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Synthesis of (±)-Isoavenaciolide and of (±)-Ethisolide from (±)-7-Oxabicyclo[2.2.1]hept-5-en-2-one.

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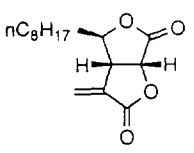
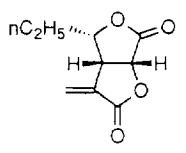
Abstract : A short total synthesis of (±)-ethisolide and (±)-isoavenaciolide was accomplished from (±)-oxanorbornenone respectively in 11 and 12 steps, using a radical cyclization as a key step.

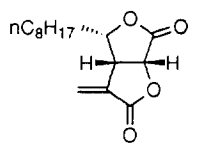
Avenaciolide **1**, ethisolide **2** and isoavenaciolide **3** are interesting antifungal metabolites isolated from *Aspergillus avenaceus*. These compounds have attracted attention due to their biological activity as well as their unique bislactone skeleton. Recently avenaciolide was found to inhibit glutamate transport in rat liver mitochondria.[1]



1
Avenaciolide



2
Ethisolide

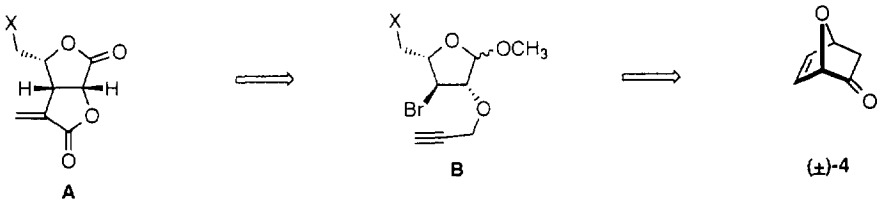


3
Isoavenaciolide

These bislactones have attracted numerous synthetic efforts that are notable for their strategic diversity.[2-3] Numerous syntheses of avenaciolide [2] have been reported, however, relatively less attention has been directed toward the synthesis of isoavenaciolide [2] and ethisolide.[3] Herein, we would like to present the synthesis of (±)-isoavenaciolide and (±)-ethisolide [4] from (±)-7-oxabicyclo[2.2.1]hept-5-en-2-one **4**, the racemic form of a "naked sugar".[5]

As isoavenaciolide and ethisolide differ only at the C-4 substituent, our plan was to prepare a hexofuranoside intermediate of type **B** which could be involved in a radical cyclization and which possesses a suitable functional group at C-4 that will then be transformed into the appropriate alkyl side chain (Scheme I).

Scheme I Retrosynthesis of ethisolide and isoavenaciolide



Our synthesis of (±)-ethisolide, (Scheme II), began with the transformation of racemic 7-oxanorbornenone **4** into the corresponding propargyl acetal **5**. The latter was obtained in 86% yield by condensation of **4** with propargyloxytrimethylsilane in the presence of trimethylsilyltriflate (TMSOTf) at 0°C. Acetal **5** reacted with Br_2 in CH_2Cl_2 at -78°C to give **6** isolated in 98% yield after quenching with aqueous $NaHCO_3$ (-78°C). This reaction was regio- and stereoselective. [4] When run at a temperature higher than -78°C, only products arising from decomposition was observed. The coupling constant ^3J = 0.0 Hz between H-C(4) and H-C(5) in compound **6** implies an *exo*-configuration for the bromine atom. The *trans* relationship for H-C(5) and H-C(6) was confirmed by the value of $^3J_{5,6}$ = 1.5 Hz. The Baeyer-Villiger oxidation of **6** with *m*-CPBA (*meta*-chloroperbenzoic acid) in CH_2Cl_2 containing $NaHCO_3$ gave lactone **7** (96%). Treatment of **7** with MeOH and $SOCl_2$ [6] led to a 8:1 mixture of the methylfuranosides **8** and **8'** (91%) which were separated by flash chromatography. The synthesis was continued only with the major isomer **8** to facilitate the analysis of the NMR data, however the same reaction pathway applied to **8'** would lead to **14**. Furthermore **8'** can be easily equilibrated with **8** by treatment with MeOH / $SOCl_2$. [7]

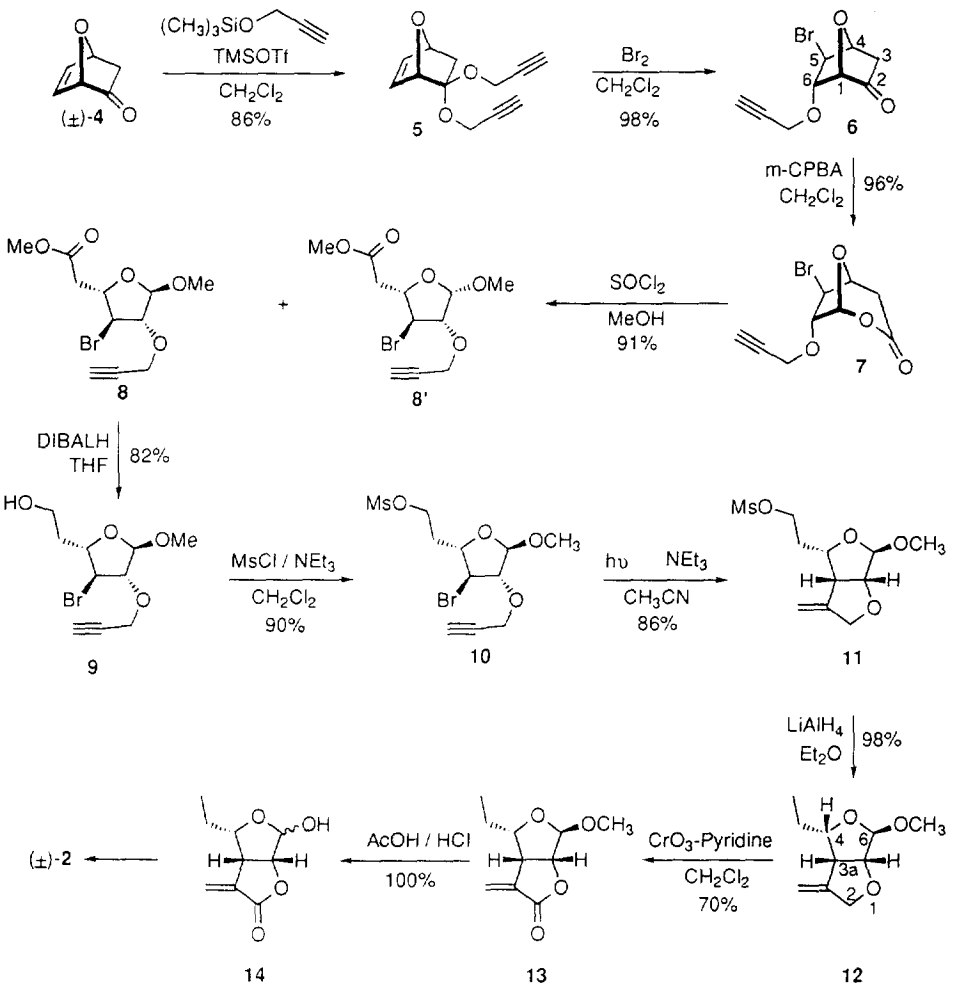
Compound **8** was then reduced with diisobutylaluminium hydride (DIBALH) in THF at -50°C and generated **9** (82%) which was then treated with methanesulfonyl chloride in the presence of triethylamine in CH_2Cl_2 (20°C) to afford the corresponding mesylate **10** (90%). The bicyclic structure of ethisolide was then built up by treating **10** with Bu_3SnH in the presence of a catalytic amount of azabisisobutyronitrile (AIBN) in refluxing toluene for twelve hours. [8] Under these conditions, a 5-exo-dig radical cyclization took place, giving **11** in 80% yield.

