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Synthesis and Insect Antifeedant Activity of C-2 and C-5 Substituted Perhydrofurofurans and 3a-Hydroxy-perhydrofurofurans (Part I).

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Abstract: A series of perhydrofuro[2,3-b]furan compounds with different functional groups at C-2, including a cyclic enol ether, and at C-5 were prepared in order to study the effect of C-2 functionalization upon the antifeedant activity of these model compounds for clerodin. Because the C-20 hydroxy group of azadirachtin is believed to be important for its antifeedant activity and because of the structural similarity between the perhydrofurofuran substructure of clerodin and the perhydrofuropyran substructure of azadirachtin a series of model compounds, based on the 3a-hydroxytetrahydro-furo[2,3-b]-furan substructure were prepared in order to test the hypothesis whether the presence of a hydroxy group could be an important element in the activity of perhydrofurofuran substructures also. A number of 3a-hydroxy-tetrahydrofuro[2,3-b]furan compounds were synthesized and the antifeedant activity tested for *Pieris brassicae* larvae was compared with those of the corresponding 3aH-perhydrofuro[2,3-b]furans. The antifeedant activity of all model compounds was moderate and the tests seem to support the conclusion that the presence of a 3a-hydroxy group in the furofuran ring system has no significant effect on the antifeedant activity.

Keywords: Alkylation; Cyano compounds; Furofuranes; Antifeedants

Introduction

Natural clerodane diterpenoids incorporating a perhydrofuro[2,3-b]furan subunit, such as clerodin (**1**), are well known for their antifeedant activity against several pest insect species.[1] These compounds constitute an interesting starting point in the search for structurally simplified insect antifeedants. Studies have demonstrated that both the decalin-fragment[2] and the perhydrofuro[2,3-b]furan-fragment[3] of these diterpenoids separately display antifeedant activity. Model compounds **2** (Figure 1) based on this structure were found to display insect antifeedant activity in laboratory bioassays.[3] However, in comparison to their natural counterparts, these analogs were markedly less potent and are therefore unsuitable for application as crop protection agents.

Analogs with a cyclic enol ether at C-2/3, similar to the moiety present in some of the most potent natural clerodane antifeedants, were not included in this test series. In the natural antifeedants, reduction of this moiety was found to increase the activity of the resulting derivatives towards some insects, but also to decrease the activity towards other species.[2c] We therefore decided to prepare a series of perhydrofuro[2,3-b]furan

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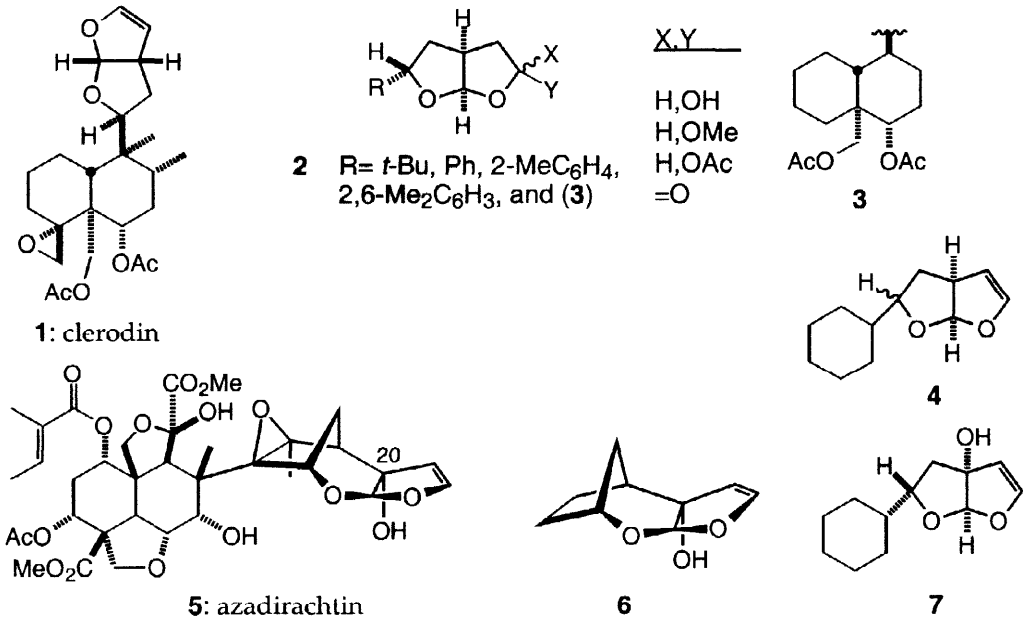
compounds with several different functional groups at C-2, including a cyclic enol ether, in order to allow the study of the effect of C-2 functionalization upon the antifeedant activity of these model compounds. The cyclohexyl substituent was chosen at C-5 to replace the decalin fragment that is present in the natural products. This substituent was considered to have modest steric requirements and to have little electronic effect and thus to introduce as little additional disturbing elements as possible.

Figure 1



The tetranortriterpenoid azadirachtin (**5**) combines a potent antifeeding and growth disrupting activity against many different pest insect species with the absence of serious adverse effects on non-target organisms.[4] Structure-activity studies have shown that for azadirachtin, too, the antifeedant activity resides in both halves of the molecule.[5] Nevertheless, simple analogs based on the furo[2,3-b]pyran fragment, such as **6**, were found to be as potent as azadirachtin itself at concentrations as low as 10 ppm.[6] Furthermore, some evidence suggests that the presence of a free C-20 hydroxy group in **5** is required to obtain full antifeedant activity.[7]

In view of the structural resemblance of the hydroxy-furo[2,3-b]pyran fragment of azadirachtin to the furo[2,3-b]furan substructure present in clerodin, we envisioned that the introduction of a similar hydroxy group into the latter moiety might increase the antifeedant activity of simple furo[2,3-b]furans.[8] This hypothesis could not be tested through literature data since no clerodane diterpenes with this type of hydroxy-furo[2,3-b]furan fragment have yet been tested.[8b] Also, to our knowledge, no reports exist of synthetic compounds containing such a moiety, that have been examined for antifeedant activity.[9,10] Therefore, we decided to prepare a series of compounds, based on 3a-*hydroxy*-tetrahydrofuro[2,3-b]furan **7**, in order to test this hypothesis through comparison of the antifeedant activity of these analogs with that of the corresponding compounds derived from 3a-*hydro*-furo[2,3-b]furan **4**.

Synthetic Part

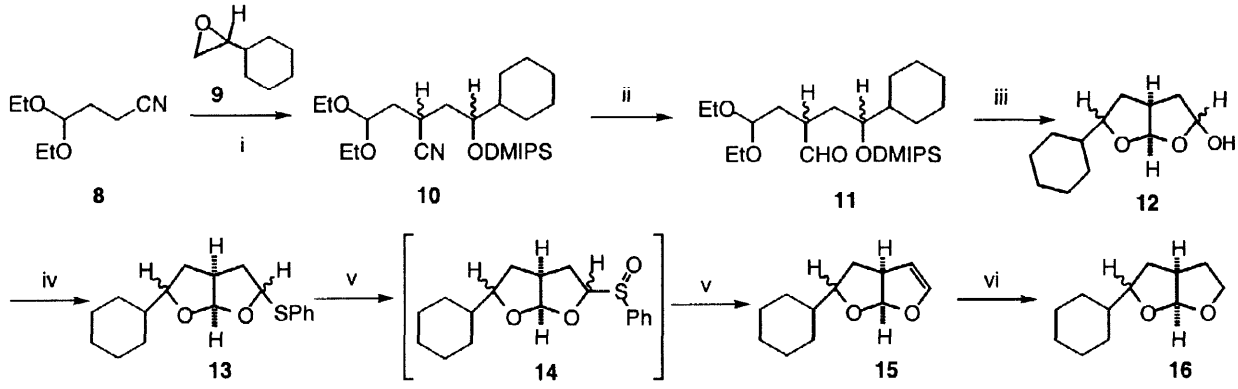
Preparation of 3aH-perhydrofuro[2,3-b]furans

The furo[2,3-b]furan ring system was prepared via a route (Scheme 1) slightly modified from the methodology developed by Vader and coworkers.[11] Regioselective addition of the anion of the commercially available nitrile **8**

onto cyclohexyl oxirane[12] **9**, followed by trapping of the intermediate alkoxide with dimethyl*iso*propylsilyl chloride (DMIPSCl), afforded the nitriles **10** in 85% yield. Reduction with di*iso*butylaluminum hydride (DibalH) and work-up with Glaubers' salt (sodium sulfate decahydrate) initially yielded an intermediate product that displayed the spectral characteristics of an imine. The desired aldehyde **11** was obtained after an overnight treatment of the intermediate product with silicagel in EtOAc in an overall yield of 93%. Finally, acid catalyzed cyclization of **11** with 1N HCl in THF yielded the perhydrofuro[2,3-b]furan-2-ols **12** in excellent yield as an inseparable mixture of all four diastereoisomers.

For the introduction of the enol ether functionality, we planned to use the phenylsulfenic acid-elimination strategy described by Anderson *et al.*[13] The perhydrofuro[2,3-b]furan-2-ols **12** could be easily transformed into the corresponding 2-phenylsulfides **13** with thiophenol in the presence of an excess of boron trifluoride etherate. However, in the subsequent oxidation reaction with *m*CPBA, no sulfoxide **14** could be isolated and instead small amounts of **12** were found. Apparently **14** is rather unstable and quickly decomposes at temperatures above 0°C; a similar thermal instability has been reported for acyclic sulfoxides of phenylthiomethyl ethers.[14] Therefore, the elimination procedure was modified so that the sulfoxide was generated *in situ* and subsequently was rapidly eliminated at higher temperatures to yield the desired tetrahydrofuro[2,3-b]furans **15**. It proved to be important to quickly raise the temperature of the sulfoxide mixture to 110°C to facilitate a smooth elimination reaction. In this manner, the tetrahydrofuro[2,3-b]furans **15** were obtained in 72% yield from **13** as an inseparable mixture of two diastereoisomers. Catalytic hydrogenation of **15** on palladium smoothly gave the corresponding perhydrofuro[2,3-b]furans **16** in excellent yield.

Scheme 1

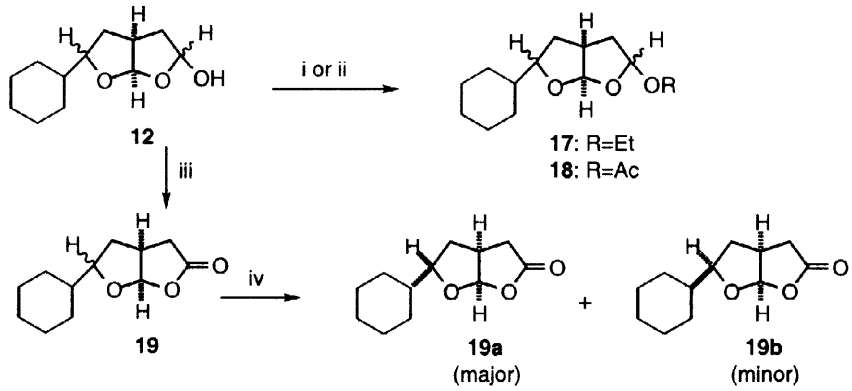


Reagents and conditions: (i) a) LDA, THF, -78°C, 30 min; b) add **9**, 0°C to r.t., 20 h; c) DMIPSCl (85%); (ii) a) DibalH, ether, -50°C; b) silicagel, 20 h (93%); (iii) 1N HCl, THF-water (98%); (iv) PhSH, BF_3•Et_2O, ether, 0°C (93%); (v) *m*CPBA, toluene, 0°C; then Et_3N, 110°C, 10 min (72%); (vi) H_2, Pd/C, MeOH (85%).

Conversion of the hemiacetal functionality of **12** into a mixed acetal as present in ethoxy derivative **17** was accomplished through acid catalyzed acetalization with ethanol (Scheme 2), yielding **17** in moderate yield as a mixture of stereoisomers. Acylation of **12** with acetyl chloride and pyridine gave the acetate **18** in 64% yield, again as a mixture of stereoisomers. In view of the complex stereochemical nature of these mixtures, separation of the individual diastereoisomers was not attempted. The oxidation of **12** with pyridinium dichromate afforded a mixture of only two diastereomers **19a** and **19b**, which could be partially separated through careful chromatography. Based on the similarity of its ^1H NMR chemical shift values and coupling constants of H-3α,

H-3β, H-3a, H-5 and H-6a with those of corresponding 3a-H-perhydrofurofuran-2-ones reported in the literature,[11] the relative stereochemistry of the less polar diastereoisomer **19a** was assigned as indicated in scheme 2, this is the same relative stereochemistry as in the natural compound clerodin (**1**).

Scheme 2



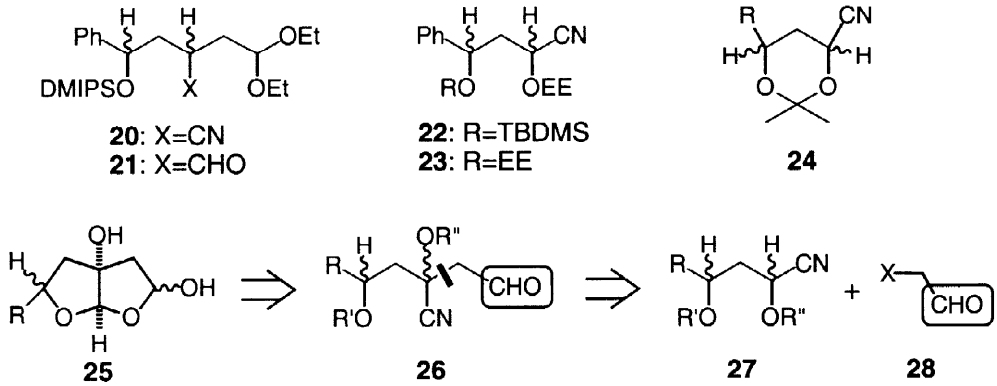
Reagents and conditions: (i) R=Et: EtOH (2 eq), TsOH, CH_2Cl_2 (54%); (ii) R=Ac: AcCl, pyr., CH_2Cl_2 (64%); (iii) PDC, CH_2Cl_2 (71%); (iv) repeated chromatography.

Synthesis of 3a-hydroxy-perhydrofuro[2,3-b]furans

The synthesis of 3a-hydroxy-perhydrofuro[2,3-b]furans was first tried *via* α-hydroxylation of the lithiated anions of either **20** or **21** with MoOPh[15] or molecular oxygen[16] but these attempts were unsuccessful in our hands.

We then embarked upon an alternative approach, involving the alkylation of appropriately functionalized cyanohydrins.[17] In order to gain access to the 3a-hydroxy-perhydrofurofuran ring system (Scheme 3), these cyanohydrins needed to be equipped with an oxygen-containing functional group at the γ-position as in **27**, which subsequently should undergo alkylation with a suitably substituted alkyl residue.

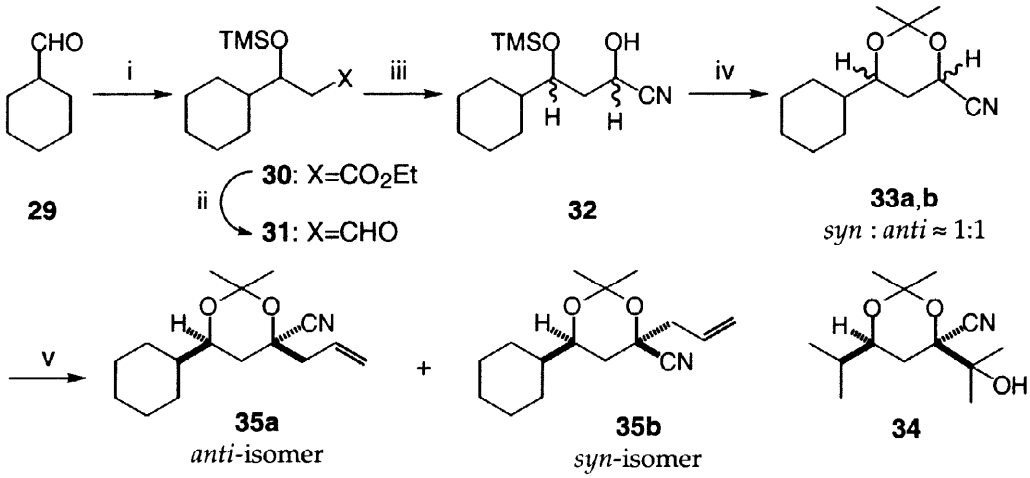
Scheme 3



Unfortunately, these cyanohydrins proved to be very reluctant towards alkylation. The only precedent of alkylations of γ-oxy-cyanohydrins we could find in the literature was the method of Rychnovsky and coworkers[18] for the stereoselective alkylation of the closely related cyanohydrin 1,3-acetonides **24** and attention was turned towards the utilization of these compounds in a synthesis of the 3a-hydroxy-perhydrofuro[2,3-b]furan ring system. The required cyanohydrin 1,3-acetonides **33** were prepared via a modified literature

procedure (Scheme 4). Addition of the lithium enolate of ethyl acetate[19] to cyclohexyl carbaldehyde **29** at low temperature yielded an intermediate alkoxide that was trapped as its silyl ether **30**. Subsequent reduction of the ester afforded the aldehyde **31** in 66% yield from **29**. The aldehyde was transformed into its cyanohydrin through exchange of hydrogen cyanide from acetone cyanohydrin under basic conditions.[20] An acid catalyzed transacetalization of the resulting diastereomeric mixture of cyanohydrins **32** with acetone dimethylacetal subsequently yielded the cyanohydrin 1,3-acetonides **33** as a 1 : 1 mixture of *syn*- and *anti*-isomers[21] in 84% yield from **31**.

Scheme 4



Reagents and conditions: (i) 1) $LiCH_2CO_2Et$, THF, -78°C; 2) TMSCl (71%); (ii) 1) DibalH, toluene, -78°C; 2) Glauber's salt (93%); (iii) Et_3N (cat.), $Me_2C(OH)CN$ (98%); (iv) $TsOH{\bullet}H_2O$ (cat.), $Me_2C(OMe)_2$ (86%); (v) 1) 3-4 equiv. LHMDS, THF, -78°C, 45 min; 2) 3-5 equiv. $H_2C{=}CH{-}CH_2Br$, -78°C to r.t., 18 h.

The first attempts to alkylate **33** or related cyanohydrin 1,3-acetonides [22] with bromoacetaldehyde dimethylacetal as the electrophile did not yield satisfactory results. Also, some of the results reported in the literature[18a,b] with more reactive alkylating agents and 1.1 equiv. of lithium di*iso*propylamide (LDA) performed poorly in our hands, with results variing from 0-58% yield. The use of other strong bases[23] or the addition of hexamethylphosphoramide (HMPA) as co-solvent[18d,f] did not improve the results satisfactory. Usually, only limited quantities of starting material could be recovered from the product mixture but one of the major side products could be identified as the acetone adduct **34**,[24] suggesting that the starting material can act as a source for acetone, which subsequently adds to another molecule of the starting compound.

