Tetrahedron Vol 45, No 7, pp 2131 to 2142, 1989
Printed in Great Britain

0040-4020/89 $3 00+ 00

THE STEREOSELECTIVE SYNTHESES OF SUBSTITUTED FURO[2,3b]FURANS.(part II)[1]

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(*Received in UK* 18 *January* 1989)

Abstract.-Substituted furo[2,3b]furans, furo[2,3b]furan-2-ols and furo[2,3b]furan-2-ones were synthesized in a stereoselective manner.The key steps were the reactions of α-lithio-nitriles and dilithio-carboxylates with mono-substituted oxiranes.

Many insect antifeedant clerodanes contain a furo[2,3b]furan moiety.The oxidation level of this moiety may vary to some extend without having a dramatic influence on the bioactivity[2]. Although many synthetic methods for such furofurans have been reported during the last decade[3], there is still a need for synthetic methods suitable for incorporation into a clerodane total synthesis. In our previous paper the stereoselective syntheses of 2-substituted perhydrofuro[2,3b]furans starting with carbonyl compounds were described. In this paper syntheses of substituted furo[2,3b]furans starting with oxiranes are described.

The construction of the correct configuration at the off template carbon atom C-11 is one of the major problems in the synthesis of clerodanes containing furo[2,3b]furan units. The use of oxiranes like **B** as intermediates in these total syntheses is one way to tackle this problem. The correct configuration at C-11 can be introduced via a proper choice of the synthesis of the oxirane ring. Once fixed this configuration is preserved during the synthesis of the furo[2,3b]furan unit. In addition the configuration at C-11 is in a position to act upon the configurations at C-13 and C-16 in the desired way when equilibrating conditions are applied (vide infra).

In this study *tert*-butyloxirane **D** was used as the principal model compound.

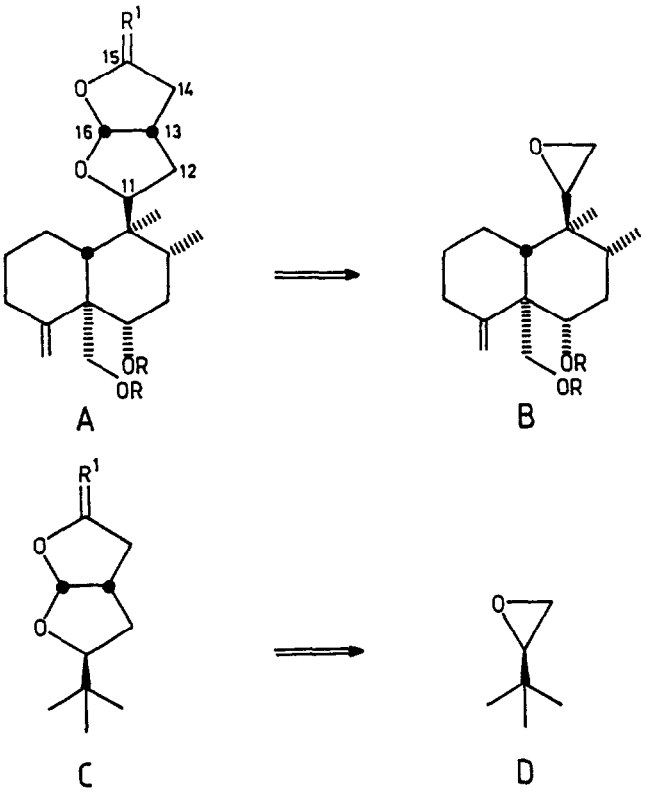
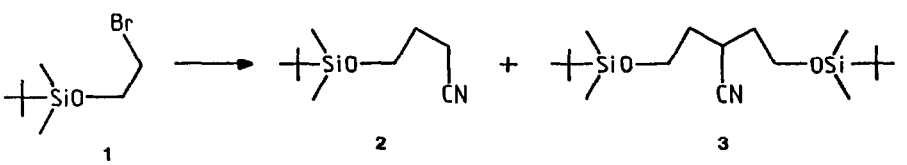


Figure 1

RESULTS AND DISCUSSION

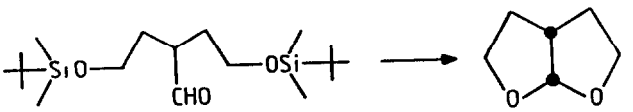
The syntheses of perhydrofuro[2,3b]furans from α-lithio-nitriles.

The nitrile **2** was considered to be a useful reagent for the conversion of oxiranes into perhydrofuro[2,3b]furans. It was synthesized in two steps from 2-bromoethanol. The hydroxyl group was protected as its *tert*-butyldimethylsilyl ether[4] to give **1** in 91% yield. The reaction of lithiated acetonitrile with **1** gave the desired nitrile **2** in 68% yield together with the dialkylated nitrile **3** in 25% yield (see scheme 1).