An alternative approach to **11** was carried out by the irradiation of **10** at 254 nm in the presence of triethylamine (5 eq) [9] for one hour. Under these conditions, **11** was obtained rapidly with a yield of 86%.

Reduction of the mesylate group of **11** with $LiAlH_4$ led to **12** in nearly quantitative yield. The large vicinal coupling constant of $^3J_{4,3a}$ = 7.1 Hz indicates that H-C(4) and H-C(3a) (ethisolide numbering) in the compound **12** are in a *cis* relationship. [10] Oxidation of **12** with CrO_3-pyridine [11] in CH_2Cl_2 afforded **13** (70%) which was then hydrolyzed (50 % aqueous AcOH, 80 °C, 4h) into lactol **14** quantitatively. The latter was transformed into (±)-ethisolide **2** with a yield of 80% using a catalytic amount of tetra-*n*-propylammonium perruthenate (TPAP) in the presence of N-methylmorpholine-N-oxide (NMO).[12]

(±)-Ethisolide was thus obtained in 11 steps from (±)-oxanorbornenone with an overall yield of 25%.

Scheme II : Synthesis of (±)-ethisolide

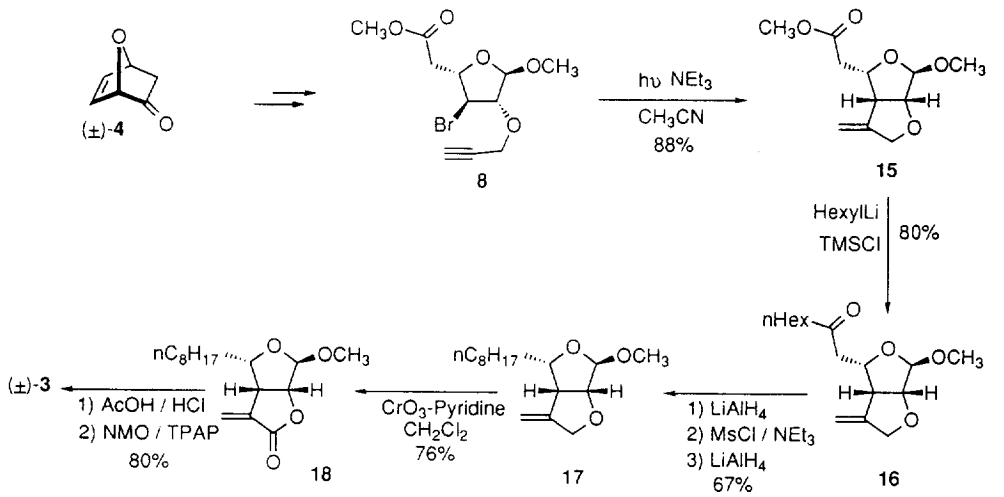


(±)-Isoavenaciolide has also been obtained from intermediate **8** in 8 steps (Scheme III). Compound **8** was cyclized reductively into derivative **15** on treatment with Bu_3SnH in the presence of AIBN or by irradiating it at 254 nm in the presence of triethylamine. As observed previously, the photoinduced reductive cyclization led to a better yield (88%) than the chemical process (81%). The ester moiety was converted *via* ketone **16** into the alkyl side chain. Addition of hexyllithium to **15** in the presence of TMSCl [13] produced the corresponding ketone **16** isolated with a yield of 80%. Treament of **16** with $LiAlH_4$ led to a 1:1 mixture of two alcohols which were not separated, but treated directly by mesyl chloride in the presence of triethylamine, followed by reduction by $LiAlH_4$. The overall yield of these three successive reactions leading to **17** was 67%. Oxidation of **17** into lactone **18** was achieved in 86% yield using chromium oxide-pyridine. After hydrolysis of **18** with a mixture of AcOH/HCl, the corresponding lactol was obtained and oxidized with NMO in the presence of a

catalytic amount of tetra-*n*-propylammonium perruthenate. (±)-Isoavenaciolide **3** was thus isolated with a yield of 80 %.

The synthesis of (±)-isoavenaciolide required 12 steps from (±)-oxanorbornenone **4** with an overall yield of 21%.

Scheme III : Synthesis of (±)-isoavenaciolide



The structures of (±)-**2** and (±)-**3** were ascertained by their spectral data and by their comparison with those reported for (±)-**2** [3] and (±)-**3** [2] Since both (-)- and (+)-7-oxanorbornenone can be obtained in optically pure forms, [14] natural (-)-ethisolide and (-)-isoavenaciolide and their enantiomers should be obtained with the same ease as (±)-ethisolide and (±)-isoavenaciolide

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EXPERIMENTAL PART

General methods :

All experiments were run under an Ar atmosphere. THF, diethyl ether were freshly distilled from sodium / benzophenone. Benzene, dichloromethane, acetonitrile and triethylamine were distilled from CaH_2, and MeOH from magnesium. Flash chromatography was carried on Kieselgel 60 (230-400 mesh) and preparative tlc on Merck silica Kieselgel 60 GF_{254}.

Irradiations were performed at 254 nm with a merry-go-round system equipped with 8 low-pressure Philips TUV lamps. 10 o. d. mm quartz tubes were used.

Microanalyses were performed at the Service de Microanalyse de l'Université Pierre et Marie Curie.