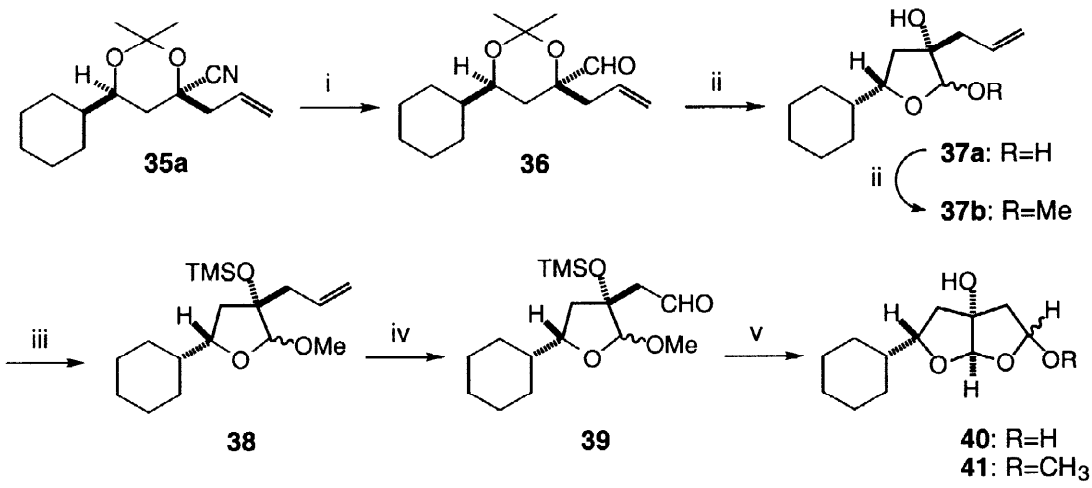
It was observed also that with lithium bis(trimethylsilyl)amide (LHMDS) as base the loss of starting material was markedly reduced and no byproducts were formed. Repeated experiments finally revealed that the use of 3-4 equiv. of LHMDS was necessary to allow a reproducible high yield alkylation of **33** with allyl bromide. In about 3.5 h at -78 to -50°C, **35** was obtained as a separable mixture of stereoisomers in a total yield of 86-91%, with a *syn- anti* ratio of approximately 1 : 30.

The configuration of the major isomer was established through analysis of the ^{13}C acetonide chemical shifts, according to a well-established method for discrimination between *syn*- and *anti*-1,3-diol acetonides.[25] The values of the acetonide methyl shifts of isomer **35a** (axial Me: δ 21.4 ppm, equatorial Me: δ 30.8 ppm) were

indicative of the presence of a 1,3-diol acetonide moiety in a chair conformation with the largest substituents at C-4 and C-6 in an equatorial position.[26] This conformational assignment was supported by ^{1}H NMR data of **35a**, which showed an axial-axial coupling of H-6 with H-5β (J=11.7 Hz), while H-6 was coupled to H-5α in an axial-equatorial fashion (J=2.1 Hz). Since the C-4 cyano-group is sterically less demanding than the allyl substituent, it followed that in the above conformation the cyano group will occupy the axial position and the isomer **35a** thus had to possess an *anti* configuration. This stereochemical assignment is in correspondance with other C-4,6 substituted cyanohydrin 1,3-acetonides with *anti* configuration, which were reported to have identical ^{13}C NMR acetonide methyl shift values.[18]

Two different strategies have been pursued to transform the *anti*-alkylated cyanohydrin 1,3-acetonide **35a** into a 3a-hydroxy-perhydrofuro[2,3-b]furan ring system. In the first method (Scheme 5), the cyanohydrin was reduced with $LiAlH(OEt)_3$[27]to afford, after treatment of the iminic intermediate with silicagel, the corresponding aldehyde **36** in 81% yield. Simultaneous acid-catalyzed deprotection and cyclization of **36** in methanol first gave rise to the formation of the diols **37a** which, due to their highly polar nature, were difficult to characterize. Upon prolonged reaction, however, these intermediate products were smoothly transformed into a separable 1 : 1 mixture of C-2 epimers of the corresponding acetals **37b** in 90% yield from **36**. Test experiments had indicated that the subsequent unmasking of the side-chain aldehyde group through ozonolysis of the allylic double bond in the presence of an unprotected hydroxy group at C-3 suffered from low yields and limited reproducability.

Scheme 5



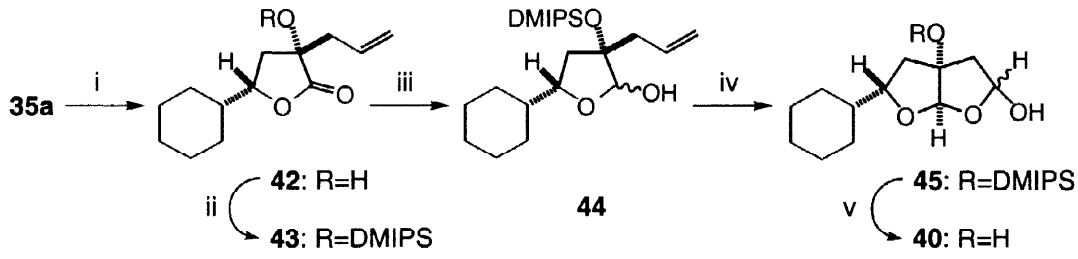
Reagents and conditions: (i) $LiAlH(OEt)_3$, ether, 0°C (81%); (ii) H^+, MeOH (90%); (iii) TMSCl, imidazole, DMF (98%); (iv) 1) O_3, MeOH, -78°C; 2) PPh_3, r.t. (78%); (v) 4N HCl, THF, r.t., 4-10 days (69%).

Therefore, the 3a-hydroxy group in **37b** was protected first as its trimethylsilyl ether **38** prior to ozonolysis. The trimethylsilyl ether turned out to be the only suitable choice for this transformation, since larger silicon-based protective groups, such as the triethylsilyl group, could only be placed on the hydroxy group of the 2αH-epimer of **37b**, the 2βH-epimer remaining unprotected. Subsequent ozonolysis of the double bond of **38** at -78°C in methanol, followed by reductive work-up with triphenylphosphine, afforded the aldehydes **39** in 78% yield. Cyclization of these aldehydes in 4N hydrochloric acid and THF for 4 days yielded a mixture of the desired 3a-

hydroxy-perhydrofuro[2,3-b]furan-2-ols **40**, together with their 2-methoxy derivatives **41** and some desilylated starting material. Separation and renewed treatment of the combined side-products with hydrochloric acid for another 10 days finally yielded **40** as a 1 : 1 mixture of C-2 epimers in a total yield of 69%.

The tedious cyclization to the perhydrofurofuran ring system was a drawback in this approach and therefore another strategy was investigated, involving the spontaneous cyclization[27] to the perhydrofurofuran ring system after ozonolysis of the allylic double bond of the unprotected lactol **44**. It was found that **35a** could be converted in excellent yield into the corresponding 2-hydroxy-lactone **42** by treatment with concentrated hydrochloric acid at elevated temperatures (Scheme 6). The hydroxy group was protected in quantitative yield as its dimethyl*iso*propylsilyl ether and the lactone **43** was reduced with DibalH in toluene at -78°C to afford an 81% yield of the corresponding lactols **44**. These were subsequently ozonized according to the procedure described before, except that methanol was replaced by methylene chloride as the solvent to avoid the possible formation of any methoxy acetals. Indeed, the intermediate lactol aldehyde was found to cyclize smoothly under these conditions and the desired 3a-silyloxy-perhydrofuro[2,3-b]furan-2-ols **45** were obtained in 82% yield. Deprotection with an aqueous solution of hydrofluoric acid afforded in 86% yield a 1 : 1 mixture of C-2 epimeric perhydrofurofuran-2,3a-diols **40**, which were identical in all respects to the diols **40** obtained previously.

Scheme 6



Reagents and conditions: (i) conc. HCl, MeOH, Δ (95%); (ii) DMIPSCl, imidazole, DMF (98%); (iii) DibalH, toluene, -78°C (81%); (iv) 1) O_3, CH_2Cl_2, -78°C; 2) PPh_3, r.t. (82%); (v) HF, MeCN-water (86%).

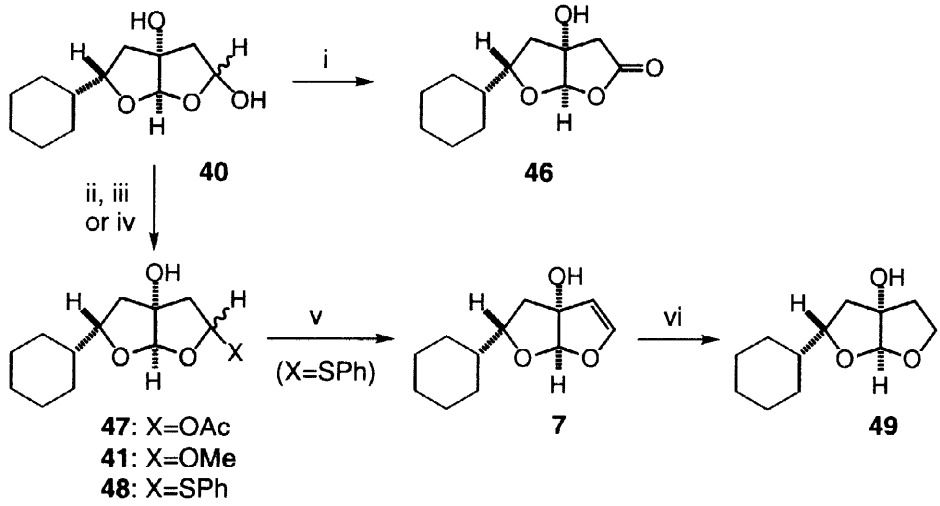
With the synthesis of the 3a-*hydroxy*-perhydrofuro[2,3-b]furan skeleton firmly established, a number of C-2 analogs were prepared for biological testing (Scheme 7). In order to allow evaluation of the influence of the 3a-hydroxy group on the biological activity of these analogs, this series obviously had to contain the same C-2 functional groups as included in the 5-cyclohexyl-3a-*hydro*-perhydrofuro[2,3-b]furan series.

Oxidation of the epimeric mixture of diols **40** with PDC gave a 75% yield of 3a-hydroxy-perhydrofuro[2,3-b]furanone **46**, thereby confirming that no partial epimerization at C-3a or C-5 had taken place during the transformation from **35a** to **40**. Based on the stereochemistry established in the synthesis of **35a**, the relative configuration of the 3a-hydroxy-perhydro-furo[2,3-b]furan skeleton was assigned as indicated in scheme 7, which is the same relative stereochemistry as found in the furo[2,3-b]furan fragment present in the natural compound clerodin (**1**).

Acylation of the diols **40** with acetyl chloride and pyridine at 0°C yielded two inseparable acetates in 77% yield; the downfield shift of all H-2 protons in the ^1H spectrum of these epimers **47** indicated that the hemiacetal functionality was acylated selectively at C-2. Methoxy derivatives **41** could be obtained in 86% yield as a 1 : 1

mixture of C-2 epimers via acid-catalyzed acetalization of **40** with a moderate excess of methanol to avoid furo[2,3-b]furan ring opening.

Scheme 7



Reagents and conditions: (i) PDC (3.4 eq), CH_2Cl_2, 5 days (75%); (ii) AcCl (2 eq), pyridine (3 eq), CH_2Cl_2, 0°C, 1 h (**47**, 77%); (iii) MeOH (2 eq), *p*-TsOH (cat.), THF, 48 h (**41**, 86%); (iv) PhSH (1.3 eq), BF_3•Et_2O (cat.), 4Å mol. sieves, Et_2O, 0°C (**48**, 97%); (v) 1) *m*CPBA (1.1 eq), 4Å mol. sieves, 0°C, 10 min; 2) Et_3N (12 eq), Δ, 20 min (79%); (vi) H_2 (4 atm), Pd/C, EtOAc (73%).

A related reaction sequence, using a catalytic amount of boron trifluoride etherate, afforded sulfides **48** as a 4 : 1 mixture of epimers in 97% yield. Subsequent *in situ* oxidation of the mixture of these sulfides into the corresponding sulfoxides with *m*CPBA, followed immediately by its thermal elimination in the presence of triethylamine, afforded the unsaturated tetrahydro-furo[2,3-b]- furan-3a-ol **7** as a single isomer in 79% yield. Finally, the enol moiety was hydrogenated with palladium on carbon to give a 73% yield of the 3a-hydroxy-perhydrofuro[2,3-b]furan **49**.

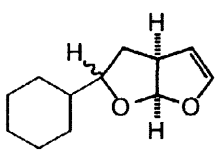
In addition to the furo[2,3-b]furans described above, with different functional groups at C-2 and a *cyclo*-hexyl substituent at C-5, a number of model compounds with other C-5 substituents were synthesized in order to study the effect of this side chain on the antifeedant activity of this system. For this purpose, two straight-chain alkyl substituents (*n*-hexyl and *n*-decyl) and a *phenyl* substituent were selected. The tetrahydro-furo[2,3-b]furan and the 3a,4,5,6a-perhydrofuro-[2,3-b]furan-2-one ring systems were synthesized, to introduce some variation at C-2 but without the complication of a large number of stereoisomers.

The preparation of these analogs followed the methods described in Schemes 1 and 2, with exception of the phenyl-substituted derivative. For this substituent, the addition of the lithium anion of **8** to styrene oxide yielded an inseparable mixture of both regioisomers. This mixture of isomers had to be converted to the stage of the final products before the desired regioisomers **51** and **55** could be obtained after careful chromatography. For the *n*-decyl- and the phenyl-substituted furo[2,3-b]furan-2-ones, the pure racemates **54** and **55** (see Figure 4) could be obtained via chromatography; the corresponding *n*-hexyl diastereomers however could not be separated.

In conclusion, synthetic routes to a series of 5-alkyl-3a-hydro-perhydrofuro[2,3-b]furan clerodin analogs, and their corresponding 3a-hydroxy analogs (Figure 4) have been developed. The extra hydroxy group on the C-3a

bridgehead position of the ring system was introduced as a structural modification that may possibly increase the insect antifeedant potency of these model compounds.

Figure 4



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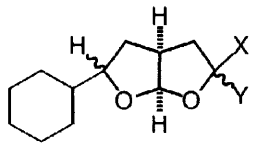
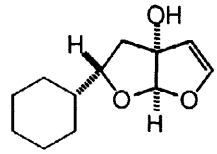


12: X,Y=H,OH
16: X,Y=H,H
17: X,Y=H,OEt
18: X,Y=H,OAc



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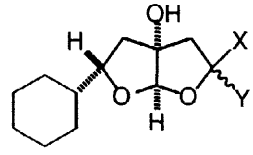
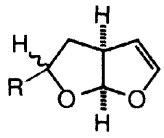
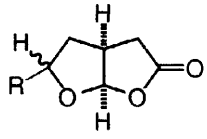


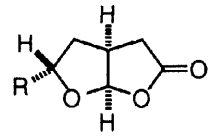
40: X,Y=H,OH
41: X,Y=H,OMe
46: X,Y=O
47: X,Y=H,OAc
49: X,Y=H,H



50: R=*n*-C_6H_{13}
51: R=Ph



19 : R=*c*-C_6H_{11}
19a: 5S-epimer only
19b: 5R-epimer only
52: R=*n*-C_6H_{13}
53: R=*n*-$C_{10}H_{21}$



54: R=*n*-$C_{10}H_{21}$
55: R=Ph

Biological Part

No-Choice Bioassay

The model compounds displayed in Figure 4 have been tested[28] for insect antifeedant activity against larvae of *Pieris brassicae* (Lepidoptera).[29] In screening compounds for potential antifeedant activity a no-choice bioassay is often considered to be more representative than a two-choice assay for the situation during application of an antifeedant in the field. For this reason, the furofuran model compounds **4**, **12**, **16-19**, **50**, and **51** were first tested in a no-choice situation. The bioassay was conducted in two consecutive periods of 1.5 h each, in order to determine if the larvae might possibly be able to adapt to the presence of less palatable compounds in their diet (short-term habituation). Conversely, a significant increase in the feeding inhibitory activity of a test compound during the second period could be indicative for the occurrence of some post-ingestive effect. Although some of the compounds did produce a statistically significant reduction in the amount of feeding (Table 1), only low levels of activity were detected. Compounds **16** and **51** were inactive under these test conditions, while **4** even somewhat stimulated the food intake of the larvae.

For the compounds showing an antifeeding effect, the initial activity usually decreased in the second period, suggesting the occurrence of short-term habituation. Such a rapid habituation has previously been observed for *Pieris brassicae* larvae in similar experiments with some drimane-type antifeedants.[30] None of the compounds showed signs of post-ingestive toxicity.

Two-Choice Bioassay

In view of the low levels of activity in the no-choice tests, the antifeedancy assays of the furofuran model compounds from Figure 4 with *Pieris brassicae* larvae were continued in a two-choice situation (Table 2). Such choice assays are often more sensitive because the insects can easily avoid food containing less palatable substances, which makes the difference between diet treated with antifeedants and non-treated diet more pronounced. Indeed, compounds **16** and **51** (inactive in the no-choice test) now displayed antifeeding activity. On the other hand, compound **4** (stimulated feeding in the no-choice test) had become virtually inactive in the two-choice situation. The other compounds tested in both situations in general did not show increased levels of activity in the two-choice experiment; in some cases (**12**, **19**, **50**) the activity had even somewhat decreased. In the literature, differences between the activity in no-choice *vs* two-choice assays have sometimes been used to

Table 1: Insect antifeedant activities of the model compounds **4**, **12**, **16-19**, **50**, and **51** against 5th instar larvae of the large cabbage white butterfly (Lepidoptera: *Pieris brassicae*) in a no-choice bioassay on cabbage leaf discs (5mM concentration). [a]

	AI (sem) [b,c] (%)			AI (sem) [b,c] (%)	
	0-1.5 h [d]	1.5-3 h [d]		0-1.5 h [d]	1.5-3 h [d]
4	-9.3 (5.2)	-12.3 (4.3)	**18**	16.7 (5.4)*	3.0 (3.8)
12	18.6 (7.6)*	15.9 (7.0)*	**19**	22.4 (5.0)**	13.9 (4.3)**
16	6.7 (6.8)*	5.4 (6.9)*	**50**	20.3 (5.3)**	10.6 (4.6)*
17	18.3 (8.5)	9.5 (5.8)	**51**	-1.7 (6.2)	-2.6 (3.0)

Notes: (a) Adapted from ref. 29. (b) Mean Antifeedant Index AI=[(C-T)/C] x 100; sem=standard error of the mean. (c) Originally reported as the 'Inhibition Percentage' (I.P.) of identical value. (d) The no-choice assay was divided over two consecutive periods, each 90 min long. Leaf discs were renewed between periods. Column '0-1.5 h contains the results obtained in the first period. (**) Statistically significant difference between control and treatment discs (Mann-Whitney U test); $p<0.01$. (*) $p<0.05$.

discuss possible modes of action of the test compounds involved (*e.g.* sensory feeding deterrency *vs.* toxicity)[31], but in our case neither the observed differences nor the actual levels of activities themselves were deemed sufficiently secure to allow such speculations.

Apart from the usual variance associated with the use of means for the antifeedant index (AI), the values obtained in this two-choice assay were demonstrated to contain an additional uncertainty. The experiments were conducted over a period of several days and for experiments repeated on different days the results varied in magnitude. Model compounds **19**, **19a**, and **51** were also tested repeatedly (N=2-3) and for these measurements the results varied no more than 11%. For the repeated tests this day-to-day variation was accounted for in Table 2 by taking the mean of the different results as the final value. However, the other compounds included in this table were only tested on a single day and it seems likely that these values too are subject to an extra uncertainty of similar magnitude. In this two-choice assay, 8 of the 21 test compounds displayed statistically significant antifeedant activity and compound **7** proved to be the most active one. In view of the applied concentration, however, none of the compounds can be considered as a particularly strong antifeedant for the *Pieris brassicae* larvae.

