0.198 mL, 1.2612 mmol) with Mg metal (31.0 mg, 1.2612 mmol) in refluxing dry ether (5 mL) under nitrogen. After all Mg metal has reacted, the Grignard solution was cooled to R.T. and then added dropwise via cannula (3 mL dry ether rinse) to a solution of the aldehyde (119.5 mg) in dry ether (2 mL) at -10°C (ice-salt bath), under nitrogen. The mixture was stirred at -10°C for 2h and then warmed slowly to R.T. After 6h, the reaction mixture was cooled to 0°C and saturated aqueous NH_4Cl (5mL) and ether (20 mL) was added. The milky mixture was diluted with aqueous 1M HCl (10 mL) and the ethereal layer separated. The aqueous phase was reextracted with ether (15 mL) and the combined ethereal phases were washed with water (10 mL), saturated aqueous $NaHCO_3$ (10 mL), brine and dried (Na_2SO_4). The filtered solution was evaporated on the evaporator and the residual oil purified by chromatography (1:8 ethyl acetate-petroleum ether) to give the alcohol as a colorless oil (154.3 mg, 91.3%). ν_{max} (neat): 3350-3600 cm^{-1}. δ_H: 0.00 (s, 9H, Me_3Si), 0.75-1.00 (m, 5H), 1.10-1.60 (m, 16H), 1.80-2.40 (m, 2H), 2.80-3.00 (m, 1H), 3.30-3.90 (m, 5H), 3.95-4.10 (m,1H), 4.50 and 4.57 (d, 1H, J= 7.6 Hz, H-6a), 4.95 and 5.10 (s,1H, H-6) and 5.10-5.25 (m, 1H, H-2). CIMS m/z : 420 ($M + NH_4$), 374 ($M - C_2H_5$).

(b) Reaction of Aldehyde with Methylmagnesium Bromide. Methylmagnesium bromide (1.158 mL, 3.477 mmol, 3M in ether) was added to the aldehyde [prepared by DIBAH (1.21 mL) reduction of the bicyclic ester (384.4 mg, 1.159 mmol) under the same conditions as described above] to furnish the secondary alcohol as a colorless oil (281.4 mg, 80.4%). ν_{max} (neat): 3250-3600, 2953 and 2922 cm^{-1}. δH: 0.00 (s, 9H, Me_3Si), 0.80-1.00 (m, 2H, CH_2Si), 1.16 and 1.18 (t, 3H, J= 7.2 Hz, Me), 1.27 and 1.28 (d, 3H, J= 6.6 Hz, Me), 1.70-2.10 (m, 2H, CH_2), 2.85-3.05 (m, 1H, H-3a), 3.30-3.60 (m, 3H), 3.65-3.75 (m, 2H), 3.80-4.00 (m, 1H), 4.15-4.20 (m, 1H), 4.48 and 4.57 (d, 1H, J= 7.2 Hz, H-6a) 4.93-4.98 (s, 1H, H-6), 5.08-5.20 (m, 1H, H-2). Anal. Calcd for $C_{13}H_{30}O_5Si$: C, 56.57; H, 9.50. Found: C, 56.17; H, 9.38.

Trimethylsilylethyl 3,5-Dideoxy-3-C-(2-ethanal)-5-C-(n-heptyl)-β-L-lyxofuranoside-2,3-[2'(α:β)-ethoxy]-tetrahydrofuran (10a). The alcohol **3a** (328.5 mg, 0.8172 mmol) was disolved in dry CH_3CN (4 mL) containing DMAP (697.5 mg, 5.720 mmol). Phenoxythiocarbonyl chloride (248 uL, 1.798 mmol) was added dropwise; a bright yellow precipitate was formed which slowly dissolved. The reaction mixture was stirred at R.T. for 18h, under argon and then ethyl acetate (30 mL) and brine (15 mL) were added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (10 mL). The combined organic

layers were washed with water (2x15 mL) and dried (Na_2SO_4). The filtered solution was concentrated and the crude product purified by chromatography (1:5 ethylacetate-petroleum ether) to give the phenylthiocarbonate as a pale yellow oil (390.2 mg, 88.7%). ν_{max} (neat): 2950, 2925, 2850, 1765, 1542 and 1491 cm^{-1}. δ_H: 0.00 (s, 9H, Me_3Si), 0.75-1.00 (m, 5H), 1.15 (t, 3H, J= 6.2 Hz, Me), 1.20-2.10 (m, 15H). 2.75-2.95 (m, 1H, H-3a), 3.35-3.85 (m, 4H, OCH_2, CH_2CH_2Si), 4.22 and 4.27 (dd, 1H, J= 9.1, 5.6 Hz, H-4), 4.50 and 4.53 (d, J= 6.7 Hz, H-6a), 4.98 and 5.03 (s, 1H, H-6), 5.08-5.18 (m, 1H, H-2) and 5.65-5.80 (m, 1H, CHOC=S). CIMS m/z: 556 (M + NH_4).