Scheme I

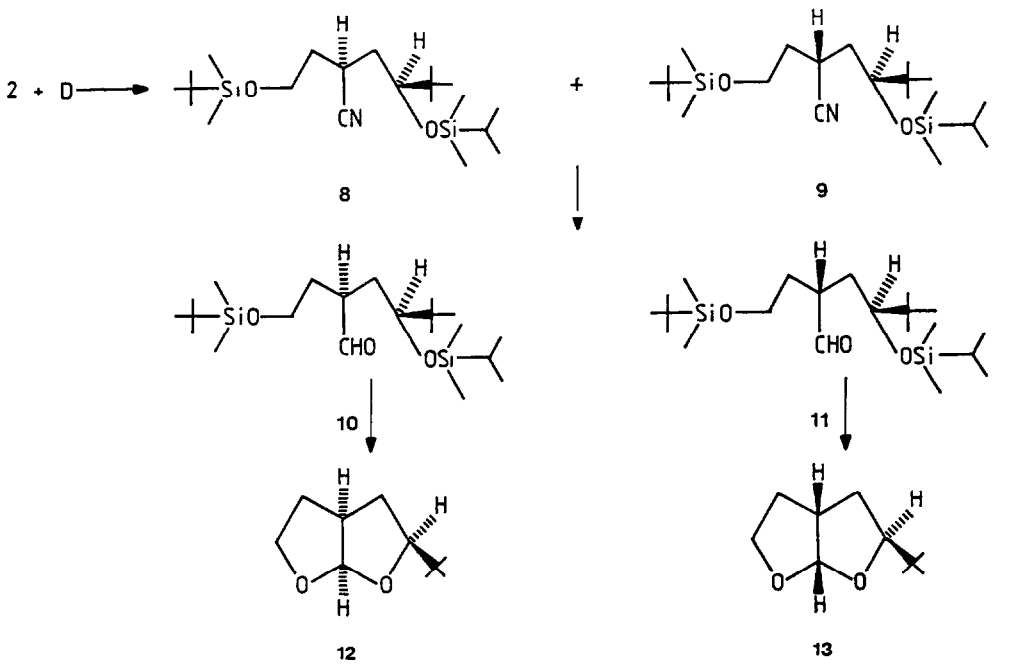
The nitrile **3** was reduced with diisobutylaluminium hydride to give the aldehyde **4** in 90% yield. Acid catalyzed cyclization furnished the unsubstituted furo[2,3b]furan **5** in 20% (unoptimized) yield[5].



4 **5**

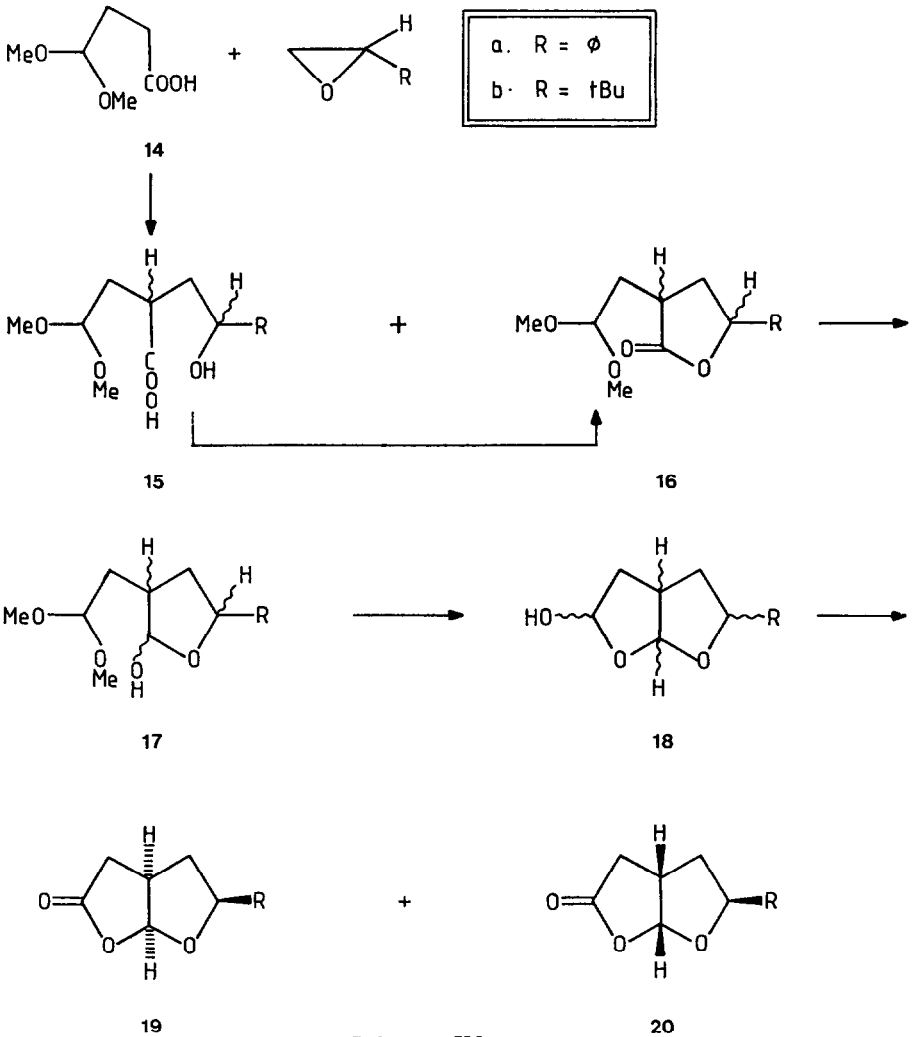
Scheme II

The reaction of lithiated **2** with *tert*-butyloxirane proceeded in a regiospecific manner[6] and the trapping of the alcoholate with isopropyldimethylsilyl chloride afforded the nitriles **8** and **9** in 81% yield. Trapping of the intermediate alcoholate was necessary in order to prevent the formation of mixtures of γ-hydroxy nitriles, γ-lactimes and γ-lactones[7] Trapping of the alcoholate with *tert*-butyldimethylsilyl chloride failed, probably due to the large steric hindrance[8]. The diastereomeric mixture of of the nitriles **8** and **9** was reduced with diisobutylaluminium hydride to give the corresponding mixture of the aldehyde **10** in 41% yield and its diastereomer **11** in 51% yield. Acid treatment of the aldehyde **10** gave exclusively the furofuran **12**[1] and likewise the aldehyde **11** gave the furofuran **13**[1]. Under these circumstances the cleavage of the silyl ethers and the subsequent cyclization evidently were faster reactions then the isomerization of the aldehydes and/or the furofurans.