Some Tentative Structure-Activity Relationships

Due to the rather high variance of the individual mean AIs, relative to their magnitudes, it is difficult to discriminate between the activities of different test compounds. Furthermore, since both the individual measurements and the differences between them often are devoid of a satisfactory degree of statistical significance, it is inappropriate to regard the differences with a high level of confidence. On the other hand, a lack of statistical significance for an observation does not necessarily imply that the observation is wrong and therefore some careful, qualitative comparisons may still provide some indication of the underlying relationships that connect the level of antifeedant activity to the molecular structure. With regard to the nature of the furofuran ring system it seems that the presence of an oxygen-containing functional group at C-2 is less favourable, since such derivatives appear to be somewhat less active than the corresponding dihydro-compounds. This trend is observed for both the regular furofurans (compare **16** with **12**, **17**, and **18**) and the modified 3a-hydroxy furofurans (compare **49** with **40**, **41**, and **47**). The presence of a cyclic enol ether in the ring system was found to significantly increase the activity in case of the 3a-hydroxy compound **7**, but had a deleterious effect on the activity of **4**. The validity of these trends could not be supported with literature data since no antifeedancy assays of *neo*-clerodane diterpenes against *Pieris brassicae* larvae have been reported. A survey of the results obtained with other Lepidopteran species[1] shows that no unequivocal picture appears to exist: hydrogenation of the cyclic enol ether moiety in the furofuran side chain of different clerodane insect antifeedants may either increase or

decrease the potency of the molecule, depending on both the structure of the compound and the insect species used in the test. Similarly, several examples can be found of antifeedants with C-2 oxygenated furofuran sidechains being either more or less potent than the corresponding dihydro derivatives.

Table 2: Insect antifeedant activities of the furofuran model compounds from Figure 4 against 5th instar larvae of the large cabbage white butterfly (Lepidoptera: *Pieris brassicae*) in a two-choice bioassay on cabbage leaf discs(5mM concentration). [a]

	AI (sem) [b] (%)		AI (sem) [b] (%)		AI (sem) [b] (%)
4	-2.5 (7)	**19b**	24 (8) *	**7**	54 (12)
12	10 (9)	**50**	11 (9)	**40**	16 (6)
16	26 (7) **	**51**	*11 (14)* [c]	**41**	18 (10)
17	20 (9)	**52**	-11 (8)	**46**	*9 (4)* [e]
18	16 (9)	**53**	41 (11)	**47**	9 (7)
19	*10 (6)* [c]	**54**	10 (6)	**49**	24 (9) *
19a	*9 (3)* [c,d]	**55**	18 (9) *		

Notes:(a) Adapted from ref. 29. Values printed in italics were calculated from the reported data. (b) Mean Antifeedant Index AI=[(C-T)/(C+T)] x 100; sem=standard error of the mean. (c) Average AI value, calculated from the results reported for the same experiment on two different days. Average sem calculated according to standard procedures regarding multiplication of errors in repeated measurements. (d) The results of these two experiments with (**19a**) differed substantially: in one experiment compound (**19a**) displayed statistically significant antifeedancy (AI=19±7*), whereas it was almost inactive in the other (AI=8±7). (e) Average value from three experiments. See note c. (**) Statistically significant difference between control and treatment areas (Wilcoxon's matched pairs test); $p<0.01$. (*) $p<0.05$.

Within this test series the choice of alkyl substituent at C-5 appeared not to be of great importance; a slight preference could be observed for the *n*-decyl substituent **53**. In combination with a cyclic enol ether in the ring system, a *cyclo*-hexyl group at C-5 **4** was less active than the corresponding phenyl-compound **51**, but this effect was not observed in the furofuran-2-one ring system (**19a** *vs.* **55**). In view of the limited stability of the enol ether moiety in this system, it is conceivable that the inactivity of **4** in these tests was caused by (partial) degradation of this compound in the test solution. The stereochemistry at C-5 appeared to be less important (**19a** *vs.* **19b**), although some preference cannot be excluded in view of observed differences between some pure compounds and their epimeric mixtures (*e.g.* **53** *vs.* **54**).

With the exception of the ring system with the cyclic enol ether moiety (*i.e.* compound **7**), all test compounds containing a 3a-hydroxy group (**40**, **41**, **46**, **47**, and **49**) were found to be about equally active as their counterparts (**12**, **16**, **17**, **18**, and **19**) without such a hydroxy group. This test series would therefore seem to support the conclusion that the presence of a 3a-hydroxy group in the furofuran ring system has no effect on the antifeedant activity, at least not for *Pieris brassicae*.

Acknowledgements

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Experimental Part

General and instrumentation.

Flash column chromatography was performed using Merck silica gel (230-400 ASTM). Solvents used for column chromatography were always distilled prior to usage. Petrol refers to petroleum ether b.p. 40-60°C. GLC analyses were carried out on a Fisons GC 8000 gas chromatograph with a flame ionization detector and a DB-5 fused silica capillary column, 30 m x 0.25 mm i.d., film thickness 0.25 mm. Peak areas were integrated electronically with a Fisons integrator DP700. Melting points were determined on a C. Reichert, Vienna, apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) or a Bruker AC-E 200 or a Bruker DPX 400 spectrometer, operating at 200 and 400 MHz, respectively. ^{13}C NMR spectra were recorded on a Bruker AC-E 200 or a Bruker DPX 400 spectrometer operating at 50 and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (δ 0.0). Infrared spectra were recorded in chloroform solution on a Jasco A-100 infrared spectrometer. Mass spectral data and accurate mass measurements were measured on an AEI-MS-902 spectrometer equipped with a VG ZAB console and were obtained via electron impact (EI) ionization, unless indicated otherwise. Elemental analyses were determined on a Carbo Elba elemental analyser 1106.

4-Cyclohexyl-2-(2,2-diethoxyethyl)-4-[[(dimethyl)isopropylsilyl]oxy]-butanenitrile (10).

To an ice-cold, stirred solution of 3.7 ml (26.4 mmol) of diisopropylamine in 30 ml of anhydrous THF was added dropwise 16.4 ml (26.2 mmol) of a 1.6M solution of n-butyllithium in hexanes; stirring was continued for 30 min. After cooling to -78°C, 4.4 ml (26.2 mmol) of 3-cyanopropionaldehyde diethylacetal **8** in 5 ml of THF was added dropwise and the mixture was stirred for 30 min. Then, a solution of 3.06 gr (24.3 mmol) of cyclohexyl oxirane **9** in 10 ml of THF was added dropwise and then the reaction mixture was allowed to warm overnight to room temperature. The resulting yellow mixture was cooled on an ice bath and 4.2 ml (26.7 mmol) of dimethyl-isopropylsilyl chloride was added and stirring was continued for 5 min at 0°C and then at room temperature for 2 h. The reaction mixture was poured into 100 ml of saturated aqueous sodium bicarbonate solution and 50 ml of water. The organic layer was separated and the aqueous layer was extracted with three 150 ml-portions of ether. The combined organic layers were washed twice with 100 ml of water and with 100 ml of brine, dried with $MgSO_4$ and concentrated under reduced pressure to yield a yellow oil. Chromatography on 180 g of silicagel with petrol-EtOAc (99.5-0.5 to 97-3) as eluent afforded 7.9 g (20.6 mmol, 85%) of **10** as a clear, pale yellow oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.05, 0.09, and 0.10 (3 s, 6H): $Si(C\underline{H}_3)_2$; 0.8-1.25 (br m, 19H): $OCH_2C\underline{H}_3$ [δ 1.19 (2 t, J=7.0 Hz)], $SiCH(C\underline{H}_3)_2$ [δ 0.94 and 0.95 (2 d, J=5.9 Hz)], $SiC\underline{H}(CH_3)_2$, and *c*-hex H-3 - H-5; 1.5-1.95 (m, 9H): H-3, H-1', and *c*-hex H-1, H-2, and H-6; 2.7-3.0 (m, 1H): H-2; 3.4-3.8 (m, 5H): H-4 and $OC\underline{H}_2CH_3$; 4.64-4.7 (m, 1H): H-2'. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ -3.7, -3.5, and -3.4 (3 q): $Si(\underline{C}H_3)_2$; 15.1, 15.2, and 15.3: $Si\underline{C}H(CH_3)_2$ and $OCH_2\underline{C}H_3$; 17.0 (q): $SiCH(\underline{C}H_3)_2$; 23.6 and 25.0 (2 d): C-2; 26.3, 26.4, 26.6, 26.7, 27.4, 28.1, 28.3, and 28.8 (8 t): *c*-hex C-2 - C-6; 35.9, 36.0, 36.4, and 36.9 (4 t): C-3 and C-1'; 43.0 and 44.5 (2 d): *c*-hex C-1; 62.0, 62.2, 62.5, and 63.0 (4 t): $O\underline{C}H_2CH_3$; 73.6 and 74.0 (2 d): C-4; 100.8 and 101.0 (2 d): C-2'; 121.9 and 122.3 (2 s): C-1. MS: *m/e* (%) 341 (26), 340 (100), 338 (25), 294 (29), 266 (22), 220 (35), 169 (20), 124 (23), 103 (23), 75 (32). HRMS: calcd. (M^+-*i*-Pr): *m/e* 340.2308; found: *m/e* 340.2307.

2-(2,2-Diethoxyethyl)-4-[[(dimethyl)isopropylsilyl]oxy]-decanenitrile (56).

Addition of the lithium anion of **8** to 4.2 ml (27.4 mmol) of 1,2-epoxyoctane according to the procedure described for **10** yielded, after purification via chromatography on silicagel with petrol-EtOAc (99-1) as eluent, 7.9 g (20.6 mmol; 75%) of **56** as an oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.0-0.10 (m [incl. δ 0.05, 0.08, and 0.09 (3 s)], 6H: $Si(C\underline{H}_3)_2$; 0.70-1.00 (br m, 11H), 1.10-1.35 (m, 13H): H-6 -H- 10, $SiCH(C\underline{H}_3)_2$ [δ 0.93 (d, J=6.0 Hz) and 0.94 (d, J=5.7 Hz)], $OCH_2C\underline{H}_3$ [δ 1.19-1.20 (3 t, J=7.1 Hz)], and $SiC\underline{H}(CH_3)_2$; 1.35-1.95 (m, 6H): H-3, H-5, and H-1'; 2.70-3.01 (m, 1H): H-2; 3.47-3.93 (m, 5H): H-4 and $OC\underline{H}_2CH_3$; 4.67 (2 t, J=5.3 Hz, 1H): H-2'. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ -3.9, -3.7, -3.5, and -3.4 (4 q): $Si(\underline{C}H_3)_2$; 14.0 (q): C-10; 14.9 and 15.0 (2 d): $Si\underline{C}H(CH_3)_2$; 15.2 and 15.3 (2 q): $OCH_2\underline{C}H_3$; 17.0 (q): $SiCH(\underline{C}H_3)_2$; 23.6 and 24.8 (2 d): C-2; 22.5, 24.9, 29.3, 29.4, 31.8, 36.4, 36.9, 37.9, 39.4, and 39.7 (10 t): C-3, C-5 - C-9, and C-1'; 62.1, 62.2, 62.5, and 62.9 (4 t): $O\underline{C}H_2CH_3$; 69.6 and 69.9 (2 d): C-4; 100.7 and 100.9 (2 d): C-2'; 121.9 and 122.2 (2 s): C-1. MS: *m/e* (%) 343 (19), 342 (100), 340 (39), 296 (35), 268 (18), 222 (76), 198 (14), 195 (9), 194 (14), 182 (11), 171 (15), 124 (10), 103 (29), 75 (28), 73 (11). HRMS: calcd. (M^+-^{i}Pr): *m/e* 342.2464; found: *m/e* 342.3012.

2-(2,2-Diethoxyethyl)-4-[(trimethylsilyl)oxy]-tetradecanenitrile (57).

According to the procedure described for **10**, the lithium anion of **8** was reacted at -78°C with 6.0 ml (27.5 mmol) of 1,2-epoxydodecane. After stirring for 2 h at 0°C the reaction was quenched by the addition of 4.0 ml (31.5 mmol) of chlorotrimethylsilane. Stirring was continued at room temperature for 1 h and the reaction mixture was

worked-up as described, yielding 11.0 g of a yellow oil as the crude product. Chromatography on 50 g of silicagel with petrol-EtOAc (98-2) as eluent afforded 9.5 g (22.9 mmol; 83%) of a mixture of nitriles **57** as an oil.
^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.08, 0.09, 0.10, 0.11, 0.12, and 0.13 (6 s, 9H): $Si(C\underline{H}_3)_3$; 0.84 (br 2 t, J=6.0 Hz, 3H): H-14; 1.10-1.35 (br, 23H), 1.35-1.52 (br, 2H), and 1.52-1.90 (m, 3H): H-3, H-5 - H-13, H-1', and $OCH_2C\underline{H}_3$ [δ 1.18 (3 t, J=7.0 Hz)]; 2.65-2.97 (m, 1H): H-2; 3.40-4.92 (m, 5H): H-4 and $OC\underline{H}_2CH_3$; 4.66 (br t, J=5.8 Hz, 1H): H-2'. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 0.3 (q): $Si(\underline{C}H_3)_3$; 14.0 (q): C-14; 15.2 and 15.3 (2 q): $OCH_2\underline{C}H_3$; 23.8 and 24.7 (2 d): C-2; 22.6, 25.1, 29.3, 29.5, 31.8, 36.3, 36.7, 37.0, 37.9, 39.4, and 39.8 (11 t): C-3, C-5 - C-13, and C-1'; 62.1, 62.4, and 62.8 (3 t): $O\underline{C}H_2CH_3$; 69.7 and 70.0 (2 d): C-4; 100.7 and 100.8 (2 d): C-2'; 121.8 and 122.1 (2 s): C-1. MS: *m/e* (%) 400 (23), 398 (100), 369 (20), 352 (27), 278 (59), 243 (34), 227 (23), 226 (90), 182 (50), 110 (34), 103 (94), 75 (20), 73 (55). HRMS: calcd. (M^+-CH_3): *m/e* 398.3090; found: *m/e* 398.3090.

4-Cyclohexyl-2-(2,2-diethoxyethyl)-4-[[(dimethyl)isopropylsilyl]oxy]-butanal (11).
A stirred solution of 7.9 g (20.6 mmol) of **10** in 50 ml of dry ether, containing 0.2 ml of n-decane as internal standard, was cooled to -50°C (external temperature) on a dry-ice acetone bath. In approx. 20 min, 19 ml of a 1.5M solution of diisobutylaluminum hydride (28.5 mmol) in toluene or 28.5 ml of a 1M solution of diisobutylaluminum hydride(28.5 mmol) in hexanes was added dropwise. Stirring at -40 to -50°C was continued for 1 h while the progress of the reaction was monitored by glc analysis (disappearance of the starting material with n-decane acting as control); after 45 min the reaction appeared to be complete. The reaction was quenched by addition of 20 g (62.1 mmol) of Glauber's salt and the mixture was warmed to room temperature. Stirring was continued for 1 h, during which time the mixture turned into a slurry which had to be diluted with ether to facilitate stirring. $MgSO_4$ was added and the slurry was filtered through a pad of hyflo on a glassfilter. The solvent was evaporated under reduced pressure and the residual oil was twice taken up in petrol and reconcentrated to remove traces of toluene, yielding 7.9 g of the intermediate reduction product as a colourless, viscous oil, with the following characteristic spectral data: IR (CHCl3) ν 1650 cm^{-1}, ^{1}H NMR δ 4.37 (br s) and 7.5 (m), and ^{13}C NMR δ 166.7 (d).
This intermediate was dissolved in 150 ml of ethyl acetate, 50 g of silicagel was added and the mixture was stirred overnight at room temperature. Filtration and evaporation of the solvent under reduced pressure yielded 7.8 g of a less viscous, colourless oil. Purification via chromatography on 100 g of silica with petrol-EtOAc (99-1 to 97-3) as eluent afforded 7.4 g (19.2 mmol, 93%) of **11** as a clear, colourless oil.
^{1}H NMR ($CDCl_3$, 200 MHz): δ -0.03-0.10 (m s, 6H): $Si(C\underline{H}_3)_2$; 0.65-1.45 (br m, 19H): $SiCH(C\underline{H}_3)_2$ [δ 0.91 (br d, J=6.6 Hz)], $SiC\underline{H}(CH_3)_2$, $OCH_2C\underline{H}_3$ [δ 1.10-1.25 (m t, J=7.0 Hz)], and *c*-hex H-3 - H-5; 1.45-2.0 (br m, 9H): H-3, H-1', and *c*-hex H-1, H-2, and H-6; 2.40-2.65 (br m, 1H): H-2; 3.35-3.75 (m, 5H): H-4 and $OC\underline{H}_2CH_3$ [δ 3.35-3.52 (m q, J=7.0 Hz)]; 4.46 and 4.47 (2 t, J=5.7 Hz, 1H): H-2'; 9.55 (d, J=2.7 Hz, 1H): H-1. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ -3.6 (q): $Si(\underline{C}H_3)_2$; 15.1 (d): $Si\underline{C}H(CH_3)_2$; 15.2 (q): $OCH_2\underline{C}H_3$; 17.0 and 17.1 (2 q): $SiCH(\underline{C}H_3)_2$; 26.4, 26.5, 26.6, 26.7, 27.7, 28.5, and 28.9 (7 t): *c*-hex C-2 - C-6; 32.6, 33.5, 34.2, and 34.4 (4 t): C-3 and C-1'; 43.7 and 43.8 (2 d): *c*-hex C-1; 44.5 and 45.3 (2 d): C-2; 61.7 and 62.1 (2 t): $O\underline{C}H_2CH_3$; 74.2 and 74.4 (2 d): C-4; 101.3 and 101.4 (2 d): C-2'; 204.2 and 204.3 (2 d): C-1. IR ($CHCl_3$): ν 1740 (s) cm^{-1}. MS: *m/e* (%) 298 (22), 297 (100), 257 (33), 251 (73), 213 (28), 185 (92), 177 (29), 157 (25), 103 (74), 75 (55), 73 (25). HRMS: calcd. (M^+- *i*-Pr): *m/e* 343.2305; found: *m/e* 343.2305.

2-(2,2-Diethoxyethyl)-4-[[(dimethyl)isopropylsilyl]oxy]-decanal (58).
Reduction of 5.3 g (13.8 mmol) of **56** with diisobutylaluminum hydride in toluene as described for **11**, yielded after purification by chromatography on 75 g of silicagel with petrol-EtOAc (95-5) as eluent 4.2 g (10.9 mmol; 79%) of **58** as an oil.
^{1}H NMR ($CDCl_3$, 200 MHz): δ -0.02 and 0.0 (2 s, 6H): $Si(C\underline{H}_3)_2$; 0.64-0.95 (br m, 11H) and 1.05-1.32 (br m, 13H): H-6 - H-10, $SiCH(C\underline{H}_3)_2$, $SiC\underline{H}(CH_3)_2$, and $OCH_2C\underline{H}_3$ [δ 1.13 (d t, J=7.0 Hz)]; 1.32-2.06 (m, 6H): H-3, H-5, and H-1'; 2.40-2.65 (br, 1H): H-2; 3.33-3.75 (m, 5H): H-4 and $OC\underline{H}_2CH_3$; 4.45 and 4.46 (2 t, J=5.7 Hz, 1H): H-2'; 9.53 (d, J=2.9 Hz) and 9.55 (d, J=2.5 Hz; total 1H): H-1. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ -3.7 and -3.5 (2 q): $Si(\underline{C}H_3)_2$; 14.0 (q): C-10; 14.9 (d): $Si\underline{C}H(CH_3)_2$; 15.2 (q): $OCH_2\underline{C}H_3$; 17.0 (q): $SiCH(\underline{C}H_3)_2$; 22.6, 25.0, 25.1, 29.4, 31.8, 34.2, 34.3, 36.5, 36.9, and 37.6 (10 t): C-3, C-5 - C-9, and C-1'; 44.4 and 45.3 (2 d): C-2; 61.8 and 62.1 (2 t): $O\underline{C}H_2CH_3$; 70.1 and 70.4 (2 d): C-4; 101.3 and 101.4 (2 d): C-2'; 204.1 and 204.3 (2 d): C-1. MS: *m/e* (%) 299 (78), 253 (71), 215 (27), 185 (100), 179 (30), 157 (28), 103 (42), 75 (44). HRMS: calcd. (M^+*i*Pr): *m/e* 345.2461; found: *m/e* 345.2463.