Propargyloxytrimethylsilane. To a solution of propargyl alcohol (20.77 mL, 357 mmol) and hexamethyldisilazane (HMDS, 37.60 mL, 178 mmol) in CH_2Cl_2 at 0°C, was added dropwise trimethylsilyl

chloride (TMSCl, 4.52 mL, 35.7 mmol). After stirring at room temperature for 12 h, the mixture was filtered through a pad of Celite to eliminate the precipitate. The CH_2Cl_2 was removed by distillation at atmospheric pressure. Purification of the residue by distillation afforded pure propargyloxytrimethylsilane as colorless oil 41 g (90%), bp 107-110°C (760 mm) (litt.[15] : bp 108-110°C (760 mm)). Spectral data were in agreement with those previously described. [15] Propargyloxytrimethylsilane was redistilled from CaH_2 immediately before used.

(±)-(1*RS*, 4*RS*)-5,5-Bis(propargyloxy)-7-oxabicyclo[2.2.1]hept-2-ene ((±)-5). Trimethylsilyltrifluoro methanesulfonate ($CF_3SO_3SiMe_3$, 0.04 mL, 0.2 mmol) was added to a stirred solution of propargyloxytrimethylsilane (5.12 g, 40 mmol) and (±)-7-oxabicyclo[2.2.1]hept-5-en-2-one ((±)-**4**, 2.05 g, 18.5 mmol) in anhydrous CH_2Cl_2 (20 mL) cooled to 0°C. After stirring at 0°C for 40 min and at 20°C for 20 min, propargyloxytrimethylsilane (2.56 g) followed by $CF_3SO_3SiMe_3$ (0.02 mL) was added. After 1 h at 20°C, saturated aqueous $NaHCO_3$ solution (20 mL) was added and the mixture was extracted with Et_2O (150 mL). The organic phase was washed with brine (10 mL), dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography (AcOEt/petroleum ether) yielding 3.27 g (86%) of **(±)-5** as a colorless oil: IR (neat) ν 3280, 2120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.53 (dd, 1H, J = 5.9, J = 1.7 Hz, HC(2)), 6.46 (dd, 1H, J = 5.9, J = 1.8 Hz , HC(3)), 5.30 (d, 1H, J = 4.9 Hz, HC(1)), 4.85 (m, 1H, HC(4)), 4.30 (dd, 2H, J = 15.5, J = 2.5 Hz, OCH_2), 4.20 (dd, 2H, J = 15.5, J = 2.4 Hz, OCH_2), 2.48 (t, 1H, J = 2.5 Hz, ≡CH), 2.46 (t, 1H, J = 2.4 Hz, ≡CH), 2.15 (dd, 1H, J = 11.6, J = 4.9 Hz , HC(6-*exo*)), 1.57 (d, 1H, J = 11.6 Hz, HC(6-*endo*)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.0, 133.0 (2 d, C(2), C(3)), 111.1 (s, C(5)), 81.1, 78.8 (2 d, C(1), C(4)), 79.6, 79.4 (2 d, 2 ≡CH), 74.2, 74.1 (2 s, 2 –C≡), 51.9, 51.2 (2 t, 2 OCH_2), 33.2 (t, C(6)); MS (70eV) *m z* 165 (2), 149 (11), 121 (11), 107 (19), 81 (58), 53 (100). Anal. Calcd. for $C_{12}H_{12}O_3$ (204.22): C, 70.58; H, 5.92. Found: C, 70.40; H, 6.12

(±)-5-*exo*-Bromo-6-*endo*-propargyloxy-7-oxabicyclo[2.2.1]heptan-2-one ((±)-6). A solution of Br_2 (0.99 mL, 19.4 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise to a vigourously stirred solution of dipropargyl acetal of 7-oxabicyclo[2.2.1]hept-5-en-2-one **(±)-5** (3.6 g, 17.6 mmol) in anhydrous CH_2Cl_2 (40 mL) cooled to -70°C under Ar atmosphere. A saturated aqueous solution of $NaHCO_3$ (15 mL) was added dropwise with stirring at -90°C, and the mixture was allowed to warm up to 0°C. The reaction mixture was then poured into a saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (5 × 25 mL). The organic phases were combined, and dried. The solvent was evaporated and the residue was purified by flash chromatography (Et_2O/petroleum ether). 4.23 g (98%) of **(±)-6** were obtained as colorless crystals: mp 68-69°C; IR (KBr) ν 3280, 2110, 1755 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.89 (d, 1H, J = 6.4 Hz, HC(4), 4.63 (m,1H, HC(6)), 4.51 (d,1H, J = 5.6 Hz, HC(1)), 4.28, 4.20 (2 dd, 2H, J = 16.1, J = 2.4 Hz, OCH_2), 4.08 (d, 1 H, J = 1.5 Hz, HC(5)), 2.60 (dd, 1H, J = 17.9, J = 6.4 Hz, HC(3-*exo*)), 2.57 (t, 1H, J = 2.4 Hz, H-C≡), 2.26 (d, 1H, J = 17.9 Hz, HC(3-*endo*)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.0 (s,C(2)), 85.3 (d, C(6)), 83.7 (d, C(4)),81.3 (d, C(1)), 77.8, 77.3 (C≡CH), 58.2 (t, OCH_2), 50.5 (d, C(5)), 41.9 (t, C(3)); MS (70 eV) *m z* 189-187 (4), 173-171(1), 165(34) 119 (52), 81 (100). Anal. Calcd. for $C_9H_9O_3Br$ (245.07): C, 44.11; H, 3.70. Found: C, 43.97; H, 3.78.