Scheme III

Potential stages for base-catalyzed isomerization, aiming at an ultimately increased yield of the desired furofuran **13**, are the nitrile and/or the aldehyde stage. Treatment of the original 3:4 mixture of the nitriles **8** and **9** with potassium *tert*-butoxide in refluxing *tert*-butyl alcohol improved the ratio to 1:4. Unfortunately these nitriles could not be separated by column chromatography, this in contrast to the aldehydes **10** and **11**. Separation of the isomeric aldehydes and equilibration of the unwanted aldehyde **10** with potassium *tert*-butoxide in *tert*-butyl alcohol resulted in a 1:2 mixture of **10**:**11**. In this way the aldehyde **11** was synthesized from the mixture of the nitriles **8** and **9** in 75% overall yield. Acid catalyzed cleavage of the silyl ethers and subsequent cyclization gave the desired *tert*-butylperhydrofuro[2,3b]furan **13**, with the relative stereochemistry of the natural clerodanes, in 95% yield.



Scheme IV

The syntheses of perhydrofuro[2,3b]furanols and perhydrofuro[2,3b]-furanones from dilithio-4,4-dimethylbutan-2-oate.

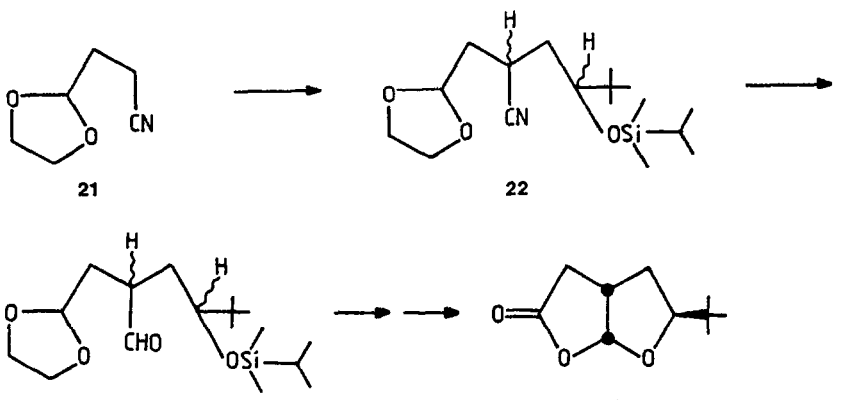
The carboxylic acid **14** was considered to be a useful reagent for the conversion of oxiranes into 5-substituted furo[2,3b]furan-2-ols and their corresponding furofuranones. The carboxylic acid was obtained by saponification of the methyl ester of **14**[9] followed by careful acidification.

The reaction of dilithiated **14** with styrene oxide afforded a mixture of γ-hydroxy carboxylic acids **15a** and γ-lactones **16a**. This mixture was converted into the lactones **16a** in 49% yield by refluxing it in benzene. Diisobutylaluminium hydride reduction then gave the corresponding lactols **17a** in almost quantitative yield. A subsequent brief treatment of the lactols with acid, followed by oxidation of the furofuranols **18a**[10]gave the furofuranones **19a** and **20a** in 44% and 35% yield respectively. Elongated treatment of the lactols with acid[10] and subsequent oxidation gave these furofuranones **19a** and **20a** in 12% and 76% yield respectively.

The reaction of dilithiated **14** with *tert*-butyloxirane gave, after cyclization, the lactones **16b** in a disappointingly low yield of 17%. Reduction of these lactones with diisobutylaluminium hydride gave the lactols **17b** in 66% yield. Elongated acid treatment of these lactols and subsequent oxidation gave the 5-*tert*-butylfuro[2,3b]furan-2-ones **19b** and **20b** in 6% and 71% yield respectively.

The synthesis of 5-*tert*-butylfuro[2,3b]furan-2-one from 3-(1,3-dioxolan-2-yl)-propionitrile

The low yield of the coupling reaction of the dilithiated carboxylate **14** with *tert*-butyloxirane prompted us to study the utility of the nitrile **21**[11] for the stereoselective synthesis of the *tert*-butylfurofuranone **20b**. The lithiated nitrile **21** gave a mixture of the nitriles **22** in 91% yield, afther successive treatment with *tert*-butyloxirane and isopropyldimethylsilyl chloride. The nitriles were reduced with diisobutylaluminium hydride to give the aldehydes **23** in 94% yield. Elongated acid treatment and subsequent oxidation gave the desired furofuranone **20b** in 72% yield together with a small amount of **19b**.



21 22 23 20b

Scheme V

The easy preparation of substituted nitriles, the high yields in the addition reaction of the lithiated nitriles to oxiranes and the ample possibilities for adjustment of the relative stereochemistry in the intermediates, make this approach very flexible and siutable for incorporation in total syntheses of natural products containing furofurans as structural elements.

EXPERIMENTAL

Boiling points and melting points are uncorrected. ^{1}H-NMR spectra were recorded on Varian EM-390 and Bruker CXP-300 spectrometers. Chemical shifts are reported in ppm downfield relative to tetramethylsilane (δ-scale), exept for the silyl compounds in which case the methyl groups attached to the silyl atom were used as intramolecular internal standard. $CDCl_3$ was used as the solvent unless stated otherwise. Mass spectral data and accurate mass measurements were obtained using AEI-MS-902 and VG Micromass 7070F spectrometers. Elemental analysis were carried out using a Carlo Erba Elemental Analyser 1106. Flash chromatography was performed on silicagel 230-400 mesh. Other silicagel used was 70-230 mesh. Light petroleum refers to petroleum ether b.p. 40-60 °C. Aqueous solutions were usually extracted three times with ether. Combined organic extracts were washed with brine and dried on magnesium sulfate prior to filtation and evaporation of the solvents under reduced pressure.