2-(2,2-Diethoxyethyl)-4-[(trimethylsilyl)oxy]-tetradecanal (59).
Reduction of 8.7 g (21.1 mmol) of **57** with diisobutylaluminum hydride as described for **11**, using toluene as the solvent, gave 9.1 g of an intermediate reduction product as an oil. Overnight treatment of this product in EtOAc

solution with 25 g of silicagel as described yielded 7.6 g (18.2 mmol; 86%) of crude **59** as an oil, which was sufficiently pure to be used in the next reaction without further purification.
^{1}H NMR ($CDCl_3$, 200 MHz): δ -0.05-0.10 (m s, 9H): $Si(C\underline{H}_3)_3$; 0.69-0.85 (br t, J=6.3 Hz, 3H): H-14; 1.00-1.27 (br, 20H), 1.27-2.02 (br m, 8H): H-3, H-5 - H-13, H-1', and $OCH_2C\underline{H}_3$ [δ 1.07 (t, J=7.1 Hz)]; 2.30-2.60 (br, 1H): H-2; 3.28-3.67 (br m, 5H): H-4 and $OC\underline{H}_2CH_3$; 4.37-4.45 (m; 1H): H-2', 9.47 (d, J=2.9 Hz) and 9.49 (d, J=2.2 Hz; total 1H): H-1. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 0.4 (q): $Si(\underline{C}H_3)_3$; 14.1 (q): C-14; 15.3 (q): $OCH_2\underline{C}H_3$; 22.7, 25.2, 25.3, 29.3, 29.6, 29.7, 31.9, 34.0, 34.3, 36.8, 37.0, and 37.6 (12 t): C-3, C-5 - C-13, and C-1'; 44.5 and 45.5 (2 d): C-2; 61.8 and 62.1 (2 t): $O\underline{C}H_2CH_3$; 70.0 and 70.6 (2 d): C-4; 101.3 and 101.4 (2 d): C-2'; 204.0 and 204.3 (2 s): C-1.

5-Cyclohexyl-perhydrofuro[2,3-b]furan-2-ol (12).
A mixture of 7.3 g (18.9 mmol) of **14** in 80 ml of THF and 80 ml of aqueous 1N HCl solution was stirred vigorously for 16 h at room temperature. Then, 100 ml of ether was added, the organic layer was separated and the aqueous layer was extracted with 50 ml of ether. The combined organic layers were washed sequentially with 50 ml of saturated aqueous sodium bicarbonate solution and 50 ml of brine. After drying with $MgSO_4$ and evaporation of the solvent under reduced pressure, 4.3 g of an oil was obtained. Chromatography on 100 g of silicagel with petrol-EtOAc (90-10 to 80-20) as eluent yielded 3.9 g (18.5 mmol, 98%) of an inseparable mixture of all four stereoisomers **12** as a colourless oil.
^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.8-2.3 (br m, 15H): H-3, H-4, and *c*-hex H-1 - H-6; 2.70-2.97 (m, 0.7H) and 2.97-3.15 (m, 0.3H): H-3a; 3.56-3.80 (m, 0.7H), 3.89 (d, J=2.0 Hz, 0.2H), 3.98 (d, J=3.0 Hz, 0.3H), and 4.05-4.30 (m, 0.8H): H-5 and OH; 5.54 (ddd, J=5.2, 2.0, 0.8 Hz, 0.3H), 5.58-5.76 (m, 1.2H), and 5.83 (t, J=5.4 Hz, 0.5H): H-2 and H-6a. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 25.7, 25.8, 25.9, 26.0, 26.4, 28.7, 28.9, 30.0, 30.1, and 30.2 (10 t): *c*-hex C-2 - C-6; 35.3, 36.0, 36.1, and 36.7 (4 t): C-3; 38.8, 39.2, and 39.9 (3 t): C-4; 40.6, 41.5, 41.7, 42.2, 42.4, 43.0, and 43.2 (7 d): C-3a and *c*-hex C-1; 82.5, 85.4, and 86.1 (3 d): C-5; 98.5, 98.7, 98.9, and 100.8 (4 d): C-2; 107.7, 108.5, 110.4, and 110.5 (4 d): C-6a. MS: *m/e* (%) 194 (3), 168 (5), 148 (3), 129 (37), 112 (6), 111 (100), 96 (5), 95 (5), 83 (11), 82 (5), 81 (6), 69 (5), 67 (5), 55 (10), 43 (3), 41 (5). HRMS: calcd. (M^+-H_2O): *m/e* 194.1307; found: *m/e* 194.1304.

5-Hexyl-perhydrofuro[2,3-b]furan-2-ol (60).
Cyclization of 3.7 g (9.6 mmol) of **58** according to the procedure described for **12** yielded, after purification by chromatography on 70 g of silicagel with petrol-EtOAc (66-34) as eluent, 1.16 g (5.4 mmol; 56%) of **60** as a mixture of four stereoisomers.
^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.75-1.0 (br m, 3H): hex H-6, 1.05-1.50 (br, 8H) and 1.50-2.30 (br m, 6H): H-3, H-4, and hex H-1 - H-5; 2.70-2.97 (br m, 0.7H) and 2.97-3.15 (m, 0.3H): H-3a; 3.40-4.12 (br m, 1.7H) and 2.97-3.15 (m, 0.3H): H-5 and OH; 5.15-5.90 (br m [incl. δ 5.82 (t, J=5.9 Hz)], 2H): H-2 and H-6a. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 14.0 (q): hex C-6; 22.5, 23.8, 26.1, 27.9, 29.3, 31.7, 34.5, 35.3, 35.7, 36.2, 37.5, 38.2, 38.4, 38.7, 38.9, 39.3, and 39.8 (17 t): C-3, C-4, and hex C-1 - C-5; 40.7, 41.6, and 42.4 (3 d): C-3a; 78.1, 78.2, 81.0, and 81.6 (4 d): C-5; 98.5, 98.7, 99.0, and 100.9 (4 d): C-2; 108.0, 108.6, and 110.5 (3 d): C-6a.

5-Decyl-perhydrofuro[2,3-b]furan-2-ol (61).
Cyclization of 6.9 g (16.6 mmol) of **59** according to the procedure described for **12** yielded, after purification by chromatography on 40 g of silicagel with petrol-EtOAc (95-5) as eluent, 4.5 g (16.6 mmol; 100%) of **61** as a mixture of all four stereoisomers.
^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.75-0.95 (br t, J=5.7 Hz, 3H): dec H-10; 1.08-1.40 (br) and 1.40-2.27 (br m; 22H): H-3, H-4, and dec H-1 - H-9; 2.71-2.95 (br m) and 2.95-3.13 (br m; 1H): H-3a; 3.81-3.90 (br m), 3.90-4.05 (br m; 1.5H), and 4.12 (br d, J=4.5Hz, 0.3H), and 4.37-4.55 (br m, 0.2H): H-5 and OH; 5.50 (dd, J=5.4, 1.9 Hz), 5.57-5.72 (m [incl. δ 5.69 (t, J=5.5 Hz)]), and 5.81 (t, J=5.6 Hz; total 2H): H-2 and H-6a. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 14.1 (q): dec C-10; 22.6, 26.1, 26.2, 29.3, 29.5, 31.8, 34.5, 35.3, 35.7, 36.2, 37.5, 38.2, 38.4, 38.7, 38.8, 38.9, 39.3, 39.8 (18 t): dec C-1 - C-9, C-3, and C-4; 40.7, 41.6, 41.8, and 42.4 (4 d): C-3a; 78.1, 78.2, 80.9, and 81.6 (4 d): C-5; 98.5, 98.7, 98.9, and 100.8 (4 d): C-2; 107.9, 108.6, 110.5, and 110.6 (4 d): C-6a. MS: *m/e* (%) 129 (67), 112 (7), 111 (100), 100 (9), 83 (13), 82 (12), 69 (15), 58 (10), 55 (12), 43 (10). HRMS: calcd. (M^+-H_2O): *m/e* 252.2089; found: *m/e* 252.2091.

5-Cyclohexyl-2-phenylthio-perhydrofuro[2,3-b]furan (13).
To an ice-cold, stirred solution of 618 mg (2.9 mmol) of a mixture of furofuranols **12** and 0.34 ml (3.3 mmol) of thiophenol in 25 ml of anhydrous ether, containing approx. 2 g of activated 4Å molecular sieves, was added dropwise via syringe 0.55 ml (4.5 mmol) of borontrifluoride etherate. After 30 min the reaction was quenched by

the addition of 50 ml of an aqueous 4N NaOH solution. The organic layer was separated and the waterlayer was extracted with 50 ml of ether. The combined organic layers were washed with 25 ml of brine, dried with $MgSO_4$ and concentrated under reduced pressure to yield 828 mg (2.7 mmol, 93%) of a mixture of all four diastereomers of sulfide **13** as a clear, colourless oil. The crude product was sufficiently pure to be used in the next reaction.
^1H NMR ($CDCl_3$, 200 MHz): δ 0.75-1.50 (br m, 9H), 1.50-1.85 (br m, 6H), and 1.85-2.33 (m, 3H): H-3, H-4, and *c*-hex H-1 - H-6; 2.50-2.68 (m, 0.3H) and 2.75-3.05 (m, 0.7H): H-3a; 3.56-4.08 (m, 0.8H) and 3.94-4.08 (m, 0.2H): H-5; 5.38-5.89 (m, 2H): H-2 and H-6a; 7.25-7.35 (m, 3H): Ph H-3 - H-5; 7.43-7.58 (m, 2H): Ph H-2 and H-6. MS: *m/e* (%) 197 (13), 195 (100), 177 (21), 151 (14), 133 (82), 109 (15), 91 (11), 81 (13), 67 (17), 55 (12). HRMS: calcd. (M^+): *m/e* 304.1497; found: *m/e* 304.1498.

5-Hexyl-2-phenylthio-perhydrofuro[2,3-b]furan (62).
Addition of thiophenol to 1.16 g (5.4 mmol) of **60** according to the procedure described for **13** yielded1.3 g (4.3 mmol; 80%) of **34** as a mixture of isomers. The crude product was used without further purification in the next reaction.
^1H NMR ($CDCl_3$, 90 MHz): δ 0.55-0.9 (br t, J=6.0 Hz, 3H): hex H-6; 0.9-1.9 (br, 12H) and 1.9-2.35 (m, 2H): H-3, H-4, and hex H-1 - H-5; 2.5-3.1 (br m, 1H): H-3a; 3.6-4.4 (br m, 1H): H-2; 5.2-5.8 (m, 2H): H-6a [δ 5.60 (d, J=4.5 Hz) and 5.70 (d, J=6.0 Hz)] and H-5; 6.9-7.3 (m, 3H): Ph H-3 - H-5; 7.3-7.5 (m, 2H): Ph H-2 and H-6. MS: *m/e* (%) 198 (13), 197 (100), 179 (11), 135 (21), 109 (13), 95 (12), 86 (23), 84 (37), 81 (11), 69 (13), 55 (14), 51 (11), 49 (34). HRMS: calcd. (M^+): *m/e* 306.1654; found: *m/e* 306.1651.

2-Cyclohexyl-2,3,3a,6a-tetrahydrofuro[2,3-b]furan (15).
A solution of 740 mg (3.0-3.2 mmol) of *m*-CPBA (70-75 wt% *m*-CPBA, remainder *m*-CBA and water) in 5 ml of anhydrous toluene was pre-dried in a dropping funnel containing activated 4Å molecular sieves. After 20 min, this solution was added dropwise in 10 min to an ice-cold solution of 828 mg (2.7 mmol) of sulfides **13** in 12 ml of toluene. Stirring at 0°C was continued until tlc-analysis indicated complete disappearance of the sulfides (approx. 10 min). The dropping funnel was replaced with a reflux condensor, 1.0 ml (7.2 mmol) of triethylamine was added and the flask containing the reaction mixture was placed in an oil bath, pre-heated at 130°C, for 15 min. Solvent and triethylamine were removed at a rotary evaporator under reduced pressure and the residual oil was purified by chromatography on 30 g of silicagel with petrol-EtOAc (99.5-0.5) as eluent, affording 379 mg (1.95 mmol, 72%) of a 2 : 1 mixture of stereoisomers of **15** as a colourless oil.
^1H NMR ($CDCl_3$, 200 MHz): δ 0.70-2.10 (br m, 13 H): H-3 and *c*-hex H-1 - H-6; 3.24-3.39 (m, 0.33H) and 3.40-3.52 (m, 0.66H): H-3a; 3.56-3.72 (m, 1H): H-2; 4.74 (t, J=2.6 Hz, 0.66H) and 4.91 (t, J=2.6 Hz, 0.33H): H-4; 5.93 (d, J=6.7 Hz, 0.33 H) and 5.98 (d, J=6.2 Hz, 0.66H): H-6a; 6.19 (t, J=2.4 Hz, 0.33H) and 6.36 (t, J=2.5 Hz, 0.66H): H-5. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT, selected peaks): *major isomer:* δ 25.8, 26.4, 29.0, 29.6, and 30.3 (5 t): *c*-hex C-2 - C-6; 35.5 (t): C-3; 42.2 (d): *c*-hex H-1; 46.4 (d): C-3a; 83.0 (d): C-2; 102.2 (d): C-4; 108.9 (d): C-6a; 146.0 (d): C-5. *minor isomer*: δ 25.9, 26.4, 29.0, 29.6, and 30.3 (5 t): *c*-hex C-2 - C-6; 34.5 (t): C-3; 42.8 (d): *c*-hex C-1; 46.2 (d): C-3a; 84.5 (d): C-2; 104.7 (d): C-4; 110.1 (d): C-6a; 143.9 (d): C-5. MS: *m/e* (%) 194 (100), 176 (27), 165 (58), 150 (15), 147 (52), 126 (16), 119 (15), 111 (52), 109 (50), 108 (18), 99 (14), 98 (17), 95 (31), 93 (16), 91 (22), 86 (42), 83 (44), 81 (60), 79 (25), 69 (26), 67 (78), 55 (48), 41 (36). HRMS: calcd. (M^+): *m/e* 194.1307; found: *m/e* 194.1310.

2-Hexyl-2,3,3a,6a-tetrahydrofuro[2,3-b]furan (50).
Oxidation followed by elimination of 1.2 g (3.9 mmol) of **62** as described for **15** afforded **25** as a 1 : 1 mixture. Careful chromatography on 30 g of silicagel with petrol-EtOAc (99-1) as eluent yielded 53 mg (0.27 mmol; 7%) of the least polar isomer of **63** and 528 mg (2.7 mmol; 69%) of a mixture of both isomers in a ratio of 1 : 1.25. Despite repeated chromatography, the most polar isomer could not be separated from the mixture in an analytically pure form.
^1H NMR ($CDCl_3$, 90 MHz): δ 0.7-1.0 (br t, J=4.5Hz, 3H): hex H-6; 1.0-2.4 (br m, 12H): H-3 and hex H-1 - H-5; 3.3-3.6 (m, 1H): H-3a; 3.8-4.3 (m, 1H): H-2; 4.80 (t, J=3.0 Hz, 0.45H): H-4 least polar isomer; 5.0 (t, J=3.0 Hz, 0.55H): H-4 most polar isomer; 5.9-6.1 (m, 1H): H-6a most polar isomer [δ 6.00 (d, J=7.5 Hz)] and H-6a least polar isomer [δ 6.03 (d, J=6.0 Hz)]; 6.25 (t, J=3.0 Hz, 0.55H): H-5 most polar isomer; 6.40 (t, 3.0 Hz, 0.45H): H-5 least polar isomer. MS: *m/e* (%) 196 (18), 167 (20), 145 (26), 127 (100), 111 (18), 98 (21), 97 (22), 95 (19), 84 (17), 83 (28), 81 (46), 73 (32), 72 (17), 70 (28), 69 (51), 66 (20), 57 (33), 55 (51), 43 (61), 41 (40). HRMS: calcd. (M^+): *m/e* 196.1463; found: *m/e* 196.1461.

2-Phenyl-2,3,3a,6a-tetrahydrofuro[2,3-b]furan (51).
This compound was synthesized as described for the cyclohexyl-derivative **15** starting with phenyloxirane. The intermediates were not purified because an unseparable mixture of regioisomers was obtained in each reactionstep. Elimination of phenylsulfenic acid from 1.1 g (3.9 mmol) of crude sulfoxide as described for **15** afforded, after chromatography on 35 g of silicagel with petrol-EtOAc (gradient elution, 99.8-0.2 to 99-1) as eluent, 342 mg of an oil, consisting for >85% (glc-analysis) of a mixture of both isomers of **51**. After extensive chromatography, only a small sample of the least polar, major (2S)-isomer **(2S*,3aS*,6aS*)-2-Phenyl-2,3,3a,6a-tetrahydrofuro[2,3-b]furan (51a)** could be obtained as a white solid (m.p. 32°C) of analytical purity.
^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.97 (ddd, J=12.3, 11.2, 8.1 Hz, 1H): H-3α; 2.20 (dd, J=12.3, 4.8 Hz, 1H): H-3β; 3.65-3.75 (m, 1H): H-3a; 4.92 (t, J=2.6 Hz, 1H): H-4; 5.04 (dd, J=11.1, 4.8 Hz, 1H): H-2; 6.26 (d, J=6.1 Hz, 1H): H-6a; 6.54 (t, J=2.5 Hz, 1H): H-5; 7.20-7.42 (m, 5H): Ph H-2 - H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 40.6 (t): C-3; 47.2 (d): C-3a; 79.8 (d): C-2; 102.1 (d): C-4; 109.1 (d): C-6a; 126.0, 127.7, and 128.4 (3 d): Ph C-2 - C-6; 140.0 (s): Ph C-1; 146.6 (d): C-5. MS: *m/e* (%) 188 (30), 159 (40), 149 (11), 129 (14), 115 (12), 105 (22), 104 (100), 91 (37), 77 (14), 69 (12), 43 (24). HRMS: calcd. (M^+): *m/e* 188.0837; found: *m/e* 188.0836.