The phenylthiocarbonate (304.8 mg, 0.565 mmol) was dissolved in dry degassed benzene (10 mL) and the solution was gently refluxed under N_2. A solution of n-Bu_3SnH (304 uL, 1.133 mmol) and AIBN (46.4 mg, 0.2832 mmol) in dry degassed benzene (10 mL) was added dropwise via a syringe infusion pump over a period of 3h. After addition was complete, the mixture was refluxed for an additional 1h. The cooled reaction mixture was concentrated, the residue taken into ether (30 mL) and aqueous 10% KF (15 mL) was added. The mixture was stirred vigorously for 1h. at R.T. The ethereal layer was separated and the aqueous phase reextracted once with ether (10 mL). The combined ether extracts were dried (Na_2SO_4), filtered and concentrated. Chromatographic purification (1:1 ethyl acetate-petroleum ether) provided the deoxygenated compound **10a** as a colorless oil (211.6 mg, 96.7%). ν_{max} (neat): 2981, 2931, 2854 and 1450 cm^{-1}. δ_H: 0.00 (s, 9H, Me_3Si), 0.75-0.95 (m, 5H), 1.17 (t, 3H, J= 6.6 Hz, Me), 1.20-1.45 (bs, 14H), 1.70-2.02 (m, 2H, H-3), 2.70-3.10 (m, 1H, H-3a), 3.35-3.58 (m, 2H), 3.60-3.80 (m, 2H), 4.00-4.18 (m, 1H, H-4), 4.46 and 4.51 (d, 1H, J= 7.3 Hz, H-6), 4.88 and 4.95 (s, 1H, H-6) and 5.07-5.25 (m, 1H, H-2). CIMS m/z: 371 (M - CH_3), 358 (M - C_2H_4), 269 (M - $O(CH_2)_2SiMe_3$). Anal. Calcd for $C_{21}H_{42}O_4Si$: C, 65.23; H, 10.96. Found: C, 64.93; H, 10.66.

Trimethylsilylethyl 3,5-Dideoxy-3-C-(2-ethanal)-5-C-(methyl)-β-L-lyxofuranoside-2,3-[2'(α:β)-ethoxy]-tetrahydrofuran (10b). Similarly, treatment of the alcohol **3b** (274.2 mg, 0.8623 mmol) with phenoxythiocarbonyl chloride (262 uL, 1.897 mmol) in the presence of DMAP (736.9 mg, 6.036 mmol) provided the corresponding phenylthiocarbonate (291.2 mg, 74.3%). ν_{max} (neat): 2952, 2925, 2875, 1761, 1591 and 1490 cm^{-1}. δ_H: 0.00 (s, 9H, Me_3Si), 0.85-1.00 (m, 2H, CH_2Si), 1.15 (t, 3H, J= 7.0 Hz, Me), 1.41 (t, 3H, J= 6.0 Hz, Me), 1.70-2.15 (m, 2H), 2.80-2.95 (m, 1H, H-3a), 3.35-3.90 (m, 4H), 4.26 (dd, 1H, J= 10.0, 6.8 Hz, H-4), 4.55 (d, 1H, J= 6.8 Hz, H-6a), 5.05 (s, 1H, H-6), 5.07-5.20 (m, 1H, H-2) and 5.56-5.73 (m, 1H, C*H*OC=S).

The phenylthiocarbonate (291.2 mg, 0.6413 mmol) was dissolved in dry degassed benzene (10 mL) and refluxed under N_2. A solution of n-Bu_3SnH (345 uL, 1.283 mmol) and AIBN (52.5 mg, 0.3206 mmol) in dry degassed benzene (10 mL) was added dropwise via a syringe infusion pump to the refluxing solution over a period of 3h. After addition was complete, the mixture was refluxed for an additional 1h and then cooled to R.T. Benzene was removed under reduced pressure and the crude product was processed in the same manner as described for **10a** to give, after chromatographic purification (1:7 ethyl acetate-petroleum ether), **10b** as an oil (147 mg, 75.9%). δ_H: 0.00 (s, 9H, Me_3Si), 0.92 (t, 3H, J= 7.0 Hz, Me), 0.85-1.00 (m, 2H), 1.18 (t, 3H, J= 7.0 Hz, Me), 1.40-2.10 (m, 4H), 2.70-3.10 (m, 1H, h_3), 3.35-3.85 (m, 4H), 3.95-

4.10 (m, 1H, H-4), 4.51 and 4.52 (d, 1H, J=7.5 Hz, H-6a), 4.95 (s, 1H, H-6) and %.05-5.25 (m, 1H, H-2). Anal. Calcd. for $C_{22}H_{34}O_6SSi$: C, 58.12; H, 7.54. Found: C, 58.28; H, 7.94.