2-Bromo-1-*tert*-butyldimethylsilyloxy-ethane (1)
To a mixture of *tert*-butyldimethylsilyl chloride (21.1 g, 140 mmol) and imidazole (12.5 g, 184 mmol) in dimethylformamide (25 mL) was added dropwise 2-bromoethanol (10 mL, 141 mmol). The reaction mixture was stirred overnight, poured into water and extracted twice with light petroleum. The combined organic extracts were washed with brine, dried and filtered. The solvent was evaporated and the residue was submitted to bulb-to-bulb distillation (70-75 °C, 2.5 mm Hg) to give the silyl ether 1 (30.4 g, 91%) as a colourless oil.
^{1}H-NMR (CCl_4): 0.00 (s, 6H), 0.84 (s, 9H), 3.27 (t, J = 7 Hz, 2H), 3.82 (t, J = 7 Hz, 2H). MS: m/e (%): 183 (63), 181 (63), 139 (100), 137 (100). Calc. for $C_4H_{10}BrOSi$ (M-tBu): 180.9685; found: 180.9685.

3-*tert*-Butyldimethylsilyloxy-propionitrile (2) and
1,5-di-*tert*-butyldimethylsilyloxy-pentane-3-carbonitrile (3)
Acetonitrile (3.5 mL, 67 mmol) in dry tetrahydrofuran (15 mL) was added dropwise to a solution of lithium diisopropylamide (58 mmol) in tetrahydrofuran (150 mL) and hexamethylphosphoric triamide (10 mL, 57 mmol) at -78 °C under N_2. The mixture was stirred for 30 min and the bromide 1 (11 mL, 50.6 mmol) in tetrahydrofuran (50 mL) was dropped to the solution. The reaction mixture was stirred for 2 h at -78 °C, saturated aqueous ammonium chloride was added and the temperature was warmed up to roomtemperature. Extraction with light petroleum, followed by the usual workup gave a residu which was submitted to flash chromatography on silica gel. Elution with light petroleum/ether (40/1) afforded the dialkylated compound 3 (2.258 g, 25%) and the mono-alkylated nitril 2 (7.270 g, 72%) both as colourless oils. Further purification of the nitrile 2 by distillation in vacuo (120 °C, 3 mm Hg) gave 6.822 g (68%).

2: ^{1}H-NMR (CCl_4): 0.00 (s, 6H), 0.85 (s, 9H), 1.7-2.0 (m, 2H), 2.38 (t, J = 7 Hz, 2H), 3.67 (t, J = 6 Hz, 2H). MS: m/e (%): 184 (2), 144 (4), 143 (13), 142 (100) , 75 (14), 73 (4), 59 (6). Calc. for $C_9H_{18}NOSi$ (M-Me): 184.1158; found: 184.1156.

3: ^{1}H-NMR (CCl_4): 0.00 (s, 12H), 0.83 (s, 18H), 1.5-1.8 (m, 4H), 2.90 (quintet, J = 8 Hz, 1H), 3.73 (t, J = 6 Hz, 4H). MS: m/e (%): 342 (4), 302 (5), 301 (14), 300 (54), 147 (57), 73 (100). Calc. for $C_{17}H_{36}NO_2Si_2$ (M-Me): 342.2284; found: 342.2273.

1,5-Di-*tert*-butyldimethylsilyloxy-pentane-3-carbaldehyde (**4**)

The nitrile **2** (3.57 g, 10 mmol) was dissolved in dry toluene (50 mL) at -78 °C under N_2. Diisobutylaluminum hydride (12 mL of a 1.0 M solution in toluene) was added and the reaction mixture was stirred for 1 h. Water (2 mL) was added and the temperature was raised to roomtemperature and stirred for 15 min. The successive addition of 4 N aqueous sodium hydroxide (2 mL), stirring for 20 min, addition of water (6 mL) and stirring for 20 min resulted in a suspension, which was dried by adding magnesium sulfate. Filtration and evaporation of the solvents gave the crude aldehyde **4** in a quantitative yield. Flash chromatography on silica gel using light petroleum/ether (20/1) as the eluant afforded the pure aldehyde **4** (3.232 g, 90%) as a colourless oil.

^{1}H-NMR (CCl_4): 0.00 (s, 12H), 0.86 (s, 18H), 1.5-2.1 (m, 4H), 2.3-2.6 (m, 1H), 3.62 (t, J = 6 Hz, 4H), 9.62 (d, J = 2 Hz, 1H). MS: m/e (%): 303 (0.5), 299 (1.3), 171 (100), 141 (27), 97 (26), 75 (96), 73 (62). Calc. for $C_{14}H_{31}O_3Si_2$ (M-tBu): 303.1812; found: 303.1819.

2,3,3aβ,4,5,6aβ-Perhydrofuro[2,3b]furan (**5**)

The aldehyde **4** (2.642 g, 6.8 mmol) was dissolved in ether (10 mL) and concentrated hydrochloric acid (1 mL) was added. After stirring for 20 h the mixture was diluted with ether and the aqueous layer was removed. The organic layer was successively washed with saturated aqueous sodium bicarbonate and brine. Work up as usual, flash chromatography on silica eluting with pentane/ether (6/1) and vacuum distillation (50-60 °C, 13 mm Hg) gave the pure furofuran **5** (157 mg, 20%) as a colourless oil.