2-Cyclohexyl-perhydrofuro[2,3-b]furan (16).
A solution of 203 mg (1.0 mmol) of a mixture of tetrahydrofurofurans **15** in 25 ml of methanol containing 162 mg of 10% Pd/C, was hydrogenated in a Parr apparatus under hydrogen pressure (4 atm) at room temperature. After 20 min the reaction mixture was filtered and the solvent was evaporated under reduced pressure. The crude product was purified by chromatography on silicagel with petrol-EtOAc (99.5-0.5 to 98-2) as eluent, affording 167 mg (0.95 mmol; 85%) of a 3 : 2 mixture of isomers of **19** as a colourless oil.
^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.75-1.80 (br m, 12H) and 1.80-2.16 (m, 3H): H-3, H-4, and *c*-hex H-1 - H-6; 2.70-2.90 (m, 1H): H-3a; 3.47 (ddd, J=12.1, 7.3, 4.9 Hz, 0.4H): H-2 minor isomer; 3.68-3.90 (m, 2.6H): H-2 major isomer and H-5; 5.58 (d, J=5.4 Hz, 0.4H): H-6a minor isomer; 5.66 (d, J=5.1 Hz, 0.6H): H-6a major isomer. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT, selected peaks): *major isomer*: δ 25.9, 26.4, 28.8, and 30.0 (4 t): *c*-hex C-2 - C-6; 32.7 (t): C-3; 36.5 (t): C-4; 42.4 (d): *c*-hex C-1; 43.2 (d): C-3a; 68.1 (t): C-2; 84.1 (d): C-5; 108.8 (d): C-6a. *minor isomer*: δ 25.7, 25.8, 28.8, and 30.0 (4 t): c-hex C-2 - C6; 32.5 (t): C-3; 34.5 (t): C-4; 42.7 and 42.9 (2 d): C-3a and *c*-hex C-1; 65.8 (t): C-2; 83.7 (d): C-5; 108.7 (d): C-6a. MS: *m/e* (%) 152 (10), 113 (100), 69 (13). HRMS: calcd. (M^+-C_6H_{11}):*m/e* 113.0603; found: *m/e* 113.0602.

5-Cyclohexyl-2-ethoxy-perhydrofuro[2,3-b]furan (17).
A solution of 50 mg (0.24 mmol) of a mixture of furofuranols **12**, 25 mg (0.54 mmol) of ethanol and 5 mg (0.03 mmol) of *p*-toluenesulfonic acid monohydrate in 10 ml of THF was stirred at room temperature for 2 days. Then, 25 ml of water and 5 ml of saturated aqueous sodium bicarbonate solution were added and the mixture was extracted with three 10 ml-portions of ether. The combined extracts were dried with $MgSO_4$ and concentrated under reduced pressure. According to tlc-analysis, the crude oil consisted of an isomeric mixture of ethoxyfuro[2,3-b]furans **17** in two distinct fractions as the major component, accompanied by a minor amount of the starting material **12**. Separation by chromatography on 10 g of silicagel with petrol-EtOAc (99-1) as eluent afforded 32 mg (0.13 mmol; 54%) of **17** as a mixture of all four diastereomers.
^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.76-1.45 (br m) and 1.45-2.10 (br m; total 21H): H-3, H-4, *c*-hex H-1 - H-6 and $OCH_2C\underline{H}_3$; 2.67-2.85 (br, 0.7H) and 2.85-3.05 (br, 0.3H): H-3a; 3.25-3.55 (m, 0.4H), 3.55-3.87 (m, 0.5H), and 4.00 (ddd, J=10.1, 7.7, 5.8 Hz, 0.1H): H-5 and $OC\underline{H}_2CH_3$; 5.02 (d, J=5.7 Hz, 0.3H) and 5.12 (d, J=5.3 Hz), 5.18 (dd, J=5.1, 1.4 Hz), 5.25 (t, J=4.7 Hz; total 0.7H): H-2; 5.63 (d, 5.2 Hz) and 5.67 (d, 5.8 Hz; total 0.2 H), 5.72 (d, 5.4 Hz, 0.4H) and 5.78 (d, 5.4 Hz, 0.4 H): H-6a. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): *Major isomers*: δ 15.1 (q): $OCH_2\underline{C}H_3$; 25.8, 36.0, 26.4, 26.5, 28.9, 29.0, 30.1, and 30.2 (8 t): *c*-hex C-2 - C-6; 36.5 and 36.6 (2 t): C-3; 38.2 and 39.6 (2 t): C-4; 40.5, 41.0, 42.4, and 42.8 (4 d): C-3a and *c*-hex C-1; 62.6 and 62.9 (2 t): $O\underline{C}H_2CH_3$; 82.3 (2 d): C-5; 103.4 and 103.8 (2 d): C-2; 108.5 and 110.2 (2 d): C-6a.
Minor isomers (separated peaks only): δ 15.0 (q): $OCH_2\underline{C}H_3$; 25.7, 26.0, 28.8, 29.8 (4 t): *c*-hex C-2 - C-6; 35.1 and 35.7 (2 t): C-3 and C-4; 41.6, 42.1, 43.0, and 43.4 (4 d): C-3a; 62.7 and 63.9 (2 t): $O\underline{C}H_2CH_3$; 86.2 (d): C-5; 104.3 and 105.2 (2 d): C-2; 108.1 and 108.5 (2 d): C-6a. MS: *m/e* (%) 195 (12), 194 (12), 157 (63), 111 (100), 86 (16), 84 (25), 83 (10), 48 (23). HRMS: calcd. (M^+-OEt): *m/e* 195.1385; found: *m/e* 195.1383.

2-Acetyl-5-cyclohexyl-perhydrofuro[2,3-b]furan (18).
A solution of 100 mg (0.47 mmol) of a mixture of furofuranol **12**, 0.07 ml (0.98 mmol) of acetylchloride and 0.08 ml (0.99 mmol) of pyridine in 5 ml of dichloromethane was stirred at room temperature for 45 min. The reaction mixture was diluted with 50 ml of ether and 30 ml of water. The organic layer was separated and the aqueous layer was extracted with 50 ml of ether. The combined organic layers were washed with 30 ml of brine, dried with $MgSO_4$

and the solvents were evaporated under reduced pressure, yielding 94 mg of a pale yellow oil. Chromatography on 15 g of silicagel with petrol-EtOAc (90-10) as eluent afforded 75 mg (0.30 mmol, 64%) of acetate **18** as a mixture of isomers.
^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.75-2.35 (br m, 18H): H-3, H-4, $C\underline{H}_3C(O)O$ [δ 1.99 and 2.01 (2 s)], and *c*-hex H-1 - H-6; 2.78-3.10 (br m, 1H): H-3a; 3.60-3.85 (m, 1H): H-5; 5.73 (d, J=5.4 Hz, 0.4H) and 5.83 (d, J=5.0 Hz, 0.6H): H-6a; 6.34 (d, J=5.0 Hz) and 6.37 (d, J=8.5 Hz; 1H): H-2. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 21.2 (q): $\underline{C}H_3C(O)O$; 25.5, 25.7, 25.9, 26.0, and 26.3 (5 t): *c*-hex C-3 - C-5; 28.8, 29.0, 29.9, and 30.1 (4 t): *c*-hex C-2 and C-6; 35.1 and 36.0 (2 t): C-3; 37.5 and 37.7 (2 t): C-4; 39.8, and 41.3, 42.1, and 43.4 (4 d): C-3a and *c*-hex C-1; 82.4 and 87.1 (2 d): C-5; 98.5 and 98.7 (2 d): C-2; 109.6 and 109.9 (2 d): C-6a; 170.1 (2 s): $CH_3\underline{C}(O)O$. MS: *m/e* (%) 195 (13), 194 (6), 171 (22), 133 (6), 112 (6), 111 (100), 81 (6), 67 (8), 54 (8), 43 (30), 41 (6). HRMS: calcd. (M^+-OAc): *m/e* 195.1385; found: *m/e* 195.1381.

(3aS*,5S*,6aR*)- and (3aS*,5R*,6aR*)-5-Cyclohexyl-3a,4,5,6a-tetra-hydrofuro[2,3-b]furan-2(3H)-one (19a and 19b).
A mixture of 2.01 g (9.5 mmol) of **12** and 4.3 g (11.4 mmol) of pyridinium dichromate in 40 ml of dichloromethane was stirred for 3 days at room temperature. The mixture was filtered through a pad of hyflo, dried with $MgSO_4$ and concentrated under reduced pressure. Purification via chromatography on 100 g of silicagel with petrol-EtOAc (95-5 to 90-10) as eluent yielded, in order of elution, 290 mg (1.4 mmol, 15%) of the 5bH isomer **19a** as a white solid (m.p. 90°C) and 1.12 gr (5.3 mmol, 56%) of a mixture of C-5 epimers **19a** and **19b** as an oil.
19a: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.8-2.0 (br m, 13H): H-4 and *c*-hex H-1 - H-6; 2.37 (dd, J=18.6, 3.9 Hz, 1H): H-3β; 2.83 (dd, J=18.6, 10.6 Hz, 1H): H-3α; 3.1-3.2 (m, 1H): H-3a; 3.83 (ddd, J=9.6, 7.2, 6.2 Hz, 1H): H-5; 6.04 (d, J=5.5 Hz, 1H): H-6a. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 25.6, 25.8, and 26.2 (3 t): *c*-hex C-3 - C-5; 28.7 and 29.7 (2 t): *c*-hex C-2 and C-6; 35.3 (t): C-4; 36.1 (t): C-3; 38.3 (d): C-3a; 42.0 (d): *c*-hex C-1; 83.1 (d): C-5; 108.0 (d): C-6a; 175.5 (s): C-2. MS: *m/e* (%) 166 (10), 129 (12), 128 (12), 127 (100), 126 (24), 109 (23), 99 (13), 83 (12), 81 (17), 55 (15), 41 (12). HRMS: calcd. (M^+-*c*-hex): *m/e* 127.0395; found: *m/e* 127.0396. Anal: calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63; found: C, 68.29; H, 8.81.

5-Hexyl-3a,4,5,6a-tetrahydrofuro[2,3-b]furan-2(3H)-one (52).
Oxidation of 82 mg (0.38 mmol) of a mixture of furofuranols **60** with PDC according to the procedure described for **19** gave, after chromatography on 10 g of silicagel with petrol-EtOAc (99-1) as eluent, 50 mg (0.24 mmol; 63%) of an inseparable mixture of **52** as an oil.
^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.80-1.0 (br m, 3H) and 1.10-1.90 (br m, 12H): H-4 and hex H-1 - H-6; 2.35-2.53 (m, 1H) and 2.72-2.92 (m, 1H): H-3; 2.95-3.25 (br m, 1H): H-3a; 4.05-4.30 (br m, 1H): H-5; 5.94 (d, J=5.2 Hz, 0.25H): H-6a minor isomer; 6.07 (d, J=5.6 Hz, 0.75H): H-6a major isomer. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 14.0 (q): hex C-6; 22.5, 29.0, 29.2, 31.6, 34.2, 35.2, 36.1, 36.6, 36.8, and 38.4 (10 t): C-3, C-4, and hex C-1 - C-5; 38.5 (d): C-3a major isomer; 39.9 (d): C-3a minor isomer; 78.8 (d): C-5 major isomer; 83.3 (d): C-5 minor isomer; 108.1 (d): C-6a major isomer; 108.7 (d): C-6a minor isomer; 175.5 (s): C-2. MS: *m/e* (%) 127 (100), 109 (14), 99 (10), 98 (10), 97 (9), 83 (9), 70 (11), 55 (16), 43 (11), 41 (13). HRMS: calcd. (M^+): *m/e* 212.1412; found: *m/e* 212.1414.

5-Decyl-3a,4,5,6a-tetrahydrofuro[2,3-b]furan-2(3H)-one (53).
Oxidation of 373 mg (1.38 mmol) of a mixture of **61** with PDC according to the procedure described for **19** gave 410 mg of a brown oil, which solidified in the freezer. Chromatography on 25 g of silicagel with petrol-EtOAc (96-4) as eluent afforded, in order of elution, 123 mg (0.46 mmol; 33%) of the least polar isomer **54** as a white solid (mp 60-61°C) and 137 mg (0.51 mmol; 37%) of a 1 : 1.5 mixture of both isomers **53** as a colourless oil.
53, (*1 : 1.5 mixture of isomers*): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.81 (br t, J=5.9 Hz, 3H): dec H-10; 1.05-1.80 (m [incl. δ 1.19 (br s)], 19H); 2.30-2.48 (m, 2H); 2.68-2.88 (m, 1H); 2.91-3.20 (br m, 1H): H-3a; 3.98-4.25 (br m, 1H): H-5; 5.89 (d, J=5.2 Hz, 0.6H): H-6a most polar isomer; 6.02 (d, J=5.6 Hz, 0.4H): H-6a least polar isomer. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 14.1 (q): dec C-10; 22.7, 26.1, 29.3, 29.4, 29.6, 31.9, 34.3, 35.3 (8 t); 36.1, 36.6 and 36.9 (3t), most polar isomer; 38.5 (t); 38.6 (d): C-3a least polar isomer; 40.0 (d): C-3a most polar isomer; 78.9 (d): C-5 least polar isomer; 83.4 (d): C-5 most polar isomer; 108.1 (d): C-6a least polar isomer; 108.7 (d): C-6a most polar isomer; 174.3 (s): C-2 most polar isomer; 175.6 (s): C-2 least polar isomer. MS: *m/e* (%) 129 (10), 127 (100), 111 (20), 109 (15), 99 (8), 98 (8), 97 (9), 83 (14), 81 (10), 70 (8), 69 (11), 57 (9), 55 (17), 43 (14), 41 (14). HRMS: calcd. (M^+): *m/e* 268.2038; found: *m/e* 268.2038.
(3aS*,5S*,6aR*)-isomer (54). Least polar. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.87 (t, J=7.0 Hz, 3H): dec H-10; 1.20-1.35 (br), 1.35-1.45 (br m), 1.47-1.56 (br m) and 1.62-1.71 (br m; total 18H): dec H-1 - H-9; 1.73-1.82 (m, 2H): H-4; 2.41 (dd, J=18.8, 4.0 Hz, 1H): H-3β; 2.85 (dd, J=18.7, 10.6 Hz, 1H): H-3α; 3.15-3.19 (m, 1H): H-3a; 4.13

(ddd, J=12.1, 10.5, 5.3 Hz, 1H): H-5; 6.07 (d, J=5.6 Hz, 1H): H-6a. ^{13}C NMR ($CDCl_3$, 125 MHz, DEPT): δ 14.1 (q): dec C-10; 22.6, 25.9, 29.3, 29.5, 31.8, and 34.2 (6 t): dec C-1 - C-9; 35.2 (t): C-4; 38.4 (t): C-3; 38.5 (d): C-3a; 78.8 (d): C-5; 108.0 (d): C-6a; 175.4 (s): C-2. Anal: calcd. for $C_{16}H_{28}O_3$: C, 71.60; H, 10.52; found: C, 71.30; H, 10.68.

5-Phenyl-3a,4,5,6a-tetrahydrofuro[2,3-b]furan-2(3H)-one (55).
Oxidation with PDC of 340 mg (1.65 mmol) of an unseparable regioisomeric mixture of furofuranols obtained by a reaction sequence identical with the reported one for the cyclohexyl derivative **19** and chromatography of the crude product on 15 g of silicagel with petrol-EtOAc (80-20) as eluent afforded, in order of elution, 90 mg (0.44 mmol; 27%) of the least polar isomer **55a** and 60 mg of a mixture of the most polar isomer of **28** and some inseparable side-products.
(3aS*,5S*,6aR*)-isomer (55a)[8]: ^1H NMR ($CDCl_3$, 90 MHz): δ 2.11 (dd, J=7.5, 3.0 Hz, 2H): H-4; 2.55 (dd, J=18.0, 4.5 Hz, 1H): H-3β; 2.95 (dd, J=18.0, 9.0 Hz, 1H): H-3α; 3.16-3.60 (br m, 1H): H-3a; 5.18 (t, J=7.5 Hz, 1H): H-5; 6.30 (d, J=6.0 Hz, 1H): H-6a; 7.20-7.41 (m, 5H): Ph H-2 - H-6.

Ethyl 3-cyclohexyl-3-[(trimethylsilyl)oxy]-propanoate (30).
To an ice-cold, stirred solution of 13 ml (61.6 mmol) of hexamethyl disilazane in 100 ml of anhydrous THF was added dropwise 39 ml (62.4 mmol) of a 1.6M solution of n-butyllithium in hexanes; stirring was continued at room temperature for 30 min. After cooling to -78°C, 5.1 ml (57.4 mmol) of anhydrous ethyl acetate was added dropwise via syringe and the resulting solution was stirred for 45 min. Subsequently, the reaction mixture was treated dropwise with 6.0 ml (50 mmol) of cyclohexyl carbaldehyde **29**, after 30 min followed by 9.0 ml (70.9 mmol) of chlorotrimethylsilane. Stirring was continued for 20 min at room temperature before the reaction mixture was poured into 50 ml of a saturated aqueous sodium bicarbonate solution and 150 ml of water. The organic layer was separated and the aqueous layer was extracted with three 150 ml-portions of petrol. The combined organic layers were washed with 100 ml of water and 100 ml of brine, dried with $MgSO_4$ and concentrated under reduced pressure to give 16.1 g of a pale yellow oil. The crude product was distilled under reduced pressure in a bulb-to-bulb apparatus, yielding 9.67 g (35.6 mmol; 71%) of ester **30** as a clear, colourless oil (b.p. 65°C at 0.7 mmHg), which was used in the next reaction without further purification.
^1H NMR ($CDCl_3$, 200 MHz, selected peaks): δ 0.09 (s, 9H): $Si(C\underline{H}_3)_3$; 0.8-1.45 (m, 9H): $OCH_2C\underline{H}_3$ [δ 1.26 (t, J=7.1 Hz)] and *c*-hex H-3 - H-5; 1.55-1.85 (br m, 5H): *c*-hex H-1, H-2, and H-6; 2.42 (d, J=7.3 Hz, 1H): H-2; 2.43 (d, J=5.3 Hz, 1H): H-2; 3.94 (ddd, J=7.3, 5.3, 5.0 Hz, 1H): H-3; 4.1 (q, J=7.1 Hz, 2H): $OC\underline{H}_2CH_3$. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 0.3 (q): $Si(\underline{C}H_3)_3$; 14.2 (q): $OCH_2\underline{C}H_3$; 26.3 (3 t): *c*-hex C-3 - C-5; 28.2 and 28.8 (2 t): *c*-hex C-2, C-6; 40.2 (t): C-2; 44.0 (d): *c*-hex C-1; 60.2 (t): $O\underline{C}H_2CH_3$; 73.8 (d): C-3; 172.4 (s): C-1. MS: *m/e* (%) 257 (24), 243 (53), 229 (51), 197 (33), 188 (28), 145 (20), 110 (22), 103 (96), 95 (26), 83 (45), 75 (39), 73 (100), 71 (24), 67 (20), 57 (49), 55 (46), 41 (37). HRMS: calcd. (M^+-CH_3): *m/e* 257.1573; found: *m/e* 257.1574.

3-Cyclohexyl-3-[(trimethylsilyl)oxy]-propanal (31).
To a stirred solution of 8.5 g (31.2 mmol) of ester **30** in 90 ml of anhydrous ether, cooled to -78°C, was added dropwise 21 ml (31.5 mmol) of a 1.5M solution of diisobutyl aluminumhydride in toluene. After stirring for 30 min the reaction was quenched by the addition of 10.05 g (31.2 mmol) of Glauber's salt. Stirring was continued at room temperature for 30 min before the reaction mixture was dried with $MgSO_4$ and filtered. The solvents were removed under reduced pressure to yield 6.6 g (28.2 mmol; 93%) of aldehyde **31** as a pale yellow oil, which was used without further purification in the next reaction. A small sample (123 mg) was chromatographed on silicagel with petrol-EtOAc (98-2) as eluent to yield, in order of elution, analytically pure **31** (74 mg) and the corresponding desilylated product, 3-cyclohexyl-3-hydroxy-propanal, which had been formed during chromatography.
^1H NMR ($CDCl_3$, 200 MHz): δ 0.0 (br s, 9H): $Si(C\underline{H}_3)_3$; 0.6-1.4 (m, 6H): *c*-hex H-3 - H-5; 1.4-1.8 (m, 5H): *c*-hex H-1, H-2, and H-6; 2.2-2.55 (m, 2H): H-2; 3.9 (2 t, J=7.0 and 5.4 Hz, 1H): H-3; 9.7 (t, J=2.1 Hz, 1H): H-1. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 0.37 (q): $Si(\underline{C}H_3)_3$; 26.2 (t) and 26.5 (t): *c*-hex C-3 - C-5; 28.5 (2 t): *c*-hex C-2 and C-6; 44.1 (d): *c*-hex C-1; 48.4 (t): C-2; 72.3 (d): C-3; 202.7 (d): C-1.