(±)-6-*exo*-Bromo-7-*endo*-propargyloxy-2,8-dioxabicyclo[3.2.1]octan-3-one ((±)-7). $NaHCO_3$ (0.197 g, 2.3 mmol) and *m*-chloroperbenzoic acid (Aldrich 80-90%, 0.354 g) were added to a stirred solution of **(±)-6** (0.380 g, 1.55 mmol) in CH_2Cl_2 (20 mL) cooled to 0°C. After 3 h at rt, the precipitate was filtered on Celite, and the solvent was evaporated. The residue was recrystallized from Et_2O/petroleum ether (1/4), yielding

0.390 g (96 %) of (±)-7 as colorless crystals: mp 75.5-76°C; IR (KBr) ν 3230, 2120, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.92 (d, 1H, *J* = 5.1 Hz, HC(1)), 4.71-4.77 (m, 2H, HC(5), HC(7)), 4.24, 4.35 (2 dd, 2H, *J* = 16.1, *J* = 2.4 Hz, OCH_2), 4.09 (d, 1H, *J* = 1.7, HC(6)), 3.10 (dd, 1H, *J* = 18.5, *J* = 6.8 Hz, HC(4-*exo*)), 2.68 (d, 1H, *J* = 18.5 Hz, HC(4-*endo*)), 2.57 (t,1H, *J* = 2.4 Hz, ≡CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.9 (s, C(3)), 99.5 (d, C(1)), 88.8, 81.7 (2 d, C(5), C(7)), 77.6 (s,-C≡), 76.6 (d, ≡CH), 57.9 (t, OCH_2), 49.4 (d, C(6)), 37.3 (t, C(4)); MS (70eV) *m z* 189-187 (7) 177-175 (8), 153 (23), 135 (36), 97 (100). Anal. Calcd. for $C_9H_9O_4Br$ (261.07): C, 41.41; H, 3.47. Found: C, 41.38; H, 3.45.

Methyl (±)-(methyl 2-*O*-propargyl-3-bromo-3,5-dideoxy-α-L-*arabino*-hexofuranosid)uronate ((±)-8). $SOCl_2$ (0.2 mL, 2.74 mmol) was added dropwise to a stirred suspension of **(±)-7** (0.35 g, 1.34 mmol) in MeOH (4 mL) at 25°C. After 4 days at rt, the mixture was cooled to 0°C and $NaHCO_3$ (0.7 g) was added portionwise in 10 min. The solvent was evaporated. The residue was dissolved with a saturated aqueous solution of $NaHCO_3$, and the mixture was extracted with CH_2Cl_2 (5 × 10 mL). The extracts were combined and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash chromatography (Et_2O/petroleum ether) to give 0.327 g of **(±)-8** (80 %) and 0.05 g of **(±)-8'** (11 %). **(±)-8** colorless oil: IR (neat) ν 3280, 2110, 1740 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$): δ 4.88 (br. s, 1H, HC(1)), 4.48 (ddd, 1H, *J* = 8.6, *J* = 8.6, *J* = 3.9 Hz, HC(4)), 4.2-4.3 (m, 3H, OCH_2 and HC(2)), 3.75 (dd, 1H, *J* = 9.0, *J* = 5.0 Hz, HC(3)), 3.70 (s, 3H, $COOCH_3$), 3.35 (s, 3H, OMe), 2.78 (dd, 1H, *J* = 15.7, *J* = 3.8 Hz, HC(5)), 2.57 (dd, 1H, *J* = 15.7, *J* = 8.3 Hz, HC(5)), 2.51 (t, 1H, *J* = 2.4 Hz, ≡CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3 (s, $COOCH_3$), 107.1 (d, C(1)), 90.9 (d, C(2)), 79.6 (d, C(4), 78.6 (s, -C≡), 75.5 (d, ≡CH), 57.9 (t, OCH_2), 55.1 (q, $COOCH_3$),51.9 (q, OCH_3), 49.6 (d, C(3)), 36.7 (t, C(5)); MS (70 eV) *m z* 277-275 (M^+-31, 1), 245-243 (1), 235-233 (1), 195 (7), 167 (100). Anal. Calcd. for $C_{11}H_{15}O_5Br$ (307.14): C, 43.02; H, 4.92. Found: C, 43.18; H, 5.07. **(±)-8'**: mp 73.5-74°C; IR (neat) ν 3280, 2110, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.84 (m, 1H, *J* = 4.2 Hz, HC(1)), 4.57 (m, 1H, HC(4)), 4.40 (AB syst., 2H, *J* = 16.1, *J* = 2.4 Hz, OCH_2), 4.32 (dd, 1H, *J* = 9.0, *J* = 4.3 Hz, HC(2)), 4.09 (t, 1H, *J* = 7.9 Hz, HC(3)), 3.74 (s, 3H, $COOCH_3$), 3.43 (s, 3H, OCH_3), 2.79 (dd, 1H, *J* = 15.3, *J* = 4.2 Hz, H C(5)), 2.59 (dd, 1H, *J* = 15.3, *J* = 8.9 Hz, H-C(5)), 2.54 (t, 1H, *J* = 2.5 Hz, ≡CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2 (s, $COOCH_3$), 100.6 (d, C(1)), 84.0, 80.0 (2 d, C(2), C(4)), 78.6 (s, -C≡), 75.6 (d, ≡C-H), 58.1 (t, OCH_2), 55.0 (q, $COOCH_3$), 51.8 (q, OCH_3), 49.1 (d, C(3)), 39.9 (t, C(5)); MS (70 eV) *m z* 277-275 (M^+-31, 0.8), 235-233 (0.6), 203-201 (3), 196 (0.8), 195 (5), 169 (1), 168 (10), 167 (100). Anal. Calcd. for $C_{11}H_{15}O_5Br$ (307.14): C, 43.02; H, 4.92. Found: C, 43.00; H, 5.00.

(±)-Methyl 2-*O*-propargyl-3-bromo-3,5-dideoxy-α-L-*arabino*-hexofuranoside ((±)-9). A 1.5 M solution of diisobutylaluminium hydride in toluene (2.6 mL, 3.9 mmol) was added over 10 min to a stirred solution of **(±)-8** (0.5 g, 1.68 mmol) in anhydrous THF (8 mL) at -50°C. The reaction mixture was warmed up to -20°C in 30 min. After 5h at -20°C, aqueous HCl (3N, 10 mL) was added to the solution. After 5 min at 25°C a saturated aqueous solution of NH_4Cl (10 mL) was added and the reaction mixture was extracted with AcOEt (2 × 10 mL). The organic phases were combined and dried ($MgSO_4$). The solvent was evaporated and the residue was purified by flash chromatography (AcOEt/petroleum ether) yielding 0.372 mg of **(±)-9** (82 %) as a colorless oil. IR (neat) ν 3600-3200, 2110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.91 (br. s, 1H, HC(1)), 4.23-4.30 (m, 4H, HC(2), HC(4), OCH_2), 3.81 (t, 2H, *J* = 5.9 Hz, HC(6)), 3.71 (dd, 1H, *J* = 9.0, *J* = 5.1 Hz, HC(3)), 3.38 (s, 3H, OCH_3), 2.51 (t, 1H, *J* = 2.3 Hz, ≡CH), 2.04-2.16 (m, 2H, OH, HC(5)), 1.84 (m, 1H, HC(5)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 107.2 (d, C(1)), 91.1 (d, C(2)), 82.1 (d, C(4)), 78.7 (s, -C≡), 75.4 (d,

H-C≡), 60.0 (t, C(6)), 58.0 (t, OCH_2), 55.2 (t, OCH_2), 55.2 (q, OCH_3), 50.5 (d, C(3)), 34.2 (t, C(5)); MS (70 eV) *m/z* 249-247 (M^+-31, 0.8), 235-233 (1), 205-203 (1), 151-149 (6), 139 (100). Anal. Calcd. for $C_{10}H_{15}O_4Br$ (279.13): C, 43.03; H, 5.42. Found: C, 43.30; H, 5.63.