^{1}H-NMR: 1.5-2.0 (m, 2H), 2.0-2.3 (m, 2H), 2.7-3.0 (m, 1H), 3.83 (dd, J_1 = 5 Hz, J_2 = 9 Hz, 4H), 5.60 (d, J = 5 Hz, 1H). MS: m/e (%): 114 (19), 113 (26), 84 (100), 83 (20), 69 (22), 68 (46), 55 (49). Calc. for $C_6H_{10}O_2$: 114.0681; found: 114.0678.

1,5-Di-*tert*-butyldimethylsilyloxy-1-phenyl-pentane-3-carbonitrile (**6**) and
1,5-Di-*tert*-butyldimethylsilyloxy-2-phenyl-pentane-3-carbonitrile (**7**)

A solution of the nitrile **2** (848 mg, 4.3 mmol) and tetramethylethylenediamine (0.65 mL, 4.3 mmol) in dry ether (10 mL) was added dropwise to a solution of lithium diisopropylamide (4.3 mmol) in ether (15 mL) at 0 °C under N_2. The mixture was stirred for 15 min and styrene oxide (0.45 mL, 3.9 mmol) in ether (2 mL) was added. The reaction mixture was stirred for 90 min and *tert*-butyldimethylsilyl chloride (650 mg, 4.3 mmol) in dimethylformamide (20 mL) was added. The reaction mixture was stirred for 90 min, taken up in light petroleum and successively washed with water and brine. Further work up as usual and flash chromatography on silica gel eluting with light petroleum/ether (30/1) afforded the alkylated and silylated compounds **6** and **7** (1.216 g, 71%). GCMS analysis showed four compounds in approximate ratio's of 3 : 1 : 3 : 1.

MS *i* : m/e (%): 418 (4), 378 (8), 377 (21), 376 (70), 302 (7), 286 (5), 244 (21), 147 (20), 143 (14), 117 (12), 101 (12), 75 (37), 73 (100).

MS *ii* : m/e (%): 418 (3), 378 (11), 377 (26), 376 (80), 302 (-), 286 (-), 244 (11), 147 (60), 143 (6), 117 (8), 101 (-), 75 (33), 73 (100).

MS *iii* : m/e (%): 418 (3), 378 (9), 377 (25), 376 (82), 302 (9), 286 (7), 244 (28), 147 (23), 143 (15), 117 (15), 101 (14), 75 (40), 73 (100).
MS *iiii*: m/e (%): 418 (5), 378 (7), 377 (20), 376 (55), 302 (-), 286 (-), 244 (24), 147 (57), 143 (5), 117 (5), 101 (-), 75 (28), 73 (100).

1-*tert*-Butyldimethylsilyloxy-6,6-dimethyl-5-isopropyldimethylsilyloxy-heptane-3-carbonitriles (**8**) and (**9**)
A solution of the nitril **2** (1.56 g, 7.9 mmol) and tetramethylethylenediamine (1.2 mL, 7.9 mmol) in dry ether (5 mL) was added dropwise to a solution of lithium diisopropylamide (7.8 mmol) in ether (10 mL) at -15 °C under N_2. The mixture was stirred for 15 min and *tert*-butyloxirane (590 mg, 5.9 mmol) was added. The reaction mixture was stirred for 30 min and isopropyldimethylsilyl chloride (3.0 mL, 19.0 mmol) was added. The reaction mixture was stirred for 90 min, poured into saturated aqueous sodium bicarbonate and further worked up as usual. Flash chromatography on silica gel using light petroleum/ether (40/1) as the eluent gave the nitriles **8** and **9** (1.916 g, 81%), and the starting nitrile **2** (0.563 g).
^{1}H-NMR: 0.0-0.1 (m, 12H), 0.8-1.0 (m, 25H), 1.3-1.8 (m, 4H), 2.5-3.0 (m, 1H), 3.2-3.5 (m, 1H), 3.6-3.8 (m, 2H). MS *i* : m/e (%): 384 (10), 356 (57), 344 (11), 343 (30), 342 (100), 224 (28), 75 (38), 73 (88). MS *ii* : m/e (%): 384 (9), 356 (56), 344 (10), 343 (28), 342 (100), 224 (28), 75 (25), 73 (54).

1-*tert*-Butyldimethylsilyloxy-6,6-dimethyl-5-isopropyldimethylsilyloxy-heptane-3-carbaldehydes (**10**) and (**11**)
A mixture of the nitriles **8** and **9** (1.916 g, 4.8 mmol) was dissolved in dry toluene (10 mL) at -78 °C under N_2. Diisobutylaluminium hydride (5 mL of a 1.2 M solution in toluene) was added and the reaction mixture was stirred for 20 min. Water (1 mL) was added and the mixture was allowed to adopt roomtemperature. After successive stirring for 30 min, addition of ether (30 mL), addition of 4 N aqueous sodium hydroxide (1 mL), stirring for 30 min, addition of water (3 mL) and stirring for 20 min, the resulting mixture was dried by direct addition of magnesium sulfate. Filtration, evaporation of the solvents and flash chromatography on silica gel using light petroleum/ether (60/1) as the eluant afforded the aldehyde **11** (989 mg, 51%) and the aldehyde **10** (792 mg, 41%). A solution of the aldehyde **10** and potassium *tert*-butoxide (150 mg) in *tert*-butyl alcohol (150 mL) was refluxed for 1 h. The reaction mixture was cooled, poured into aqueous ammonium chloride and worked up as usual. Chromatographic separation gave the aldehyde **11** (460 mg) and the aldehyde **10** (292 mg). So the ultimate yields of de aldehydes **11** and **10** were 75% and 15% respectively.
^{1}H-NMR **10** : 0.0-0.1 (m, 12H), 0.8-0.9 (m, 25H), 1.5-1.9 (m, 4H), 2.3-2.5 (m, 1H), 3.29 (dd, J_1 = 8 Hz, J_2 = 3 Hz, 1H), 3.60 (t, J = 6 Hz, 2H), 9.55 (d, J = 2 Hz, 1H). MS: m/e (%): 345 (4), 227 (57), 157 (57), 135 (28), 95 (75), 75 (100), 73 (80).
^{1}H-NMR **11** : 0.0-0.1 (m, 12H), 0.8-0.9 (m, 25 H), 1.6-2.0 (m, 4H), 2.3-2.6 (m, 1H), 3.26 (br d, J = 9 Hz, 1H), 3.61 (t, J = 6 Hz, 2H), 9.51 (d, J = 3 Hz, 1H). MS: m/e (%): 345 (3), 227 (65), 157 (53), 135 (28), 95 (83), 75 (100), 73 (88).