4-Cyclohexyl-2-hydroxy-4-[(trimethylsilyl)oxy]-butanenitrile (32).
A mixture of 5.95 g (26.1 mmol) of crude aldehyde **31,** 3.5 ml (38.3 mmol) of acetone cyanohydrin and 0.2 ml (1.4 mmol) of triethylamine was stirred at room temperature for 45 min until tlc-analysis indicated complete transformation of the starting material. The reaction mixture was concentrated under reduced pressure to yield 6.49 g (25.5 mmol; 98%) of a 1 : 1 mixture of diastereomeric isomers of cyanohydrin **32** as a yellow oil. The crude product was sufficiently pure to be used without further purification in the next reaction. A small sample (180 mg) was chromatographed on silicagel with petrol-EtOAc (10-1) as eluent to afford, in order of elution, analytically pure

32 as a mixture of isomers (102 mg) and the corresponding desilylated diol, which had been formed during chromatography.
^{1}H NMR ($CDCl_3$, 200 MHz, selected peaks): δ 0.14 and 0.17 (2 s, 9H): Si($C\underline{H}_3$)$_3$; 0.75-1.35 (br m, 6H): *c*-hex H-3 - H-5; 1.35-1.57 (br m, 1H): *c*-hex H-1; 1.57-1.81 (br m, 4H): *c*-hex H-2 and H-6; 1.81-2.10 (m, 2H): H-3; 3.67 (d, J=4.8 Hz, 0.5H): OH; 3.70-3.77 and 3.96-4.04 (2 m, 1H): H-4; 4.31 (d, J=7.6 Hz, 0.5H): OH; 4.54-4.68 (m, 1H): H-1. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 0.4 (q): Si($\underline{C}H_3$)$_3$; 26.3 (3), 26.9, and 27.3 (5 t): *c*-hex C-3 - C-5; 29.0 (2), 35.7, and 37.6 (4 t): *c*-hex C-2 and C-6; 43.7 and 43.9 (2 d): *c*-hex C-1; 60.0 and 60.4 (2 d): C-2; 74.8 (2 d): C-4; 119.9 (2 s): $\underline{C}$N.

(4R*,6S*)-*trans*-and (4S*,6S*)-*cis*-4-Cyano-6-cyclohexyl-2,2-dimethyl-1,3-dioxane (33a and 33b).
A mixture of 6.49 g (25.5 mmol) of crude cyanohydrin **32**, 5 ml (40.7 mmol) of 2,2-dimethoxypropane and 150 mg (0.8 mmol) of *p*-toluenesulfonic acid monohydrate in 25 ml of acetone was stirred at room temperature for 16 h until tlc-analysis indicated complete transformation of the starting material. The reaction mixture was diluted with 200 ml of ether and 80 ml of saturated aqueous sodium bicarbonate solution was added. The organic layer was separated and the aqueous layer was extracted with 100 ml of ether. The combined organic layers were washed with 100 ml of brine, dried with $MgSO_4$ and concentrated under reduced pressure to give 5.32 g of a 1 : 1.1 mixture of isomers as a yellow oil. Careful chromatography on 80 g of silicagel with petrol-EtOAc (98-2) as eluent yielded, in order of elution, 630 mg (2.8 mmol; 11%) of the *anti*-isomer **33a** as a colourless oil, 3.74 g (16.8 mmol; 66%) of a mixture of isomers and 550 mg (2.5 mmol; 10%) of the *syn*-isomer **33b** as a white solid (m.p. 35.5-37°C).
Anti-isomer **33a**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.8-1.45 (m, 9H): $C\underline{H}_3$ [δ 1.35 (s, 3H)] and *c*-hex H-3 - H-5; 1.5-1.80 (m, 7H): $C\underline{H}_3$ [δ 1.62 (s, 3H)] and *c*-hex H-2 and H-6; 1.80-1.93 (m, 3H): H-5 and *c*-hex H-1 [δ 1.9 (br d, J=12.5 Hz)]; 3.81 (ddd, J=10.5, 6.9, 3.6 Hz, 1H): H-6; 4.83 (dd, J=5.8, 3.5 Hz, 1H): H-4. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 21.8 (q): $\underline{C}H_3$; 25.7, 25.8, 26.4, 27.8, and 28.4 (5 t): *c*-hex C-2 - C-6; 29.5 (q): $\underline{C}H_3$; 31.0 (t): C-5; 42.1 (d): *c*-hex C-1; 58.9 (d): C-4; 69.7 (d): C-6; 100.9 (s): C-2; 120.0 (s): $\underline{C}$N. MS: *m/e* (%) 208 (78), 148 (86), 140 (48), 139 (100), 121 (78), 59 (48), 55 (19), 43 (55), 41 (26). HRMS: calcd. (M^+-CH_3): *m/e* 208.1338; found: *m/e* 208.1333.

Syn-isomer **33b**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.75-1.5 (m, 12H): $C\underline{H}_3$ [δ 1.4 (s, 6H)] and *c*-hex H-3 - H-5; 1.5-1.95 (m, 7H): H-5 and *c*-hex H-1 [δ 1.86 (br d, J≈10.1 Hz)], H-2, and H-6; 3.52 (dd, J=14.1, 6.7 Hz) and (ddd, J=10.0, 6.4, 4.0 Hz; total 1H): H-6 (two conformers); 4.71 (dd, J=10.5, 4.5 Hz) and (dd, J=8.2, 6.8 Hz; total 1H): H-4 (two conformers). ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 19.1 (q): $\underline{C}H_3$; 25.7, 25.8 and 26.4 (3 t): *c*-hex C-3 - C-5; 27.8 and 28.4 (2 t): *c*-hex C-2 and C-6; 29.6 (q):$\underline{C}H_3$; 31.9 (t): C-5; 42.3 (d): *c*-hex C-1; 59.4 (d): C-4; 72.1 (d): C-6; 99.9 (s): C-2; 118.1 (s): $\underline{C}$N. MS: *m/e* (%) 208 (50), 148 (37), 140 (100), 139 (40), 121 (20), 95 (13), 59 (42), 55 (12), 43 (36), 41 (12). HRMS: calcd. (M^+-CH_3): *m/e* 208.1338; found: *m/e* 208.1335. Anal: calcd. for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27; found: C, 70.05; H, 9.78; N, 6.21.

(4S*,6S*)-*trans*-4-Cyano-2,2-dimethyl-4-[(1-hydroxy-1-methyl)ethyl]-6-(methyl)ethyl-1,3-dioxane (34).
Several attempts to alkylate a cyanohydrin 1,3-acetonide related to **33** (the cyclohexyl substituent replaced by an isopropyl one) with bromoacetaldehyde dimethylacetal as electophile and LDA as base only resulted in the isolation of nitrile **34** originating from the starting material in yields variing from 10 to 35%.
^{1}H NMR ($CDCl_3$, 200 MHz, selected peaks): δ 0.91 and 0.95 (2 d, J=7.5 Hz, 6H): CH($C\underline{H}_3$)$_2$; 1.28 (s, 3H): $C\underline{H}_3$; 1.38 and 1.40 (2 s, 6H): C(OH)($C\underline{H}_3$)$_2$; 1.60-1.75 (m, 6H): H-5, $C\underline{H}_3$ [δ 1.68 (s, 3H)] and $C\underline{H}$(CH_3)$_2$; 2.24 (br s, 1H): OH; 3.79 (ddd, J=9.5, 6.7, 4.4 Hz, 1H): H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 17.7 and 18.0 (2 q): CH($\underline{C}H_3$)$_2$; 21.4 (q):$\underline{C}H_3$ *ax*; 22.7 and 24.3 (2 q): C(OH)($\underline{C}H_3$)$_2$; 30.3 (t): C-5; 30.7 (q): $\underline{C}H_3$ *eq*; 32.7 (d): $\underline{C}$H(CH_3)$_2$; 70.9 (d): C-6; 74.2 and 75.8 (2 s): C-4 and $\underline{C}$(OH)(CH_3)$_2$; 101.3 (s): C-2; 121.3 (s): $\underline{C}$N. IR ($CHCl_3$): n 3550 (br, OH); 2350 (w, CN) cm^{-1}. GC/MS: *m/e* (%) 226 (8, M^+-CH_3), 183 (5), 140 (6), 139 (8), 125 (9), 124 (10), 110 (20), 108 (10), 98 (23), 97 (6), 70 (40), 69 (42), 59 (100), 55 (22), 43 (71), 41 (34).

(4S*,6S*)-*trans*- and (4R*,6S*)-*cis*-4-Cyano-6-cyclohexyl-2,2-dimethyl-4-(prop-2-enyl)-1,3-dioxane (35a and 35b).
A stirred solution of 6.1 ml (28.9 mmol) of hexamethyldisilazane in 50 ml of anhydrous THF was treated with 20 ml (32 mmol) of a 1.6M solution of n-butyllithium in hexanes. After 45 min the solution was cooled to -78°C and a solution of 2.15 g (9.6 mmol) of **33** as a mixture of *syn*- and *anti*-isomers in 10 ml of THF was added dropwise. Stirring was continued for 1 h before 4.5 ml (52 mmol) of neat allylbromide was added. The temperature of the reaction mixture was slowly raised to about -50°C, while the progress of the reaction was monitored via glc-analysis. After 3.5 h the reaction was quenched by the addition of 200 ml of water. The organic layer was separated and the aqueous layer was extracted with three 100 ml-portions of petrol. The combined organic layers were washed with 80

ml of water and 80 ml of brine, dried with $MgSO_4$ and concentrated under reduced pressure to yield 3.31 g of a 30 : 1 mixture of *anti* **35a** and *syn* **35b** as a yellow oil. The crude product was purified via chromatography on 60 g of silicagel with petrol-EtOAc (99.5-0.5 to 99-1) as eluent, affording in order of elution 1.48 g (5.6 mmol; 58%) of the desired *anti*-isomer **35a** as an oil and 0.7 g (2.7 mmol; 28%) of a mixture of both isomers (**35a** : **35b** ≈ 9 : 1). Exhaustive chromatography of the isomeric mixture finally gave a small quantity of analytically pure **35b**.
Anti-isomer **35a:** ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.8-1.4 (m, 9H): C<u>H</u>3 [δ 1.36 (s, 3H)] and *c*-hex H-3 - H-5; 1.44 (dd, J=13.5, 11.7 Hz, 1H): H-5β; 1.55-1.82 (m, 8H): H-5α [δ 1.78 (dd, J=13.0, 2.1 Hz, 1H)], C<u>H</u>3 [δ 1.65 (s, 3H)] and *c*-hex H-2 and H-6; 1.90 (br d, J=12.6 Hz, 1H): *c*-hex H-1; 2.35-2.65 (m, 2H): allyl H-1; 3.81 (ddd, J=11.6, 6.9, 2.0 Hz, 1H): H-6; 5.16-5.26 (m, 2H): allyl H-3 (*E*) [δ 5.22 (dm, J=16.6 Hz)], and H-3(*Z*) [δ 5.24 (dm, J=9.9 Hz)]; 5.77-5.91 (m, 1H): allyl H-2. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 21.4 (q): <u>C</u>H3 *ax*; 25.7, 25.9, 26.4, 27.9, and 28.5 (5 t): *c*-hex C-2 - C-6; 30.8 (q): <u>C</u>H3 *eq*; 36.1 (t): C-5; 42.1 (d): *c*-hex C-1; 46.6 (t): allyl C-1; 69.7 (s): C-4; 70.4 (d): C-6; 100.9 (s): C-2; 120.7 (t): allyl C-3; 121.8 (s): <u>C</u>N; 130.0 (d): allyl C-2. MS: *m/e* (%) 248 (100), 188 (83), 179 (75), 161 (13), 137 (11), 95 (69), 81 (11), 67 (15), 59 (41), 55 (18), 43 (34). HRMS: calcd. (M^+-CH_3): *m/e* 248.1651; found: *m/e* 248.1651.
Syn-isomer **35b**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.80-1.81 (br m, 16H): C<u>H</u>3 [δ 1.34 (s, 3H)], C<u>H</u>3 [δ 1.57 (s, 3H)], and *c*-hex H-2 - H-6; 1.85-2.09 (m, 3H): H-5α [δ 1.90 (dd, J=13.8, 6.8 Hz)], H-5β [δ 2.03 (dd, J=13.8, 8.4 Hz)], and *c*-hex H-1[δ 1.88-2.08 (br)]; 2.39-2.62 (m, 2H): allyl H-1; 3.54 (ddd, J=8.4, 7.6, 6.8 Hz, 1H): H-6; 5.16-5.26 (m, 2H): allyl H-3 (*E*) [δ 5.22 (dm, J=17.9 Hz)] and H-3 (*Z*) [δ 5.24 (dm, J=10.0 Hz)]; 5.74-5.95 (m, 1H): allyl H-2. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 25,9 (q): <u>C</u>H3 *ax*; 26.7 (2 t); 27.4 (t); 28.3 (q): <u>C</u>H3 *eq*; 28.8 (t); 29.5 (t); 38.4 (t): C-5; 43.3 (d): *c*-hex C-1; 46.5 (t): allyl C-1; 68.3 (s): C-4; 70.5 (d): C-6; 103.0 (s): C-2; 121.6 (t): allyl C-3; 123.0 (s): <u>C</u>N; 131.3 (d): allyl C-2. MS: *m/e* (%) 248 (94), 188 (96), 179 (59), 161 (16), 137 (15), 122 (37), 95 (89), 81 (19), 67 (24), 59 (100), 55 (18), 43 (48). HRMS: calcd. (M^+-CH_3): *m/e* 248.1651; found: *m/e* 248.1652.

(2R*,3R*,5R*)- and (2S*,3R*,5R*)-5-Cyclohexyl-3-hydroxy-2-methoxy-3-(prop-2-enyl)-tetrahydrofuran (37b).
To a vigorously stirred solution of 13.5 mmol of lithium aluminumhydride in 50 ml of ether (prepared by diluting 13.5 ml of a commercial 1.0M etheral solution of $LiAlH_4$ with anhydrous ether) was added dropwise 1.6 ml (16.4 mmol) of anhydrous EtOAc while cooling on an ice-bath. After 15 min the resulting white slurry was treated dropwise with a solution of 1.37 gr (5.2 mmol) of *anti*-adduct **35a** in 15 ml of ether. Stirring at 0°C was continued for 1.5 h while the reaction was monitored via glc-analysis. The reaction was quenched by addition of 4.2 g (13 mmol) of Glauber's salt. The mixture was warmed to room temperature and stirred for 30 min, dried with $MgSO_4$, filtered and the solvent was evaporated. The residual oil was dissolved in 100 ml of EtOAc, 20 g of silicagel was added and stirred overnight. The slurry was filtered and the filtrate was concentrated under reduced pressure to give 1.34 g of a yellow oil. Chromatography on 25 g of silicagel with petrol-EtOAc (99-1) as eluent afforded 1.12 g (4.2 mmol; 81%) of aldehyde **36** as a clear, colourless oil which was used as such in the following reaction.

A mixture of 250 mg (0.94 mmol) of aldehyde **36** and 30 mg (0.15 mmol) of *p*-toluenesulfonic acid monohydrate in 10 ml of methanol was stirred overnight at room temperature, after which tlc-analysis indicated complete transformation of the starting material into a highly polar product. The solvent was removed under reduced pressure and the residue was dissolved in 75 ml of ether. Saturated aqueous sodium bicarbonate solution (20 ml) was added, the organic layer was separated and the aqueous layer was extracted with 25 ml of ether. The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure, yielding 206 mg (0.91 mmol) of diol **37a**. Due to its highly polar nature no attempts were undertaken to purify it.
^{1}H NMR ($CDCl_3$, 90 MHz, selected peaks): δ 0.8-2.2 (br m, 17H); 2.4 (d, J=7.5 Hz, 2H): allyl H-1; 2.55 (s, 1H): OH; 3.25 (d, J=6 Hz, 1H): OH; 3.5-3.8 (m, 1H): H-5; 4.9 (d, J=6 Hz, 1H): H-2; 5.1 (m, 1H): allyl H-3 (*E*); 5.25 (s, 1H): allyl H-3 (*Z*); 5.7-6.1 (m, 1H): allyl H-2.

Diol **37a** was dissolved in 15 ml of methanol and 25 mg (0.13 mmol) of *p*-toluene-sulfonic acid monohydrate was added. (Alternatively, a few drops of concentrated sulfuric acid have been used succesfully). The mixture was stirred at room temperature for 2 days. Work up as described above yielded 204 mg (0.85 mmol; 90%) of a 1 : 1.4 mixture of C-2 epimers of **37b** as a clear, colourless oil, which was sufficiently pure to be used in the next reaction. The isomers could be separated by columnn chromatography with petrol-EtOAc (95-5) as eluent to give, in order of elution, the minor 2αH-isomer as a white solid (mp 84-85°C) and the major 2βH-isomer as an oil.
37b, 2αH-isomer: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.7-1.4 (br m, 6H): *c*-hex H-3 - H-5; 1.4-1.85 (br m, 5H): *c*-hex H-1, H-2, and H-6; 1.98-2.07 (m, 2H): H-4; 2.3 (d, J=7.1 Hz, 2H): allyl H-1, 2.7 (s, 1H): OH; 3.4 (s, 3H): O<u>C</u>H3; 3.56-3.68 (m, 1H): H-5; 4.4 (s, 1H): H-2; 5.08 (d, J=5.7 Hz, 1H): allyl H-3 (*E*); 5.15 (s, 1H): allyl H-3 (*Z*); 5.8-6.1 (m, 1H): allyl H-2. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 25.8 (2 t) and 26.5 (t): *c*-hex C-3 - C- 5; 28.6 and 29.7 (2

t): *c*-hex C-2 and C-6; 39.7 and 41.0 (2 t): C-4; 44.9 (d): *c*-hex C-1 ; 54.6 (q): O<u>C</u>H3; 79.7 (s): C-3; 82.6 (d): C-5; 104.4 (d): C-2; 118.4 (t): allyl C-3; 133.2 (d): allyl C-2. MS: *m/e* (%) 180 (13), 167 (13), 139 (100), 121 (51), 97 (57), 95 (19), 85 (22), 83 (17), 81 (14), 67 (13), 55 (74), 41 (19). HRMS: calcd. (M^+-OCH3): *m/e* 209.1542; found: *m/e* 209.1538. Anal: calcd. for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07; found: C, 70.03; H, 10.34.