(±)-Methyl-2-*O*-propargyl-3-bromo-3,5-dideoxy-6-*O*-(methylsulfonyl)-α-L-*arabino*-hexofuranoside ((±)-10). CH_3SO_2Cl (0.06 mL, 0.77 mmol) was added dropwise to a stirred solution of **(±)-9** (0.18 g, 0.64 mmol) and Et_3N (0.108 mL, 0.77 mmol) in anhydrous CH_2Cl_2 (2 mL) cooled to 0°C. After stirring at 0°C for 2.5 h, the reaction mixture was poured into a mixture of ice (1.5 g) and saturated aqueous solution of $NaHCO_3$ (3 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic phases were combined and dried ($MgSO_4$), and the solvent was evaporated. After purification by flash chromatography (Et_2O/petroleum ether) 0.206 g of **(±)-10** (90 %) was obtained as a colorless oil: IR (neat) ν 3290, 2110, 1350, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.90 (s, 1H, HC(1), 4.38 (t, 2H, *J* = 6.8 Hz, HC(6)), 4.19-4.28 (m, 4H, H(C2), HC(4), OCH_2), 3.67 (dd, 1H, *J* = 8.9, *J* = 5.0 Hz, HC(3)), 3.38 (s, 3H, OCH_3), 3.03 (s, 3H, CH_3SO_2), 2.54 (t, 1H, *J* = 2.3 Hz, ≡CH), 2.29 (m, 1H, HC(5)), 1.91-2.02 (m, 1H, HC(5)); ^{13}C NMR (75 MHz, $CDCl_3$): δ 107.0 (d, C(1)), 91.0 (d, C(2)), 81.8 (d, C(4), 79.4 (s, -C≡), 75.4 (d, ≡CH), 66.1 (t, C(6)), 57.7 (t, OCH_2), 54.9 (q, OCH_3), 49.5 (d, C(3)), 37.2 (q, CH_3SO_2), 31.5 (t, C(5)); MS (70 eV) *m/z* 245 (M^+-112, 0.4), 235-233 (1), 217 (11), 121 (100). Anal. Calcd. for $C_{11}H_{17}BrO_6S$ (357.21): C, 36.99; H, 4.80. Found: C, 36.67; H, 4.84.

(±)-(3a*SR*, 4*SR*, 6*RS*, 6a*RS*)-6-Methoxy-3-methylidene hexahydrofuro[3,4-*b*]furan-4-ethanol methanesulfonate ((±)-11). A solution of **(±)-10** (0.34 g, 0.95 mmol) in dry toluene, containing a catalytic amount of AIBN (0.08 g) and *n*-Bu_3SnH (0.27 mL, 1 mmol), was refluxed under an Ar atmosphere. After 12 h, the solvent was evaporated and residue purified by flash chromatography (AcOEt/petroleum ether) to afford **(±)-11** (0.21 g) in 83 % yield; IR (neat) ν 1660, 1350, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.15 (br. s, 1H, HC=), 5.00 (br.s, 1H, HC=), 4.90 (s, 1H, HC(6)), 4.51 (d, 1H, *J* = 6.3 Hz, HC(6a)), 4.40 (dd, 2H, *J* = 7.7, *J* = 5.3 Hz, CH_2-OSO_2Me), 4.15-4.30 (m, 3H, HC(2), HC(4)), 3.30 (m, 4H, HC(3a), OCH_3), 3.00 (s, 3H, CH_3-SO_2), 2.05-1.80 (m, 2H, CH_2-CH_2-OSO_2Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.4 (s, C(3)), 108.6 (t, CH_2=), 107.6 (d, C(6)), 88.3 (d, C(6a)), 74.8 (d, C(4)), 72.5 (t, C(2)), 67.7 (t, CH_2OSO_2Me), 54.3 (q, OCH_3), 49.8 (d, C(3a)), 37.2 (q, CH_3SO_2), 31.4 (t, $CH_2CH_2OSO_2Me$); MS (70 eV) *m/z* 247 (M^+-31, 3), 126 (100). Anal. Calcd. for $C_{11}H_{18}O_6S$ (278.31): C, 47.47; H, 6.52. Found: C, 47.12; H, 6.33.

The irradiation of **(±)-10** (0.25 g, 0.70 mmol) was achieved in CH_3CN (1.5×10^{-2} M), in the presence of triethylamine (5 eq), for 1 hour. After evaporation of the solvent, the crude material was purified by flash chromatography, and afforded 0.168 g of **(±)-11** (86 %).

(±)-(3a*SR*, 4*SR*, 6*RS*, 6a*RS*)-4-Ethyl-6-methoxy-3-methylidene hexahydrofuro[3,4-*b*]furan ((±)-12). To a slurried solution of $LiAlH_4$ (0.27 g, 7.2 mmol) in anhydrous Et_2O (25 mL) was added at once a solution of **(±)-11** (0.2 g, 0.72 mmol) in Et_2O (5mL). This mixture was stirred at room temperature for 15 min and treated with a saturated NH_4Cl solution. After filtration on Celite, the organic layer was washed with a 10 % sodium thiosulfate solution and brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (AcOEt/petroleum ether) to afford 0.130 g of **(±)-12** (98 %) as a colorless oil; IR (neat) ν 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.09 (m, 1H, HC=), 5.00 (m, 1H, HC=), 4.90 (s, 1H, HC(6)), 4.59 (d, 1H, *J* = 6.5 Hz, HC(6a)), 4.29-4.16 (m, 2H, HC(2)), 4.01 (ddd, 1H, *J* = 8.2, *J* = 7.1, *J* = 5.2 Hz, HC(4)), 3.33 (s, 3H, OCH_3), 3.25 (dd, 1H, *J* = 7.1, *J* = 6.5 Hz, HC(3a)), 1.6-1.4 (m, 2H, CH_2CH_3), 1.03 (t, 3H, *J* = 7.5 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.7 (s, C(3)), 107.9 (t, H_2C=), 107.7 (d, C(6)), 88.5 (d,

C(6a)), 81.0 (d, C(4)), 72.6 (t, C(2)), 54.2 (q, OCH_3), 49.8 (d, C(3a)), 24.2 (t, CH_2CH_3), 11.3 (q, CH_2-CH_3); MS (70 eV) *m z* 153 (M^+- 31, 13), 135 (2), 89 (89), 95 (100). Anal. Calcd. for $C_{10}H_{16}O_3$ (184.23): C, 65.20; H, 8.75. Found: 64.97; H, 8.82.