2β-*tert*-Butyl-2a,3,3aβ,4,5,6aβ-hexahydrofuro[2,3b]furan (**13**)[1]
The aldehyde **11** (1.45 g, 3.6 mmol) was dissolved in acetone (40 mL) and 4 N hydrochloric acid (1 mL) was added. The mixture was stirred for 2 h and poured into aqueous sodium bicarbonate. Work up as usual and flash chromatography on silica gel eluting with light petroleum/ether (7/1), gave the furofuran **13** (582 mg, 95%).

^{1}H NMR: 0.87 (s, 9H), 1.5-2.3 (m, 4H), 2.6-3.0 (m, 1H), 3.7-4.0 (m, 3H), 5.68 (d, J=5Hz, 1H). MS: m/e (%): 169 (0,1), 155 (3), 113 (100), 69 (90). Calc. for $C_{10}H_{17}O_2$ (M-H): 169.1228; found: 169.1230.

4,4-Dimethoxybutan-1-oic acid (**14**)

Aqueous sodium hydroxide (10 mL of a 1 N solution) was added dropwise to a solution of the methyl ester of **14**[9] (1.34 g, 8.3 mmol) in methanol (11 mL). The reaction mixture was stirred overnight, cooled to 0 °C and carefully acidified to pH ≈ 4. Work up as usual afforded the crude carboxylic acid **14** (1.22 g, 99%) as a colourless oil, which was used without further purification.

^{1}H-NMR: 1.99 (dt, J_1 = 6 Hz, J_2 = 7 Hz, 2H), 2.43 (t, J = 7 Hz, 2H), 3.34 (s, 6H), 4.45 (t, J = 6 Hz, 1H), 9.4 (br s, 1H). MS: m/e (%): 147 (1), 131 (5), 117 (40), 85 (100), 75 (98), 72 (21). Calc. for $C_6H_{11}O_4$ (M-H): 147.0657; found: 147.0656.

3-(2,2-Dimethoxyethyl)-5-phenyl-4,5-dihydrofuran-2(3H)-one (**16a**)

A solution of n-butyllithium in hexane (9.0 mL, 1.6 M) was added to a solution of diisopropylamine (1.9 mL, 14 mmol) in dry tetrahydrofuran (25 mL) at -78 °C under N_2. The mixture was stirred for 10 min and carboxylic acid **14** (1.0 g, 6.8 mmol) in tetrahydrofuran (10 mL) was added dropwise. The mixture was allowed to warm up to 0 °C, stirred additionally for 1 h and styrene oxide (0.69 mL, 6.1 mmol) was added dropwise to the solution. The reaction mixture was stirred overnight, water was added and the mixture was carefully acidified to pH = 4. Further work up as usual gave a mixture hydroxy acids **15a** and lactones **16a**. This mixture was taken up in benzene (100 mL) and refluxed for 4 h in a Dean-Stark trap. Work up as usual and flash chromatography on silica gel eluting with light petroleum/ether (7/3) afforded the lactone **16a1** (275 mg, 18%) as a colourless oil.

^{1}H-NMR: 1.6-2.8 (m, 5H), 3.33 (s, 6H), 4.52 (t, J = 6 Hz, 1H), 5.56 (t, J = 6 Hz, 1H), 7.3 (br s, 5H). MS : m/e (%): 250 (0.6), 249 (1), 235 (3), 219 (14), 218 (42), 187 (12), 186 (10), 115 (28), 105 (22), 75 (100). Calc. for $C_{14}H_{18}O_4$: 250.1205; found: 250.1196.

Further elution afforded the isomeric lactone **16a2** (474 mg, 31%) as a colourless oil.

^{1}H-NMR: 1.1-2.9 (m, 5H), 3.33 (s, 6H), 4.53 (t, J = 6 Hz, 1H), 5.32 (dd, J_1 = 6 Hz, J_2 = 11 Hz, 1H), 7.3 (br s, 1H). MS: m/e (%): 250 (3), 249 (3), 235 (9), 219 (9), 218 (2), 187 (9), 115 (21), 75 (100). Calc. for $C_{14}H_{18}O_4$: 250.1205; found: 250.1193.

5-Phenyl-perhydrofuro[2,3b]furan-2-ols (**18a**)[10]

To a solution of the lactones **16a** (797 mg, 3.2 mmol) in dry tetrahydrofuran (10 mL) at -30 °C under N_2 was added dropwise a solution of diisobutylaluminum hydride in toluene (4 mL of a 1.6 M solution). The reaction mixture was stirred for 3.5 h, water (2 mL) was added and the mixture was diluted with ether (50 mL). The resulting suspension was stirred vigorously for 30 min and 7 N potassium hydroxide in water (3 mL) was added. The suspension was stirred for 30 min and dried on magnesium sulfate. Filtration and evaporation of the solvents afforded the crude lactols **17a** (793 mg).