37b, 2βH-isomer: ^{1}H NMR (CDCl3, 200 MHz, selected peaks): δ 0.8-1.35 (br m, 6H): *c*-hex H-3 - H-5; 1.55-1.8 (br m, 5H): *c*-hex H-1, H-2, and H-6; 1.9 (br s, 1H): OH; 1.96-2.07 (m, 2H): H-4; 2.3-2.55 (m, 2H): allyl H-1; 3.3 (s, 3H): O<u>C</u>H3; 3.73-3.84 (m, 1H): H-5; 4.5 (s, 1H): H-2; 5.11 (s, 1H): allyl H-3 (*E*); 5.18 (d, J=5.7 Hz, 1H): allyl H-3 (*Z*); 5.75-6.0 (m, 1H): allyl H-2. ^{13}C NMR (CDCl3, 50 MHz, DEPT): δ 25.8 (2 t) and 26.5 (t): *c*-hex C-3 -C-5; 29.0 and 29.5 (2 t): *c*-hex C-2 and C-6; 39.6 and 39.9 (2 t): C-4; 43.0 (d): *c*-hex C-1, 54.3 (q): O<u>C</u>H3; 81.4 (s): C-3; 81.6 (d): C-5; 108.7 (d): C-2; 118.9 (t): allyl C-3; 134.0 (d): allyl C-2. MS: *m/e* (%) 157 (33), 139 (100), 125 (16), 121 (47), 97 (57), 95 (18), 85 (37), 67 (18), 55 (77), 41 (26). HRMS: calcd. (M^+-OCH3): *m/e* 209.1542; found: *m/e* 209.1539.

(2R*,3R*,5R*)- and (2S*,3R*,5R*)-5-Cyclohexyl-2-methoxy-3-[(trimethylsilyl)oxy]-3-(prop-2-enyl)-tetrahydrofuran (38).

A solution containing 522 mg (2.2 mmol) of a 1 : 1 mixture of isomers **37b,** 0.7 ml (5.5 mmol) of trimethylsilyl chloride and 739 mg (11.0 mmol) of imidazole in 10 ml of anhydrous DMF was stirred at room temperature for 40 min. The reaction mixture was poured into 40 ml of half-saturated aqueous sodium bicarbonate solution and the resulting mixture was extracted with three 50 ml-portions of petrol. The combined organic layers were washed with 30 ml of water and 30 ml of brine, dried with MgSO4 and concentrated under reduced pressure, to yield 667 mg (2.1 mmol; 98%) of a 1 : 1 mixture of C-2 epimers of **38** as a clear, colourless oil. The product was sufficiently pure to be used in the next reaction without further purification.

^{1}H NMR (CDCl3, 200 MHz): δ -0.03 and 0.0 (2 s, 9H): Si(C<u>H</u>3)3; 1.7-0.6 (br m, 11H): *c*-hex H-1 - H-6; 1.75-2.0 (br m, 2H): H-4; 2.14 (m, 1H): allyl H-1, *epimer 1*; 2.29 (m, 1H): allyl H-1, *epimer 2*; 3.1 (s, 3H): O<u>C</u>H3; 3.2 and 3.57 (2 ddd, 1H): H-5; 4.21 and 4.53 (2 s, 1H): H-2; 4.9 (s) and 5.0 (m, total 2H): allyl H-3; 5.5-5.9 (m, 1H): allyl H-2. ^{13}C NMR (CDCl3, 50 MHz, DEPT, selected peaks): δ 2.2 and 2.4 (2 q): Si(<u>C</u>H3)3; 43.0 and 45.2 (2 d): *c*-hex C-1; 54.0 and 54.6 (2 q): O<u>C</u>H3; 81.9 and 82.1 (2 d): C-5; 82.5 and 85.0 (2 s): C-3; 104.9 and 109.0 (2 d): C-2; 117.2 and 118.1 (2 t): allyl C-3; 133.8 and 135.0 (2 d): allyl C-2. MS: *m/e* (%) 271 (14), 251 (9), 211 (13), 170 (16), 169 (100), 156 (10), 155 (21), 122 (37), 121 (19), 89 (10), 75 (11), 73 (58). HRMS: calcd. (M^+-OCH3): *m/e* 281.1937; found: *m/e* 281.1940.

(2R*,3S*,5R*)- and (2S*,3S*,5R*)-5-Cyclohexyl-3-formylmethyl-2-methoxy-3-[(trimethyl-silyl)oxy]-tetrahydrofuran (39).

A stirred solution of 637 mg (2.0 mmol) of a 1 : 1 epimeric mixture of **38** in 30 ml of methanol and 10 ml of dichloromethane was cooled under nitrogen atmosphere on an dry-ice/acetone bath. An ozone/oxygen mixture was passed through the solution until a bright blue colour appeared and tlc-analysis indicated complete disappearance of the starting material. The solution was purged with nitrogen until the blue colour disappeared and then warmed to room temperature. Subsequently, 588 mg (2.2 mmol) of triphenylphosphine was added and the reaction mixture was stirred for 1 h at ambient temperature. The solvent was removed under reduced pressure and the residue (1.26 g) was purified by chromatography on 20 g of silicagel with petrol-EtOAc (99-1 to 95-5) as eluent, yielding 498 mg (1.6 mmol; 78%) of a 1.2 : 1 mixture of C-2 epimers of aldehyde **39** as a clear, colourless oil.

Least polar isomer: ^{1}H NMR (CDCl3, 200 MHz): δ 0.0 (s, 9H): Si(C<u>H</u>3)3; 0.65-1.7 (br m, 11H): *c*-hex H-1 - H-6; 1.75 and 1.95 (2 dd, J=12.9, 7.3 Hz, 2H): H-4α and H-4β; 2.49 (dd, J=16.0, 2.7 Hz) and 2.62 (dd, J=16.0, 2.5 Hz; total 2H): C<u>H</u>2CHO; 3.2 (s, 3H): O<u>C</u>H3; 3.6 (ddd, J=7.5, 7.3, 7.3 Hz, 1H): H-5; 4.7 (s, 1H): H-2; 9.6 (dd, J=2.7, 2.5 Hz, 1H): C<u>H</u>O. ^{13}C NMR (CDCl3, 50 MHz, DEPT): δ 2.2 (q): Si(<u>C</u>H3)3; 25.7, 25.9, and 26.5 (3 t): *c*-hex C-3 - C-5; 29.0 and 29.7 (2 t): *c*-hex C-2 and C-6; 42.2 (t): C-4; 42.8 (d): *c*-hex C-1; 50.3 (t): <u>C</u>H2CHO; 54.7 (q): O<u>C</u>H3; 81.7 (d): C-5; 83.3 (s): C-3; 108.9 (d): C-2; 201.7 (d): <u>C</u>HO. MS: *m/e* (%) 172 (14), 171 (100), 157 (9), 143 (10), 75 (7), 73 (15), 55 (25). HRMS: calcd. (M^+-OCH3): *m/e* 283.1729; found: *m/e* 283.1726.

Most polar isomer: ^{1}H NMR (CDCl3, 200 MHz): δ 0.0 (s, 9H): Si(C<u>H</u>3)3; 0.6-1.7 (br m, 11H): *c*-hex H-1 - H-6; 1.8-2.0 (m, 2H): H-4α and H-4β; 2.36 (dd, J=15.0, 3.1 Hz) and 2.48 (ddd, J=15.0, 2.7, 1.4 Hz; total 2H): C<u>H</u>2CHO; 3.2 (s, 3H): O<u>C</u>H3; 3.46 (ddd, J=8.9, 8.9, 6.8 Hz, 1H): H-5; 4.3 (s, 1H): H-2; 9.7 (dd, J=3.1, 2.7 Hz, 1H): C<u>H</u>O). ^{13}C NMR (CDCl3, 50 MHz, DEPT): δ 2.2 (q): Si(<u>C</u>H3)3; 25.7, 25.8, and 26.5 (3 t): *c*-hex C-3 - C-5; 28.6 and 29.7 (2 t): *c*-hex C-2 and C-6; 39.2 (t): C-4; 45.0 (d): *c*-hex C-1; 51.3 (t): <u>C</u>H2CHO; 54.0 (q): O<u>C</u>H3; 81.3 (s): C-3; 82.0 (d): C-5; 104.6 (d): C-2; 201.9 (d): <u>C</u>HO). MS: *m/e* (%) 172 (13), 171 (100), 73 (13), 55 (19). HRMS: calcd. (M^+-CH3): *m/e* 299.1679; found: *m/e* 299.1676.

(2R*,3aS*,5R*)- and (2S*,3aS*,5R*)-5-Cyclohexyl-perhydrofuro-[2,3-b]furan-2,3a-diol (40).
A mixture of 498 mg (1.6 mmol) of aldehyde **39** in 15 ml of THF and 4 ml of an aqueous 4N solution of HCl was stirred at room temperature for 4 days. The reaction mixture was poured into 75 ml of EtOAc and washed sequentially with water (10 ml), saturated aqueous sodium bicarbonate solution (15 ml) and brine (25 ml). The combined washings were extracted with EtOAc (50 ml) and the combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure to yield a white solid (275 mg). Purification was achieved by chromatography on 15 g of silicagel with petrol-EtOAc (75-25 to 66-33) as eluent to give, in order of elution, 99 mg of a mixture containing both desilylated starting material and 2-methoxy-furofuran-3a-ol **41**, and 167 mg (0.73 mmol, 46%) of an C-2 epimeric mixture of furofuran-2,3a-diol **40** as a white solid. Byproducts were taken up in 10 ml of THF and 5 ml of a 1N aqueous HCl solution and stirred for another 10 days. Work-up as described before yielded another 82 mg (0.36 mmol, 23%) of **40**.

A stirred solution of 2.08 g (6.45 mmol) of **45** in 50 ml of acetonitrile at room temperature was treated dropwise with a 40% solution of hydrogen fluoride in water (20 drops, ≈ 1 ml) until tlc-analysis indicated complete transformation of the starting material. The reaction mixture was poured into 150 ml of water and extracted with four 100 ml-portions of ether. The combined extracts were washed with 80 ml of brine, dried with $MgSO_4$ and concentrated under reduced pressure to afford 1.5 g of a white solid. The product was purified via chromatography on 40 g of silicagel with petrol-EtOAc (75-25 to 66-33) as eluent to give 1.26 g (5.5 mmol; 86%) of a mixture of C-2 epimers of diol **40** as a white solid.
40, (*7 : 3 epimeric mixture*): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.75-2.01 (br m, 12H) and 2.01-2.50 (br m, 3H): H-3, H-4, and *c*-hex H-1 - H-6; 2.60 (br s, 0.3H) and 3.33 (br s, 0.7H): OH; 3.77 (ddd, J=11.3, 7.2, 4.3 Hz, 0.7H): H-5; 3.96 (br s, 0.3H) and 4.09 (br s, 0.7H): OH; 4.20 (ddd, J=10.1, 8.6, 5.5 Hz, 0.3H): H-5; 5.45 (s, 0.3H) and 5.54 (s, 0.7H): H-6a; 5.65 (br m, 1H): H-2. ^{13}C NMR ($CDCl_3$, 50 MH, DEPT): δ 25.7, 25.8, and 26.3 (3 t): *c*-hex C-3 - C-5; 28.5 and 29.6 (2 t): *c*-hex C-2 and C-6; 42.1 (t): C-3; 42.5 and 42.9 (2 d): *c*-hex C-1; 44.9 and 47.1 (2 t): C-4; 83.7 and 84.2 (2 d): C-5; 86.9 and 87.8 (2 s): C-3a; 98.8 and 99.4 (2 d): C-2; 112.7 and 113.5 (2 d): C-6a. MS: *m/e* (%) 127 (23), 109 (10), 99 (29), 95 (10), 83 (10), 81 (17), 73 (10), 70 (12), 67 (9), 61 (11), 55 (17), 45 (17), 43 (100), 41 (11). HRMS: calcd. (M^+-H_2O): *m/e* 210.1256; found: *m/e* 210.1253.

(3R*,5R*)-5-Cyclohexyl-3-hydroxy-3-(prop-2-enyl)-4,5-dihydrofuran-2(3H)-one (42).
A stirred mixture of 2.5 g (9.6 mmol) of **35a** and 3 ml of conc. HCl in 30 ml of methanol was heated under reflux for 2 h. After cooling to room temperature the mixture was diluted with 50 ml of water and extracted with three 100 ml-portions of ether. The combined extracts were washed with 100 ml of a saturated aqueous sodium bicarbonate solution, dried with $MgSO_4$ and concentrated under reduced pressure to give 2.2 g of a yellow solid. The crude product was purified via chromatography on 50 g of silica with petrol-EtOAc (95-5 to 85-15) as eluent, yielding 2.04 g (9.1 mmol; 95%) of hydroxy lactone **42** as a white solid (m.p. 67-68°C).
^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.80-1.90 (br m, 10H): *c*-hex H-2 - H-6; 1.90-2.15 (m, 2H): H-4α [δ 2.01 (dd, J=22.9, 10.7 Hz)] and *c*-hex H-1; 2.31-2.57 (m, 3H): H-4β and allyl H-1; 2.91-3.23 (br, 1H): OH; 4.03 (ddd, J=9.0, 7.8, 6.8 Hz, 1H): H-5; 5.18 (dd, J=9.4, 0.6 Hz, 1H): allyl H-3 (*E*); 5.25 (d, J=0.7 Hz, 1H): allyl H-3 (*Z*); 5.72-5.90 (m, 1H): allyl H-2. ^{13}C NMR ($CDCl_3$, 50 MH, DEPT): δ 25.4, 25.6, and 26.2 (3 t): *c*-hex C-3 - C-5; 27.5 and 28.9 (2 t): *c*-hex C-2 and C-6; 38.3 and 41.8 (2 t): C-4 and allyl C-1; 42.8 (d): *c*-hex C-1; 75.4 (s): C-3; 81.3 (d): C-5; 121.0 (t): allyl C-3; 130.7 (d): allyl C-2; 179.0 (s): C-2. MS: *m/e* (%) 224 (M^+, 2), 183 (11), 165 (16), 139 (76), 121 (59), 97 (55), 95 (31), 83 (19), 81 (15), 69 (17), 67 (17), 55 (100), 41 (49). HRMS: calcd. (M^+): *m/e* 224.1412; found: *m/e* 224.1415. Anal: calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99; found: C, 69.64; H, 9.25.

(3R*,5R*)-5-Cyclohexyl-3-[[(dimethyl)isopropylsilyl]oxy]-3-(prop-2-enyl)-4,5-dihydro-furan-2(3H)-one (43).
A mixture of 2.04 g (9.1 mmol) of hydroxy lactone **42**, 2.0 ml (12.7 mmol) of dimethyl*iso*propylsilyl chloride and 987 mg (14.5 mmol) of imidazole in 50 ml of anhydrous DMF was stirred overnight at room temperature. The reaction mixture was poured into 200 ml of saturated aqueous sodium bicarbonate solution and the resulting mixture was extracted with three 100 ml-portions of petrol. The combined organic layers were washed with 100 ml of water, dried with $MgSO_4$ and concentrated under reduced pressure to yield 3.15 g of an oil. The crude product was purified by chromatography on 50 g of silicagel with petrol-EtOAc (98-2) as eluent to give 2.88 g (8.9 mmol, 98%) of silyloxy lactone **43** as a colourless oil.
^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.08 and 0.14 (2 s, 6H): $Si(C\underline{H}_3)_2$; 0.60-1.82 (br m, 17H): $SiCH(C\underline{H}_3)_2$ [δ 0.92 (d, J=4.5 Hz)], $SiC\underline{H}(CH_3)_2$, and *c*-hex H-2 - H-6; 1.85-2.03 (m, 2H): H-4α [δ 1.91 (dd, J=12.9, 9.8 Hz)] and *c*-hex H-1 [d 1.95 (br d, J≈12.6 Hz)]; 2.31-2.54 (m, 3H): H-4β [δ 2.37 (dd, J=12.9, 6.0 Hz)] and allyl H-1; 3.93 (ddd, J=9.7, 7.6, 6.0 Hz, 1H): H-5; 5.10 (dm, J=10.1 Hz, 1H): allyl H-3 (*E*); 5.18 (m, 1H): allyl H-3 (*Z*); 5.71-5.88 (m, 1H): allyl

H-2. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ -2.4 and -2.2 (2 q): $Si(\underline{C}H_3)_2$; 15.5 (d): $Si\underline{C}H(CH_3)_2$; 16.8 (q): $SiCH(\underline{C}H_3)_2$; 25.4, 25.6, and 26.2 (3 t): *c*-hex C-3 - C-5, 27.5 and 28.8 (2 t): *c*-hex C-2 and C-6; 39.6 and 42.4 (2 t): C-4 and allyl C-1; 42.8 (d): *c*-hex C-1; 77.7 (s): C-3; 80.6 (d): C-5; 119.5 (t): allyl C-3; 131.7 (d): allyl C-2; 177.3 (s): C-2. MS: *m/e* (%) 281 (49), 266 (16), 263 (45), 253 (13), 189 (16), 169 (29), 161 (47), 127 (21), 101 (13), 95 (29), 75 (100), 73 (24), 59 (16). HRMS: calcd. (M^+-*i*-Pr): *m/e* 281.1573; found: *m/e* 281.1578.

(2R*,3aS*,5R*)- and (2S*,3aS*,5R*)-5-Cyclohexyl-3a-[[(dimethyl)isopropylsilyl]oxy]-perhydrofuro[2,3-b]furan-2-ol (45).

A stirred solution of 2.88 g (8.9 mmol) of silyloxy lactone **43** in 75 ml of anhydrous toluene was cooled on a dry-ice-acetone bath while 9.6 ml (9.6 mmol) of a 1.0M solution of diisobutylaluminum hydride in hexanes was added dropwise in 15 min. Stirring at -78°C was continued for 1.5 h before the reaction was quenched by the addition of 3.68 g (11.5 mmol) of Glauber's salt. The mixture was warmed to room temperature and stirred for another 30 min, during which time a homogenous white slurry formed. $MgSO_4$ was added and the mixture was filtered through a pad of hyflo. Evaporation of the solvents yielded 2.36 g (7.2 mmol; 81%) of an C-2 epimeric mixture of lactol **44** as an oil, which was used in the next reaction without further purification.

A stirred solution of 2.36 g (7.2 mmol) of **44** in 75 ml of methylene chloride was cooled to -78°C. An oxygen-ozone mixture was passed through the solution until the colour turned blue and the starting material had disappeared, as judged by tlc-analysis. The solution was purged with nitrogen until the blue colour disappeared. Then, 1.93 g (7.4 mmol) of triphenylphosphine was added and the reaction mixture was warmed to room temperature and stirring was continued for 4.5 h before the solvent was evaporated under reduced pressure to give 4.80 g of a colourless oil. The residue was purified by chromatography on 60 g of silicagel with petrol-EtOAc (99-1 to 90-10) as eluent, yielding 1.95 g (5.9 mmol; 82%) of an inseparable 1 : 1 mixture of C-2 epimers of 3a-DMIPSoxy-furofuranol **45** as a white solid.

^1H NMR ($CDCl_3$, 200 MHz): δ 0.08 (2 s) and 0.13 (s, total 6H): $Si(C\underline{H}_3)_2$; 0.60-2.00 (br m, 19H) and 2.03-2.43 (m, 3H): H-3, H-4, $SiCH(C\underline{H}_3)_2$ [δ 0.91 and 0.93 (2 d, J=6.2 Hz)], $SiC\underline{H}(CH_3)_2$, and *c*-hex H-1 - H-6; 3.51 (d, J=8.3 Hz, 0.5H): OH; 3.74 (ddd, J=10.8, 7.3, 4.7 Hz, 0.5H): H-5; 3.85 (br, 0.5H): OH; 4.17 (ddd, J=10.2, 7.2, 5.0 Hz, 0.5H): H-5; 5.43 and 5.52 (2 s, 1H): H-6a; 5.53-5.65 (m, 1H): H-2. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ -2.1 (q): $Si(\underline{C}H_3)_2$; 15.3 (d): $Si\underline{C}H(CH_3)_2$; 16.7 (q): $SiCH(\underline{C}H_3)_2$; 25.7 (2), 25.9 (2), 26.3, and 26.4 (6 t): *c*-hex C-3 - C-5; 28.6, 29.5, and 29.6 (3 t): *c*-hex C-2 and C-6; 42.7 and 43.0 (2 d): *c*-hex C-1; 43.3, 45.3, 46.3, and 48.0 (4 t): C-3 and C-4; 83.5 and 84.1 (2 d): C-5; 88.7 and 89.5 (2 s): C-3a; 98.9 and 99.8 (2 d): C-2; 112.6 and 114.1 (2 d): C-6a. MS: *m/e* (%) 267 (12), 239 (31), 223 (11), 200 (16), 199 (100), 157 (18), 147 (29), 143 (12), 129 (20), 109 (11), 101 (16), 95 (14), 75 (32), 73 (18), 59 (14), 55 (17). HRMS: calcd. (M^+-*i*-Pr): *m/e* 285.1522; found: *m/e* 285.1518. Anal: calcd. for $C_{17}H_{32}O_4Si$: C, 62.17; H, 9.82; found: C, 62.10; H, 10.08.