(±)-(3a*RS*, 4*SR*, 6*RS*, 6a*RS*)-4-Ethyl-6-methoxy-3-methylidene tetrahydrofuro[3, 4-*b*]furan-2 (3H)-one ((±)-13). A mixture of **(±)-12** (0.14 g, 0.76 mmol), pyridine (1.09 mL, 13.5 mmol) and CrO_3 (1.09 g, 11 mmol) in CH_2Cl_2 (15 mL) was refluxed for 12 h. The reaction mixture was cooled to room temperature. After decantation, the solid residue was dissolved in an aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layers were washed sequentially with aqueous $NaHCO_3$ solution, water, aqueous HCl (2N) and brine. The organic layer was filtered through a small pad of silica gel and the solvent was evaporated. The residue was purified by flash chromatography (AcOEt/petroleum ether) to furnish **(±)-13** (0.100 g) in 70 % yield as a colorless oil; IR (neat) ν 1770, 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.43 (d, 1H, *J* = 2.3 Hz, HC=), 5.68 (d, 1H, *J* = 2.0 Hz, HC=), 5.02 (s, 1H, HC(6)), 4.88 (d, 1H, *J* = 6.9 Hz, HC(6a)), 4.10 (m, 1H, HC(4)), 3.57 (m, 1H, HC(3a)), 3.38 (s, 3H, OCH_3), 1.60-1.45 (m, 2H, CH_2CH_3), 1.05 (t, 3H, *J* = 7.38 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5 (s, C(2)), 133.1 (s, C(3)), 125.8 (t, H_2C=), 105.2 (d, C(6)), 84.3 (d,C(6a)), 80.3 (d, C(4)), 54.2 (q, OCH_3), 44.4 (d, C(3a)), 23.6 (t, CH_2CH_3), 11.0 (q, CH_2CH_3); MS (70 eV) *m z* 167 (M^+-31, 4), 140 (100). Anal. Calcd. for $C_{10}H_{14}O_4$ (198.21): C, 60.60; H, 7.12. Found: C, 60.81; H, 7.01.

(±)-(3a*RS*, 4*SR*, 6a*RS*)-4-Ethyl-6-hydroxy-3-methylidene tetrahydrofuro[3,4-*b*]furan-2(3*H*)-one ((±)-14). Compound **(±)-13** (0.08 g, 0.4 mmol) in 50 % aqueous AcOH (6 mL) containing 2 drops of conc. HCl was heated at 80 °C for 4h. Reaction mixture was cooled to room temperature, treated with solid $NaHCO_3$, ether and water. The aqueous layer was separated and extracted with ether. The combined organic phases were washed with an aqueous $NaHCO_3$ solution, water and then dried ($MgSO_4$). The solvent was evaporated to afford the lactol **(±)-14** (0.073 g) in quantitative yield; IR (neat) ν 3400, 1770, 1655 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.44 (d, 1H, *J* = 2.3 Hz, HC=), 5.68 (d, 1H, *J* = 2.0 Hz, HC=), 5.52 (s, 1H, HC(6)), 4.92 (d, 1H, *J* = 6.9 Hz, HC(6a)), 4.36 (ddd, 1H, *J* = 8.6, *J* = 7.1, *J* = 4.8 Hz, HC(4)), 3.63 (dddd, 1H, *J* = 7.0, *J* = 7.0, *J* = 2.1, *J* = 2.1 Hz, HC(3a)), 2.79 (br s, 1H, OH), 1.40-1.62 (m, 2H, CH_2CH_3), 1.04 (t, 3H, *J* = 7.4 Hz, CH_2CH_3), ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5 (s, C(2)), 133.1 (s, C(3)), 125.8 (t, H_2C=), 99.4 (d, C(6)), 84.8 (d, C(2)), 80.8 (d, C(4)), 44.4 (d, C(3a)), 23.8 (t, CH_2CH_3), 11.0 (q, CH_2CH_3); MS (70 eV) *m z* 167 (M^+-17, 2), 155 (5), 138 (6), 126 (100), 109 (35), 97 (60). Anal. Calcd. for $C_9H_{12}O_4$ (184.18):C, 58.69; H, 6.57. Found: C, 58.81 H, 6.64.

(±)-(3a*SR*, 4*SR*, 6a*SR*)-4-Ethyl-3-methylidene dihydrofuro[3,4-*b*]furan-2,6(3*H*, 4*H*)-dione ((±)-2). To a mixture of **(±)-14** (0.06 g, 0.33 mmol) and freshly activated 4 Å molecular sieve (0.17 g) in CH_3CN (2 mL) was added 4-methylmorpholine-N-oxide (NMO) (0.065 g, 0.5 mmol) and tetra-*n*-propylammonium perruthenate (TPAP) (0.007 g, 0.02 mmol). The reaction mixture was stirred for 12 h at room temperature, and then filtered through a pad of silica gel. The solvent was evaporated *in vacuo*. The residue was purified by flash chromatography (AcOEt/petroleum ether). 0.048 g of **(±)-2** (81%) was obtained. The ^1H and ^{13}C NMR data are identical to those previously reported by S. D. Burke.[3b]

Methyl (±)-(3a*SR*, 4*SR*, 6*RS*, 6a*RS*)-6-methoxy-3-methylidene hexahydrofuro[3,4-*b*]furan-4-acetate ((±)-15). Irradiation of **(±)-8** (0.92 g, 3 mmol) afforded after flash chromatography (Et_2O/petroleum ether) 0.6 g of **(±)-15** (88%) as a colorless oil; IR (neat) ν 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.11 (m,

1H, HC =), 4.92 (m, 1H, HC =), 4.91 (s, 1H, HC(6)), 4.62-4.55 (m, 2H, HC(4), HC(6a)), 4.29-4.18 (m, 2H, HC(2)), 3.71 (s, 3H, CO_2CH_3), 3.42 (dd, 1H, J = 6.9, J = 7.0 Hz, HC(3a)), 3.33 (s, 3H, OCH_3), 2.64 (dd, 1H, J = 16.5, J = 7.3 Hz, C*H*CO_2Me), 2.56 (dd, 1H, J = 16.5, J = 7.0 Hz, C*H*CO_2Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3 (s, *C*O_2CH_3), 146.3 (s, C(3)), 108.4 (t, H_2C=), 107.5 (d, C(6)), 88.2 (C(6a)), 75.2 (d, C(4)), 72.3 (t, C(2)), 54.2 (q, CO_2CH_3), 51.6 (OCH_3), 49.3 (d, C(3a)), 35.9 (t, $CH_2CO_2CH_3$); MS (70 eV) *m/z* 197 (M^+-31, 10), 168 (20), 165 (25), 126 (100), 108 (38). Anal. Calcd. for $C_{11}H_{16}O_5$ (228.24): C, 57.89; H, 7.07. Found: C, 58.18; H, 7.25.