^{1}H-NMR: 1.2-2.6 (m, 5H), 3.28 (s, 6H), 3.6 (br s, 1H), 4.4-4.5 (m, 1H), 4.8-5.5 (m, 2H), 7.2-7.3 (br s, 5H).

The crude lactol mixture was dissolved in tetrahydrofuran (20 mL) and 2 N hydrochloric acid (20 mL) and stirred for 1 h. The reaction mixture was poured into saturated aqueous sodium bicarbonate, worked up as usual and chromatographed on silica gel using light petroleum/ether (1/1) as the eluant to afford the furofuranols **18a**

(498 mg, 76%).
^{1}H-NMR: 1.5-2.5 (m, 4H), 2.7-3.1 (m, 1H), 4.5-5.1 (m, 2H), 5.3-5.6 (m, 2H), 7.2-7.3 (m, 5H).

5α-Phenyl-3aβ,4,5,6aβ-tetrahydrofuro[2,3b]furan-2(3H)-one (**19a**)[10] and
5β-Phenyl-3aβ,4,5,6aβ-tetrahydrofuro[2,3b]furan-2(3H)-one (**20a**)[10]
A By direct oxidation.
The furofuranol mixture **18a** (58 mg, 0.28 mmol) was dissolved in dichloromethane (5 mL) and pyridinium dichromate (200 mg) was added. The reaction mixture was stirred for 3 days, diluted with ether, filtered and chromatographed on silica gel using light petroleum/ether (2/3) as the eluant to afford the lactone **20a** (20 mg, 35%) as a colourless oil.
^{1}H-NMR: 2.0-2.2 (m, 2H), 2.56 (dd, J_1 = 4 Hz, J_2 = 18 Hz, 1H), 2.95 (dd, J_1 = 10 Hz, J_2 = 18 Hz, 1H), 3.2-3.5 (m, 1H), 5.17 (dd, J_1 = 7 Hz, J_2 = 8 Hz, 1H), 6.26 (d, J = 6 Hz, 1H), 7.3 (br s, 5H). MS: m/e (%): 204 (79), 160 (20), 107 (82), 105 (44), 104 (89), 98 (38), 91 (31), 77 (38), 70 (100), 42 (39).
Further elution gave the lactone **19a** (25 mg, 44%), as a colourless oil.
^{1}H-NMR: 1.80 (dt, J_1 = 9 Hz, J_2 = 13 Hz, 1H), 2.48 (dd, J_1 =18 Hz, J_2 = 3 Hz, 1H), 2.6-3.0 (m, 2H), 3.1-3.4 (m, 1H), 5.35 (dd, J_1 = 7 Hz, J_2 = 9 Hz, 1H), 6.16 (d, J = 5 Hz, 1H), 7.3 (br s, 5H). MS: m/e (%): 204 (82), 160 (23), 107 (84), 105 (44), 104 (100), 98 (38), 91 (31), 77 (38), 70 (95), 42 (39).

B By equilibration followed by oxidation.
The lactones **19a** and **20a** can also be synthesized in 12% resp 76% by treatment with 3 N hydrochloric acid/acetone (1/10) for 45 h and subsequent oxididation with pyridinium dichloromate.

5-*tert*-Butyl-3-(2,2-dimethoxyethyl)-4,5-dihydrofuran-2(3H)-one (**16b**)
The lactone **16b** was prepared in the same way from *tert*-butyloxirane as described for **16a**. The lactone **16b** was obtained as a colourless oil in 17% yield.
^{1}H-NMR: 0.94 (s, 9H), 1.5-2.0 (m, 2H), 2.0-2.5 (m, 2H), 2.5-2.9 (m,1H), 3.32 (s, 6H), 3.9-4.3 (m, 1H), 5.51 (t, J = 6 Hz, 1H). MS: m/e (%): 199 (2), 198 (5), 155 (5), 113 (43), 97 (67), 84 (100), 75 (20).

5-*tert*-Butyl-perhydrofuro[2,3b]furanols (**18b**)[10]
The lactone **16b** was reduced with diisobutylaluminium and subsequently cyclized with 2 N hydrochloric acid as described for **18a** to give the furofuranol mixture **18b** in 66% yield.
^{1}H-NMR: 0.9 (m, 9H), 1.5-2.3 (m, 4H), 2.7-3.1 (m, 1H), 3.5-4.3 (m, 2H), 5.5-5.9 (m, 2H).

5α-*tert*-Butyl-3aβ,4,5,6aβ-tetrahydrofuro[2,3b]furan-2(3H)-one (**19b**)[3a,10] and
5β-*tert*-Butyl-3aβ,4,5,6aβ-tetrahydrofuro[2,3b]furan-2(3H)-one (**20b**)[3a,10]
Equilibration of the furofuranol mixture **18b** was effectuated by treatment with 8 N hydrochloric acid in acetone for 6 days. Subsequent oxidation as described for the lactones **19a** and **20a** and separation of the isomers afforded the furofuranones **19b** and **20b** as white solids in 6% and 71% yield respectively.
19b: ^{1}H-NMR (300 MHz): 0.92 (s, 9H), 1.44 (dt, J_1 = 13 Hz, J_2 = 11 Hz, 1H), 2.19 (ddd, J_1 = 13 Hz, J_2 = 9 Hz, J_3 = 6 Hz, 1H), 2.50 (dd, J_1 = 18 Hz, J_2 = 1 Hz, 1H), 2.75 (dd, J_1 = 13 Hz, J_2

= 8 Hz, 1H), 3.0-3.1 (m, 1H), 3.96 (dd, J_1 = 11 Hz, J_2 = 6 Hz, 1H), 5.93 (d, J = 5 Hz, 1H). MS: m/e (%): 169 (20), 140 (10), 129 (50), 128 (100), 127 (100), 100 (27), 71 (63). Calc. for $C_9H_{13}O_3$ (M-Me): 169.0865; found: 169.0868.