(3aR*,5S*)-5-Cyclohexyl-3a-hydroxy-3a,4,5,6a-tetrahydrofuro[2,3-b]-furan-2(3H)-one (46).

A mixture of 20 mg (0.09 mmol) of **40** and 115 mg (0.31 mmol) of pyridinium dichromate in 10 ml of dichloromethane was stirred for 5 days at room temperature. The mixture was diluted with ether and filtered through a pad of hyflo. The solvents were removed under reduced pressure and the brownish residue was purified by chromatography on 10 g of silicagel with petrol-EtOAc (90-10 to 80-20) as eluent, yielding 15 mg (0.07 mmol; 75%) of **46** as a white solid (m.p. 97-98.5°C).

^1H NMR ($CDCl_3$, 200 MHz): δ 0.80-1.35 (br m, 5H) and 1.40-1.80 (br m, 5H): *c*-hex H-2 - H-6; 1.82-2.01 (br m, 2H): H-4β [δ 1.90 (dd, J=11.9, 11.9 Hz)] and *c*-hex H-1; 2.22 (dd, J=12.7, 4.9 Hz, 1H): H-4α; 2.9 (s, 2H): H-3; 3.45 (br s, 1H): OH; 3.83 (ddd, J=11.1, 7.2, 4.9 Hz, 1H): H-5; 5.8 (s, 1H): H-6a. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 25.5, 25.7, and 26.2 (3 t): *c*-hex C-3 - C-5; 28.5 and 29.4 (2 t): *c*-hex C-2 and C-6; 42.1 (d): *c*-hex C-1; 42.9 (t): C-3; 44.2 (t): C-4; 83.5 (s): C-3a; 84.5 (d): C-5; 112.4 (d): C-6a; 174.8 (s): C-2. Anal: calcd. for $C_{12}H_{18}O_4 \cdot 0.5\ H_2O$: C, 61.26; H, 8.14; found: C, 61.61; H, 8.42.

(2S*,3aR*,5S*)- and (2R*,3aR*,5S*)-2-Acetoxy-5-cyclohexyl-3a-hydroxy-perhydrofuro-[2,3-b]furan (47).

A stirred, ice-cold solution of 150 mg (0.66 mmol) of **40** in 7.5 ml of dichloromethane was treated sequentially with 0.15 ml (1.9 mmol) of pyridine and 0.1 ml (1.4 mmol) of acetyl chloride. Stirring was continued for 1 h at 0°C before the reaction mixture was poured into a mixture of 50 ml of ether and 25 ml of water. The organic layer was separated and the aqueous layer was extracted with 40 ml of ether. The combined organic layers were washed with 25 ml of brine, dried with $MgSO_4$ and concentrated under reduced pressure to yield 164 mg of a yellow solid. Purification by chromatography on 20 g of silicagel with petrol-EtOAc (90-10 to 80-20) as eluent afforded 137 mg (0.51 mmol; 77%) of an inseparable 1 : 4 mixture of C-2 epimers **47** as a white solid.

^1H NMR ($CDCl_3$, 200 MHz): δ 0.78-1.33 (br m, 5H) and 1.33-2.00 (br m, 7H): H-4β [H-4β, *major isomer*: δ 1.77 (dd, J=11.7, 11.7 Hz)], *c*-hex H-1 [δ 1.86 (br d, J=11.7 Hz)], and *c*-hex H-2 - H-6; 2.03 (s, 0.6H): $C\underline{H}_3C(O)$, *minor*

isomer; 2.05 (s, 2.4H): $C\underline{H}_3C(O)$, *major isomer*; 2.07-2.53 (several m, 3H): *major isomer*: H-4α [δ 2.12 (dd, J=12.2, 4.4 Hz)], H-3α or H-3β [δ 2.24 (dd, J=14.8, 1.2 Hz)], H-3β or H-3α [δ 2.38 (dd, J=14.7, 4.7 Hz)], and *minor isomer*: H-3α or H-3β [δ 2.55 (dd, J=14.7, 7.6 Hz)], H-4α, H-3β or H-3α; 2.74 (br, 1H): OH; 3.77 (ddd, J=11.5, 7.3, 4.3 Hz, 0.8H): H-5, *major isomer*; 4.06 (ddd, J=10.6, 7.5, 5.5 Hz, 0.2H): H-5, *minor isomer*; 5.47 (s, 0.2H): H-6a, *minor isomer*; 5.53 (s, 0.8H): H-6a, *major isomer*; 6.31-6.37 (2 m, 1H): H-2, *minor isomer* [δ 6.34 (dd, J=7.6, 1.2 Hz)] and H-2, *major isomer* [δ 6.35 (dd, J=4.9, 1.3 Hz)]. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT, selected peaks): *Major isomer*: δ 21.4 (q): $\underline{C}H_3C(O)$; 25.6, 25.9, and 26.3 (3 t): *c*-hex C-3 - C-5; 28.7, and 29.7 (2 t): *c*-hex C-2 and C-6; 42.3 (d): *c*-hex C-1; 43.8 and 44.5 (2 t): C-3 and C-4; 84.2 (d): C-5; 86.8 (s): C-3a; 98.9 (d): C-2; 114.0 (d): C-6a; 170.1 (s): $CH_3\underline{C}(O)$. *Minor isomer:* δ 21.4 (q); 25.6, 25.9, 26.3, 28.7 and 29.7 (5 t); 42.8 (d); 44.8 and 45.8 (2 t); 83.8 (d); 87.1 (s); 97.9 (d); 114.3 (d); 170.0 (s). MS: *m/e* (%) 211 (40), 187 (12), 183 (26), 181 (30), 165 (33), 164 (60), 142 (20), 137 (26), 127 (90), 121 (16), 110 (21), 109 (53), 99 (64), 95 (36), 86 (16), 83 (22), 81 (69), 71 (26), 67 (27), 55 (39), 43 (100). HRMS: calcd. (M^+-CH_3CO): *m/e* 227.1283; found: *m/e* 227.1286. Anal: calcd. for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20; found: C, 62.42; H, 8.47.

(2R*,3aR*,5S*)- and (2S*,3aR*,5S*)-5-Cyclohexyl-3a-hydroxy-2-methoxy-perhydrofuro-[2,3-b]furan (41).

A mixture of 150 mg (0.66 mmol) of furofuran-2,3a-diols **40**, 40 mg (1.25 mmol) of methanol and a few grains of *p*-toluenesulfonic acid in 50 ml of THF was stirred at room temperature for 48 h. The reaction mixture was poured into 20 ml of water and extracted with three 30 ml-portions of ether. The combined extracts were washed with 20 ml of saturated aqueous sodium bicarbonate solution, dried with $MgSO_4$ and concentrated under reduced pressure to give 154 mg of a yellow oil. The product was purified via chromatography on 10 g of silicagel with petrol-EtOAc (90-10) as eluent, affording 137 mg (0.57 mmol; 86%) of **41** as a 1 : 1 mixture of C-2 epimers. Repeated chromatography yielded a small quantity of analytically pure least polar isomer **45** as a white solid (m.p. 101-102°C)

Least polar isomer: ^1H NMR ($CDCl_3$, 200 MHz): δ 0.80-1.35 (br m, 5H) and 1.35-1.88 (br m, 6H): H-4β [δ 1.73 (dd, J=11.0, 11.0 Hz)] and *c*-hex H-2 - H-6; 1.94 (br d, J=12.5 Hz, 1H): *c*-hex H-1; 2.06 (dd, J=12.2, 4.4 Hz, 1H): H-4α; 2.13 (2 d, J_1=4.0 Hz and J_2=2.13 Hz, 2H): H-3; 2.78 (br s, 1H): OH; 3.36 (s, 3H): $OC\underline{H}_3$; 3.78 (ddd, J=11.5, 7.5, 4.3 Hz, 1H): H-5; 5.12 (dd, J=3.5, 1.7 Hz, 1H): H-2; 5.40 (s, 1H): H-6a. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 25.7, 25.9, and 26.4 (3 t): *c*-hex C-3 - C-5; 28.7 and 29.7 (2 t): *c*-hex C-2 and C-6; 42.1 (t): C-3; 42.5 (d): *c*-hex C-1; 44.5 (t): C-4; 54.9 (q): $O\underline{C}H_3$; 84.2 (d): C-5; 86.8 (s): C-3a; 105.4 (d): C-2; 112.8 (d): C-6a. MS: *m/e* (%) 196 (41), 164 (34), 141 (65), 127 (41), 115 (31), 113 (100), 100 (50), 95 (32), 81 (79), 67 (36), 58 (74), 55 (49), 41 (33). HRMS: calcd. (M^+-OCH_3): *m/e* 211.1334; found: *m/e* 211.1333. Anal: calcd. for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15; found: C, 64.66; H, 9.43.

Most polar isomer: MS: *m/e* (%) 211 (26), 196 (33), 164 (27), 159 (39), 141 (100), 127 (64), 113 (73), 100 (41), 95 (32), 94 (45), 85 (68), 81 (45), 67 (38), 59 (31), 58 (79), 55 (31), 43 (20), 41 (30). HRMS: calcd. (M^+-OCH_3): *m/e* 211.1334; found: *m/e* 211.1329.

(2R*,3aS*,5R*)- and (2S*,3aS*,5R*)-5-Cyclohexyl-3a-hydroxy-2-phenylthio-perhydrofuro-[2,3-b]furan (48).

To an ice-cold solution of 104 mg (0.45 mmol) of hydroxy-furofuranols **40** and 0.06 ml (0.6 mmol) of thiophenol in 25 ml of anhydrous ether, containing 5 g of activated 4Å molecular sieves, was added via syringe 80 ml (0.65 mmol) of borontrifluoride etherate. After 30 min the reaction was quenched by the addition of 30 ml of an aqueous 2N NaOH solution. The organic layer was separated and the waterlayer was extracted with two 50 ml-portions of ether. The combined organic layers were washed with 30 ml of water and 30 ml of brine, dried with $MgSO_4$ and concentrated under reduced pressure to yield 141 mg (0.44 mmol, 97%) of a 4 : 1 mixture of C-2 epimers of sulfide **53** as a white solid, which was sufficiently pure to be used in the next reaction .The epimers could be separated by chromatography on silicagel with petrol-EtOAc (96-4 to 90-10) as eluent to give, in order of elution, the major isomer (m.p. 91-92°C) and the minor isomer (m.p. 133-136°C), both as white solids.

Major isomer: ^1H NMR ($CDCl_3$, 200 MHz): δ 0.75-1.30 (br m, 6H) and 1.30-1.96 (br m, 6H): H-4β [δ 1.77 (dd, J=11.8, 11.7 Hz)], *c*-hex H-1 [δ 1.89 (br d, J=12.4 Hz)], and *c*-hex H-2 - H-6; 2.12 (dd, J=12.6, 4.9 Hz, 1H): H-4α; 2.24 (dd, J=14.3, 4.0 Hz, 1H): H-3; 2.48-2.62 (m, 2H): H-3 [δ 2.55 (dd, J=14.5, 6.8 Hz)] and OH [approx. δ 2.56 (br)]; 3.78 (ddd, J=11.1, 7.5, 4.7 Hz, 1H): H-5; 5.54 (s, 1H): H-6a; 5.67 (dd, J=6.8, 3.8 Hz, 1H): H-2; 7.15-7.30 (m, 3H): Ph H-3 - H-5; 7.38-7.50 (m, 2H): Ph H-2 and H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 25.6, 25.8, and 26.3 (3 t): *c*-hex C-3 - C-5; 28.7 and 29.6 (2 t): *c*-hex C-2 and C-6; 42.6 (d): *c*-hex C-1; 43.7 and 45.7 (2 t): C-3 and C-4; 84.4 (d): C-5; 86.3 (d): C-2; 87.5 (s): C-3a; 113.2 (d): C-6a; 127.6, 129.0 and 131.8 (3 d): Ph C-2 - C-6; 133.7 (s): Ph C-1. MS: *m/e* (%) 213 (13), 211 (100), 193 (17), 181 (14), 175 (17), 167 (13), 157 (12), 149 (36), 147 (12),

121 (24), 110 (12), 109 (11), 95 (21), 81 (16), 72 (11), 67 (21), 55 (16), 41 (13). HRMS: calcd. (M^+): *m/e* 320.1446; found: *m/e* 320.1445. Anal: calcd. for $C_{18}H_{24}O_3S$: C, 67.46; H, 7.55; found: C, 67.63; H, 7.77.
Minor isomer: ^1H NMR ($CDCl_3$, 200 MHz): δ 0.80-2.28 (br m, 15H): H-4β [δ 1.72 (dd, J=11.6, 11.5 Hz)], H-3α H-4α [δ 2.10-2.21 (m)], OH, *c*-hex H-1 [δ 1.92 (br d, J=12.7 Hz)], and *c*-hex H-2 - H-6; 2.56 (dd, J=14.1, 6.8 Hz, 1H): H-3β; 5.40 (s, 1H): H-6a; 5.59 (ddd, J=14.3, 6.8, 6.8 Hz, 1H): H-2; 7.20-7.39 (m, 3H): Ph H-3 - H-5; 7.45-7.60 (m, 2H): Ph H-2 and H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 25.6, 25.8, and 26.4 (3 t): *c*-hex C-3 - C-5; 28.5 and 29.5 (2 t): *c*-hex C-2 and C-6; 42.6 (d): *c*-hex C-1; 44.3 and 45.0 (2 t): C-3 and C-4; 84.0 (d): C-5; 85.3 (d): C-2; 87.8 (s): C-3a; 113.6 (d): C-6a; 127.5, 128.8 and 132.3 (3 d): Ph C-2 - C-6; 133.5 (s): Ph C-1. MS: *m/e* (%) 212 (12), 211 (100), 193 (18), 181 (48), 157(19), 149 (39), 121 (26), 110 (19), 109 (18), 99 (18), 95 (38), 83 (18), 81 (32), 71 (22), 69 (18), 67 (32), 55 (36), 43 (34), 41 (34). HRMS: calcd. (M^+): *m/e* 320.1446; found: *m/e* 320.1448.

(2S*,3aR*,6aR*)-2-Cyclohexyl-2,3,3a,6a-tetrahydrofuro[2,3-b]furan-3a-ol (7).
A solution of 40 mg (0.16-0.17 mmol) of *m*-CPBA (70-75 wt% *m*-CPBA, remainder *m*-CBA and water) in 2 ml of anhydrous toluene was pre-dried in a dropping funnel containing activated 4Å molecular sieves. After 20 min, this solution was added dropwise into an ice-cold solution of 48 mg (0.15 mmol) of the crude sulfide mixture **53** in 5 ml of toluene. Stirring at 0°C was continued until tlc-analysis indicated complete disappearance of the sulfide (approx. 10 min). The dropping funnel was replaced by a reflux condensor, 0.25 ml (1.8 mmol) of triethylamine was added and the flask containing the reaction mixture was placed in an oil bath, pre-heated at 130°C. The mixture was refluxed for approx. 20 min, while the disappearance of the sulfoxide was monitored via tlc-analysis. Then, both solvent and triethylamine were removed at a rotary evaporator under reduced pressure and the residual oil (92 mg) was purified by chromatography on 12 g of silicagel with petrol-EtOAc (95-5 to 90-10) as eluent, affording 25 mg (0.12 mmol, 79%) of tetrahydrofurofuran-3a-ol **7** as a white solid.
^1H NMR ($CDCl_3$, 200 MHz, selected peaks): δ 0.75-1.38 (br m, 5H) and 1.38-1.80 (br m, 5H): *c*-hex H-2 - H-6; 1.80-2.02 (br dd, 2H): H-3β [δ 1.91 (dd, J=11.7, 11.7 Hz)] and *c*-hex H-1; 2.02-2.40 (br dd, 2H): H-3α [δ 2.17 (dd, J=12.0, 4.3 Hz)] and OH; 3.77 (ddd, J= 11.5, 7.4, 4.3 Hz, 1H): H-2; 5.01 (d, J=2.8 Hz, 1H): H-4; 5.65 (s, 1H): H-6a; 6.57 (d, J=2.8 Hz, 1H): H-5. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 25.7, 25.9, and 26.4 (3 t): *c*-hex C-3 - C-5; 28.7 and 29.8 (2 t): *c*-hex C-2 and C-6; 42.27 (d): *c*-hex C-1; 42.3 (t): C-3; 85.6 (d): C-2; 90.5 (s): C-3a; 104.9 (d): C-4; 113.1 (d): C-6a; 150.4 (d): C-5.

(2S*,3aS*,6aS*)-2-Cyclohexyl-perhydrofuro[2,3-b]furan-3a-ol (49).
A solution of 80 mg (0.38 mmol) of **7** in 30 ml of EtOAc containing 47 mg of 10% Pd/C was hydrogenated in a Parr apparatus under hydrogen pressure (4 atm) at room temperature. After 25 min the reaction mixture was filtered and the solvent was evaporated under reduced pressure. The crude product was purified via chromatography on silicagel with petrol-EtOAc (92-8 to 85-15) as eluent, affording 59 mg (0.28 mmol; 73%) of perhydrofurofuran-3a-ol **49** as a white solid (m.p. 81-82.5°C).
^1H NMR ($CDCl_3$, 200 MHz): δ 0.75-1.78 (br m, 11H): *c*-hex H-2 - H-6; 1.84 (dd, J=11.7, 11.7 Hz, 1H): H-3β; 1.95 (br d, J=11.7 Hz, 1H): *c*-hex H-1; 2.13-2.27 (m, 3H): H-4 [δ 2.16 (dd, J=6.8, 6.8 Hz)] and H-3α [δ 2.22 (dd, J=12.5, 5.1 Hz)]; 2.4 (br s, 1H): OH; 3.85 (ddd, J=10.7, 7.5, 5.1 Hz, 1H): H-2; 3.9-4.1 (m, 2H): H-5; 5.3 (s, 1H): H-6a. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 25.7, 25.9, and 26.4 (3 t): *c*-hex C-3 - C-5; 28.6 and 29.6 (2 t): *c*-hex C-2 and C-6; 40.2 (t): C-3; 43.2 (d): *c*-hex C-1; 44.2 (t): C-4; 68.2 (t): C-2; 84.7 (s): C-3a; 88.3 (d): C-5; 112.3 (d): C-6a. MS: *m/e* (%) 166 (11), 129 (100), 116 (10), 111 (21), 84 (10), 83 (88), 70 (19), 55 (36), 43 (40), 41 (14). HRMS: calcd. (M^+): *m/e* 212.1412; found: *m/e* 212.1409. Anal: calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50; found: C, 67.92; H, 9.69.

References and Notes

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