3-C-(Carboxymethyl)-3,5-dideoxy-5-C-(n-heptyl)-L-lyxono-1,4-lactone-2,3-γ-lactone (13a). The bis-ketal **10a** (211.6 mg, 0.5482 mmol) was dissolved in a mixture of dioxane and 0.5% aqueous H_2SO_4 (5:2, 8 mL). The mixture was refluxed for 3h, allowed to attain R.T. and then cooled to 0°C in an ice-bath. Excess solid $NaHCO_3$ was added to neutralize the acid, the reaction mixture was concentrated on the evaporator and the residue azeotroped twice with toluene (15 mL). The residue was extracted with ethyl acetate (3x15 mL); the combined organic extracts were dried (Na_2SO_4), filtered and concentrated. Chromatographic purification of the residue (1:5 ethyl acetate-peteroleum ether) provided the monolactol **11a** as an oil(33.1 mg), $\nu_{max.}$ (neat): 3209-3552 cm^{-1}. δ_H: 0.00 (s, 9H, Me_3Si), 0.89 (t, 3H, J= 6.6 Hz, Me), 0.85-0.95 (m, 2H), 1.15-1.60 (m, 15H), 1.80-2.10 (m, 2H), 2.80-2.90 and 2.95-3.10 (m, 1H, H-3a), 3.40-3.60 (m, 1H, C*H*CH_2Si), 3.65-3.80 (m, 1H, C*H*CH_2Si), 4.05-4.20 (m< 1H, H-4), 4.57 and 4.61 (d, 1H, J= 6.3 Hz, H-6a), 4.87 (s) and 5.00 (s)(1H, H-6), 5.33 (bd) and 5.55 ('t')(1H, H-2), and the known bislactol[36] **12a** (97.6 mg). The monolactol was resubjected to hydrolysis under the same conditions to give in a combined yield of bislactol (109.9 mg, 77.7%).

The bislactol **12a** (109.9 mg, 0.4260 mmol) was dissolved in reagent grade acetone (5 mL) and then cooled to 0°C. A solution of chromic acid[12] was added dropwise to the solution until a persistent reddish-brown mixture resulted. The reaction mixture was stirred for 1h at R.T. and Celite (600 mg) was added followed by a few drops of isopropanol. Solid anhydrous Na_2CO_3 (500 mg) was added, the mixture stirred briefly and then filtered. The acetone solution was concentrated and the residue flash chromatographed (1% acetone in CH_2Cl_2) to give the bislactone **13a** (75.0 mg, 70%). mp (ethyl acetate-petroleum ether): 111-113°C (lit.[36,44] 110.5-111.5°C). $[\alpha]_D^{28}$ -7.50° (c. 1.37, $CHCl_3$) {lit.[36] $[\alpha]_D^{20}$ -7.52 (c. 1.08, $CHCl_3$); lit.[44] $[\alpha]_D^{20}$ -7.35 (c. 1.00, $CHCl_3$)}. $\nu_{max.}$ (CH_2Cl_2): 3036, 2925, 2855 and 1789 cm^{-1}. δ_H: 0.85 (t, 3H, J= 6.6 Hz, Me), 1.15-1.90 (m, 15H), 2.60 (d, 2H, J= 10.8 Hz, H-3), 3.46 (qd, 1H, J= 9.3, 9.3, 9.3, 5.4 Hz, H-3), 4.60 (dt, 1H, J=4.8, 9.3, 4.8 Hz, H-4) and 5.15 (d, 1H, J= 8.4 Hz, H-6a). δ_C: 14.08, 22.82(-), 25.46(-), 28.87(-), 29.13(-), 29.19(-), 29.28(-), 31.39(-), 31.78(-), 39.40, 76.98, 78.76, 170.80 and 173.76. EIMS m/z (relative intensity): 255 (M + 1, 4.5), 141 (M - C_8H_{17}, 8), 97 (M - C_8H_{17} - CO_2, 100).

3-C-(Carboxymethyl)-3,5-dideoxy-5-C-(methyl)-L-lyxono-1,4-lactone-2,3- γ -lactone (13b). The deoxy-compound **10b** (176 mg, 0.5827 mmol) was dissolved in the dioxane-0.5% aqueous H_2SO_4 mixture (4 mL) and then refluxed for 3h yielded a mixture of monolactol **11b** (72.0 mg) and bislactol (48.0 mg) as oils. Resubjection of the monolactol to the same hydrolytic conditions gave the oily bislactol **12b** in a final yield of 78.7% (80.0 mg). Jones[12] oxidation of the bislactol (75.0 mg) in acetone gave, after chromatographic purification (1:8 acetone-CH_2Cl_2), white crystalline bislactone **13b** (47.0 mg, 63.3%). mp (ethylacetate): 97-100°C. $[\alpha]_D^{28}$ -27.2° (c. 1.39, $CHCl_3$). $\nu_{max.}$ (CH_2Cl_2): 3057, 2976, 2941, 2885 and 1794 cm^{-1}. δ_H: 1.01 (t, 3H, J= 7.5 Hz, Me), 1.50-1.70 (m, 1H, C*H*Me), 1.72-1.95 (m, 1H, C*H*Me), 2.60 (d, 2H, J= 9.9 Hz, CH_2CO_2), 3.50 (qd, 1H, J= 10.1, 10.1, 10.1, 5.2 Hz, H-3), 4.53 (dt, 1H, J= 10.4, 7.8, 7.8 Hz, H-4) and 5.16