20b: white solid, mp: 96-97 °C, (lit[10]: 70-72 °C).Elemental analysis: calc. for $C_{10}H_{16}O_3$: 65.19% C, 8.75% H; found: 65.01% C, 8.84% H

^{1}H-NMR (300MHz): 0.92 (s, 9H), 1.63 (ddd, J_1 = 13 Hz, J_2 = 6 Hz, J_3 = 2 Hz, 1H), 1.94 (ddd, J_1 = 13 Hz, J_2 = 10 Hz, J_3 = 9 Hz, 1H), 2.44 (dd, J_1 = 18 Hz, J_2 = 4 Hz, 1H), 2.85 (dd, J_1 = 18 Hz, J_2 = 10 Hz, 1H), 3.1-3.2 (m, 1H), 3.89 (dd, J_1 = 11 Hz, J_2 = 6 Hz, 1H), 6.08 (d, J = 6 Hz, 1H). MS: m/e (%): 169 (10), 140 (4), 127 (100), 109 (20), 99 (16), 71 (47). Calc. for $C_9H_{13}O_3$ (M-Me): 169.0865; found: 169.0867.

5,5-Dimethyl-1-(1,3-dioxolan-2-yl)-4-isopropyldimethylsilyloxy-2-carbonitrile (**22**)

To a solution of n-butyl lithium (10.7 mL of a 1.45 M solution in hexane) in dry ether (15 mL) at 0 °C was added diisopropylamine (2.2 mL, 15.7 mmol). The solution was stirred for 10 min and a solution of the nitrile **21**[11] (1.98 g, 15.6 mmol) and tetramethylethylenediamine (2.4 mL) in ether (10 mL) was added. The solution was stirred for 30 min and *tert*-butyloxirane (12.0 mmol) in ether (5 mL) was added. The reaction mixture was stirred for 1 h and quenched with isopropyldimethylsilyl chloride (7 mL, 45 mmol). The temperature was raised to roomtemperature and the reaction mixture was stirred additionally for 1 h. Work up as usual and flash chromatography eluting with light petroleum/ether (8/1) afforded the nitriles **22** (3.83 g, 91%).

^{1}H-NMR: 0.0 (s, 6H), 0.9-1.0 (m, 16H), 1.4-2.1 (m, 4H), 2.5-3.0 (m, 1H), 3.2-3.6 (m, 1H), 3.8-4.0 (m, 4H), 4.9-5.1 (m, 1H). MS *i* : 326 (1), 312 (7), 284 (46), 272 (3), 271 (14), 270 (63), 166 (37), 119 (25), 101 (46), 75 (100), 73 (94), 59 (36). MS *ii* : 326 (1), 312 (4), 284 (35), 272 (4), 271 (8), 270 (46), 166 (38), 119 (26), 101 (39), 75 (100), 73 (92), 59 (36).

5,5-Dimethyl-1-(1,3-dioxolan-2-yl)-4-isopropyldimethylsilyloxy-2-carbaldehyde (**23**)

The nitrile mixture **22** (851 mg, 2.6 mmol) was dissolved in dry toluene (50 mL) and cooled to -40 °C under N_2. Diisobutylaluminium hydride (2.6 mL of a 1.2 M solution in toluene) was added and the reaction mixture was stirred for 20 min, 4 N aqueous sodium hydroxide (0.5 mL) was added and the suspension was stirred for 1 h! (this long period proved necessary to effect complete decomposition of the intermediate aluminates). Work up as usual and flash chromatography eluting with light petroleum/ether (8/1) afforded the aldehyde mixture **23** (806 mg, 94%).

^{1}H-NMR: 0.0 (m, 6H), 0.8-0.9 (m, 16H), 1.1-2.1 (m, 4H), 2.2-2.7 (m, 1H), 3.1-3.2 (m, 1H), 3.7-3.9 (m, 4H), 4.82 (t, J = 4 Hz, 1H), 9.36 (d, J = 4 Hz, 1/2H), 9.47 (d, J = 2 Hz, 1/2H)

MS *i* : 287 (2), 274 (1), 273 (4), 155 (12), 101 (8), 75 (54), 73 (100).

MS *ii* : 287 (2), 274 (1), 273 (5), 155 (9), 101 (7), 75 (56), 73 (100).

5β-*tert*-Butyl-3aβ,4,5,6aβ-tetrahydrofuro[2,3b]furan-2(3H)-one (**20b**)

The aldehyde mixture **23** (806 mg, 2.4 mmol) was dissolved in acetone (20 mL), 5 drops 8 N hydrochloric acid were added and the reaction mixture was stirred for 3 days. Work up as usual and subsequent oxidation gave the aimed furofuranone **20b** (324 mg, 72%).

ACKNOWLEDGEMENTS

The authors wish to thank A. van Veldhuizen for NMR spectroscopic data, M.A. Posthumus, C.J. Teunis and H. Jongejan for mass spectroscopic data, and H. Jongejan for carrying out the elemental analyses. J.V. wishes to thank the Netherlands Organization for Scientific Research (NWO) for financial support.

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