(±)-(3a*SR*, 4*SR*, 6*RS*, 6a*RS*)-1-(6-Methoxy-3-methylidene hexahydrofuro[3,4-*b*]furan-4-yl) octan-2-one ((±)-16). To a solution of **(±)-15** (0.53 g, 2.32 mmol) in THF (6 mL) with TMSCl (1.47 mL, 11.6 mmol), cooled to -78°C, was added dropwise a solution of *n*-hexyllithium [16] (1M in Et_2O, 2.9 mL, 2.9 mmol) over a 3 min period. After 30 min at -78°C, and the temperature was raised to 0°C, EtOH (0.7 mL) was added, followed by the addition of water (1 mL), of HCl (4N) (1 mL) and of a saturated aqueous solution of NH_4Cl. The reaction mixture was extracted with Et_2O (2 × 10 mL). The organic phases were combined and dried ($MgSO_4$). The solvent was evaporated. Separation by flash chromatography (AcOEt/petroleum ether) gave 0.52 g of **(±)-16** (80%) as a colorless oil; IR (neat) ν 1710, 1610, 1460 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.06 (br. s, 1H, HC=), 4.88 (s, 1H, HC(6)), 4.84 (br. s, 1H, HC=), 4.59 (d, 1H, J = 6.4 Hz, HC(6a)), 4.27-4.16 (m, 3H, HC(2), HC(4)), 3.43 (dd, 1H, J = 6.5 J = 6.5 Hz, HC(3)), 3.31 (s, 3H, OCH_3), 2.77 (dd, 1H, J =17.3, J = 6.3 Hz, C*H*-C=O), 2.02 (dd, 1H, J = 17.3, J = 7.4 Hz, C*H*-C=O), 2.38 (m, 2H, $C_5H_{11}CH_2C$=O), 1.71-1.23 (m, 8H, 4 × CH_2), 0.71 (t, 3H, J = 6.8 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.6 (s, C=O), 146.8 (s, C(3)), 108.1 (t, =CH_2), 107.3 (d, C(6)), 88.1 (d, C(6a)), 75.1 (d, C(4)), 72.3 (t, C(2)), 54.1 (q, OMe), 49.2 (d, C(3a)), 43.9 (t, $CH_2C(O)C_6H_{13}$), 24.8 (t, $C_5H_{11}CH_2C$=O), 31.4 (t, CH_2), 28.7 (t, CH_2), 23.4 (t, CH_2), 22.3 (t, CH_2), 13.9 (q, CH_3); MS (70 eV) *m z* 251 (M^+-31, 2), 222 (4), 165 (2), 126 (100). Anal. Calcd. for $C_{16}H_{26}O_4$ (282.37): C, 68.06; H, 9.28. Found: C, 68.24; H, 9.16.

(±)-(3a*SR*, 4*SR*, 6*SR*, 6a*SR*)-6-Methoxy-3-methylidene hexahydrofuro[3,4-*b*]furan-4-acetate ((±)-17). To a slurried solution of $LiAlH_4$ (0.015 g, 0.43 mmol) in anhydrous Et_2O (8 mL), cooled to 0°C, was added dropwise a solution of **(±)-16** (0.12 g, 0.43 mmol) in Et_2O (2mL). This mixture was stirred at 0°C for 1h and treated with a saturated ammonium chloride solution. The reaction mixture was extracted with Et_2O (3 × 10 mL). The organic layer was washed with a 10% sodium thiosulfate solution and brine, and dried ($MgSO_4$). Concentration *in vacuo* gave 0.103 g (85%) of the corresponding alcohol.

Without further handling, the obtained alcohol was transformed to the corresponding mesylate (0.122 g, 94%) using CH_3SO_2Cl (0.034 mL, 0.42 mmol) and Et_3N (0.06 mL, 0.42 mmol) in anhydrous CH_2Cl_2 (2 mL).

Reduction of the mesylate by $LiAlH_4$ (0.128 g, 3.4 mmol) in anhydrous Et_2O (12 mL) furnished after work-up and purification by flash chromatography (AcOEt/petroleum ether) 0.076 g of **(±)-17** (84%) as a colorless oil; IR (neat) ν 1665, 1460 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10 (dd, 1H, J = 3.4, J = 1.8 Hz, HC=), 4.96 (d, 1H, J = 1.8 Hz, HC=), 4.89 (s, 1H, HC(6)), 4.59 (d, 1H, J = 6.6 Hz, HC(6a)), 4.21 (m, 2H, HC(2)), 4.07 (m, 1H, HC(4)), 3.32 (s, 3H, OCH_3), 3.23 (dd, 1H, J = 6.6, J = 6.6 Hz, HC(3a)), 1.54-1.21 (m, 14 H, 7 × CH_2), 0.88 (t, 3H, J = 6.8 Hz, CH_3), ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.5 (s, C(3)), 107.8 (t, H_2C=), 107.6 (d, C(6)), 88.3 (d, C(6a)), 79.3 (d, C(4)), 72.5 (t, C(2)), 54.0 (q, OCH_3), 49.8 (d, C(3a)), 31.7, 31.0, 29.5, 29.4, 29.1, 26.8, 22.5 (7 t, 7 × CH_2), 14.0 (q, CH_3), MS (70eV) *m z* 237 (M^+-31, 3), 208 (3), 193

(0.4), 179 (0.5), 155 (3), 141 (6), 126 (100). Anal. Calcd. for $C_{16}H_{28}O_3$ (268.39): C, 71.60; H, 10.52. Found: C, 71.89; H, 10.76.