(d, 1H, J= 10.4 Hz, H-6a). δ_C: 9.73, 24.51(-), 26.65(-), 39.02, 78.99, 80.05, 170.7 and 173.8. EIMS m/z (relative intensity): 171 (M + 1, 18), 141 (M - C_3H_5, 6), 97 (M - C_2H_5 - CO_2, 100), 57 ($C_2H_5CO^+$, 91).

Synthetic (-)-Isoavenaciolide (2a). α-Methylenation of the bislactone **13a** (27.3 mg) was performed as described by Parker and Johnson[31] to give, after chromatographic purification (1:4 ether-benzene), (-)-isoavenaciolide (15.5 mg, 65%) as a white crystalline solid. mp (ether-petroleum ether): 130-132°C (lit.[1b] 129-130°C; lit.[3e] 127-128°C). $[\alpha]_D^{28}$ -150 (c, 0.58, ethanol) {lit.[1b] $[\alpha]_D^{27}$ -154° (1.1% in ethanol); lit.[3e] $[\alpha]_D^{27}$ -167° (c. 1.20, ethanol)}. $\nu_{max.}$ (CH_2Cl_2): 3054, 2927, 2856, 1783 and 1654 cm^{-1}. δ_H: 0.89 (t, 3H, J= 7.2 Hz, Me), 1.15-1.40 (bs, 12H), 1.40-1.70 (m, 5H), 3.97 (tt, 1H, J= 8.7, 8.7, 2.8, 2.8 Hz, H-3a), 4.75 (dq, 1H, J= 10.7, 8.6, 3.6 Hz, H-4), 5.09 (d, 1H, J= 8.7 Hz, H-6a), 5.85 (d, 1H, J= 2.2 Hz, =CH) and 6.58 (d, 1H, J= 2.2 Hz, =CH). δ_C: 14.03, 22.59(-), 26.03(-), 29.12(-), 29.31(-), 31.75(-), 32.35(-), 41.69, 74.71, 80.40, 128.88(-), 130.81, 167.34 and 169.93. EIMS m/z (relative intensity): 267 (M + 1, 2), 141 (M - $C_8H_{17}CO^+$, 6), 96 ($C_5H_4O_2^+$, 100).

Synthetic (-)-Ethisolide (2b). Similarly, α-methylenation[31] of the bislactone **13b** (27.1 mg) yielded white crystalline (-)-ethisolide (14.5 mg, 50%). mp (acetone-petroleum ether): 116-118°C. $[\alpha]_D^{28}$ -214 (c, 0.481, ethanol). {lit.[1b] mp. 122-123°; $[\alpha]_D^{27}$ -214° (c. 1.2% in ethanol}. $\nu_{max.}$ (CH_2Cl_2): 3055, 2983, 1782 and 1656 cm^{-1}. δ_H: 1.10 (t, 3H, J=7.2 Hz, Me), 1.50-1.57 (m, 2H, CH_2), 3.97 (tt, 1H, J= 8.6, 8.6, 2.8, 2.8 Hz, H-3a), 4.66 (dq, 1H, J= 8.6, 8.6, 4.4 Hz, H-4), 5.10 (d, 1H, J= 8.6 Hz, H-6a), 5.86 (d, 1H, J=2.6 Hz, =CH) and 6.59 (d, 1H, J= 2.6 Hz, =CH). δ_C: 10.58, 25.67(-), 41.60, 74.76, 81.82, 128.85(-), 130.79, 167.50 and 170.00. EIMS m/z (relative intensity): 183 (M + 1, 1), 125 (M - $C_2H_5CO^+$, 6), 96 ($C_5H_4O_2^+$, 100), 57 ($C_2H_5CO^+$, 22).

Acknowledgement: We would like to thank Professors D. Clive, University of Alberta and P. Smith, University of Saskatchewan for their assistance in obtaining elemental analyses and mass spectra. We gratefully acknowledge the President's NSERC fund, University of Regina, for financial support and also for providing travel assistance to the University of Alberta for running N.M.R. experiments during the initial part of this work.

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