(±)-(3a*RS*, 4*SR*, 6*RS*, 6a*RS*)-6-Methoxy-3-methylidene-4-octyl tetrahydrofuro[3,4-*b*]furan-2(3*H*)-one ((±)-18). Following the same procedure as for the preparation of **(±)-13**, the compound **(±)-18** was synthesized from **(±)-17** (0.05 g, 0.19 mmol), using pyridine (0.226 mL, 2.80 mmol) and CrO_3 (0.336 g, 3.36 mmol) in CH_2Cl_2 (5 mL). Purification by flash chromatography (AcOEt/petroleum ether) afforded pure **(±)-18** (0.041 g, 76%) as an oil; IR (neat) ν 1770, 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.44 (d, 1H, J = 2.3 Hz, HC=), 5.67 (d, 1H, J = 1.9 Hz, HC=), 5.01 (s, 1H, HC(6)), 4.87 (d, 1H, J = 6.9 Hz, HC(6a)), 4.18 (m, 1H, HC(4)), 3.55 (dddd, 1H, J = 6.9, J = 6.9, J = 2.1, J = 2.1 Hz, HC(3a)), 3.36 (s, 3H, OCH_3), 1.50-1.23 (m, 14 H, 7 × CH_2), 0.88 (t, 3H, J = 6.9 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6 (s, C(2)), 133.1 (s, C(3)), 125.8 (t, H_2C=), 105.2 (d, C(6)), 84.2 (d, C(6a)), 78.8 (d, C(4)), 54.2 (q, OCH_3), 44.5 (d, C(3a)), 31.6, 30.5, 29.4, 29.3, 29.1, 26.6, 22.5 (7 t, 7 × CH_2), 14.0 (q, CH_3); MS (70 eV) *m/z* 251 (M^+-31, 0.4), 222 (0.6), 193 (0.2), 177 (0.4), 169 (6), 151 (0.4), 140 (100). Anal. Calcd. for $C_{16}H_{26}O_4$ (282.37): C, 68.06; H, 9.28. Found: C, 67.90; H, 8.98.

(±)-(3a*SR*, 4*SR*, 6a*SR*)-3-Methylidene-4-octyl dihydrofuro[3,4-*b*]-furan-2,6(3*H*, 4*H*)dione ((±)3). Compound **(±)-18** (0.03 g, 0.11 mmol) was transformed to the corresponding lactol (0.028 g, 100%) using 50% aqueous AcOH (1.5 mL) and conc. HCl (1 drop). The oxidation of 0.015 g (0.06 mmol) of the lactol, using NMO (0.010 g, 0.08 mmol), TPAP (0.002 g, 0.006 mmol) and 4 Å molecular sieves (0.03 g) in anhydrous CH_3CN (0.5 mL), gave after usual work-up and purification by flash chromatography (AcOEt/petroleum ether) 0.012 g (80%) of **(±)-3**. The ^1H and ^{13}C NMR data are identical to those previously reported by S. D. Burke.[3b]

REFERENCES AND NOTES

1. (a) Meyer, J.; Vignais, P. M. *Biochem. Biophys. Acta* **1973**, *325*, 375-384. (b) Mc Givan, J. D.; Chappell, J. B. *Biochem. J.* **1970**, *116*, 37P-38P.
2. For the syntheses of avenaciolide and isoavenaciolide, see: Burke, S. D.; Kyung, W. J.; Perri, R. E. *Tetrahedron Lett.* **1994**, *35*, 5841-5844 and references cited therein.
3. For the syntheses of ethisolide, see : (a) Burke, S. D.; Pacofsky, G. J. *Tetrahedron Lett.* **1986**, *27*, 445-448. (b) Burke, S. D.; Pacofsky, G. J.; Piscopio, A.D. *J. Org. Chem.*, **1992**, *57*, 2228-2235. (c) Wee, A. G. H. *Tetrahedron* **1990**, *46*, 5065-5076 and for correction *Tetrahedron* **1993**, *49*, 1335. (d) Chida, N.; Tobe, T.; Suwarma, M.; Ohtsuka, M.; Ogawa, S. *J. Chem. Soc. Perkin Trans 1* **1992**, 2667-2673.
4. For the preceding paper, see : Cossy, J.; Ranaivosata, J.-L. ; Bellosta, V. *Tetrahedron Lett.* **1994**, *35*, 1205-1207.
5. (a) Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1982**, *65*, 1700. (b) Black, K. A. ; Vogel, P. *Helv. Chim. Acta* **1984**, *67*, 1612-1615.
6. Ferrari, T.; Vogel, P. *Synlett* **1991**, 233-234.
7. For a similar reequilibration, see : Reymond, J.-L.; Pinkerton, A. A.; Vogel, P. *J. Org. Chem.* **1991**, *56*, 2128-2135.
8. Giese, B. *Radicals in Organic Synthesis. Formation of Carbon-Carbon Bonds* Pergamon Press : Oxford **1986**.
9. Cossy, J.; Ranaivosata, J.-L.; Bellosta, V. *Tetrahedron Lett.* **1994**, *35*, 8161-8162.
10. The alternate *trans* arrangement would be expected to result in a vicinal coupling constant of $^3J < 1$ Hz.[3c]
11. (a) Dauben, W. G.; Lorber, M.; Fullerton, D. S. *J. Org. Chem.* **1969**, *34*, 3587-3792. (b) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000-4002.
12. Griffith, W. P.; Ley, S. V. *Aldrichimica Acta* **1990**, *23*, 13-19 and references therein.
13. Cooke, M. P. *J. Org. Chem.*, **1986**, *51*, 951-953.
14. (a) Vieira, E.; Vogel, P. *Helv. Chim. Acta* **1983**, *66*, 1865-1871. (b) Warm, A.; Vogel, P. *Helv. Chim. Acta* **1987**, *70*, 690-700. (c) Reymond, J.-L.; Vogel, P. *Tetrahedron Asymmetry* , **1990**, *1*, 729-736. (d) Saf, R.; Faber, K.; Penn, G.; Griengl, H. *Tetrahedron* **1988**, *44*, 389-392. (e) Ronan, B.; Kagan, H. B. *Tetrahedron Asymmetry* **1991**, *2*, 75-90. (f) Corey, E. J.; Loh, J.-P. *Tetrahedron Lett.* **1993**, *34*, 3979-3982.
15. Aizpurua, J. M.; Palomo, C. *Bull. Soc. Chim. Fr.* **1982**, *II*, 265-268.
16. Gilman, H.; Beel, J. A.; Brannen, C. G.; Bullock, M. W.; Dunn, G. E.; Miller, L. S. *J. Am. Chem. Soc.* **1949**, *71*, 1499-1500.

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