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STEREOSELECTIVE SYNTHESES OF 2-SUBSTITUTED PERHYDROFURO[2,3b]FURANS

JAN VADER, RIMCO KOOPMANS, AEDE DE GROOT*,

ALBERTUS VAN VELDHUIZEN AND SIES VAN DER KERK

Laboratory of Organic Chemistry, Agricultural University Wageningen,

De Dreijen 5, 6703 BC Wageningen, The Netherlands

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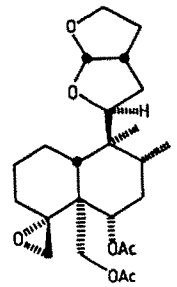
Abstract. - New reagents for the stereoselective synthesis of 2-substituted perhydrofuro[2,3b]furans are described. In the successful approach towards the latter compounds, the key steps were the addition of a monolithio-2α-methoxy-3β-[(phenylsulfonyl)-methyl]perhydrofuran to an aldehyde and a dilithio-2α-methoxy-3β-[(phenylsulfonyl)-methyl]perhydrofuran to a carboxyl derivative, respectively.
The structures and conformations of the 2-tert-butyl- and 2-isopropylperhydrofuro[2,3b]furans were examined by means of ^{1}H-NMR double resonance and the 2D-NOE spectroscopy.

Fused ring cyclic acetals make up a structural part of many natural products. The insect-antifeedant azadirachtin for example contains a furo[2,3b]pyran moiety, while several clerodanes with insect-antifeedant activity, and aflatoxin contain a furo[2,3b]furan. Prompted by these important biological activities, many research groups have aimed extensive efforts towards the synthesis of furopyrans[1] and furo-furans.[2]

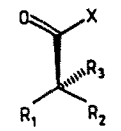
RESULTS AND DISCUSSION

In our investigations involving the synthesis of clerodanes (e.g. dihydroclerodin A), the carbonyl compound **B** was considered to be a promising precursor for the furo-furan side chain **C**. Consequently, the introduction of a functionalized methylene-perhydrofuran via addition of a stabilized carbanion to the carbonyl group of **B** was investigated. To this extent the dithiane **1** and the sulfones **2**, **3** and **4** were chosen as reagents, likely to lead to positive results.

Figure 1

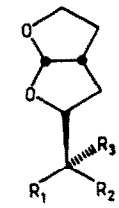


A

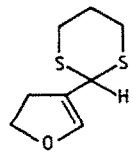


X = H, OMe, Cl

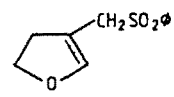
B



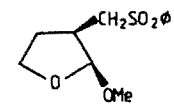
C



1



2



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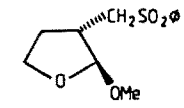
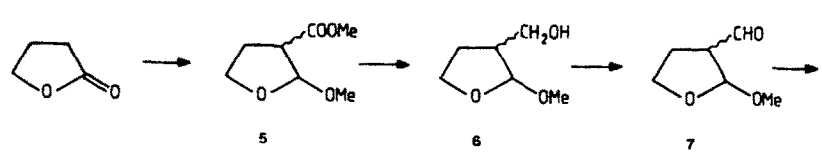


4

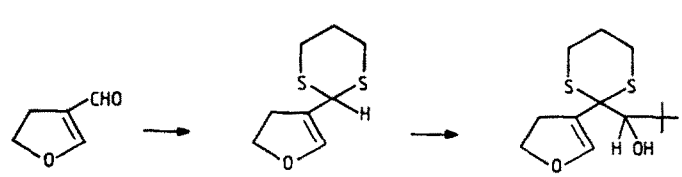
In view of the stereochemical problems to be expected in the built-up of a furofuran side chain in dihydroclerodin A, the symmetrical dithiane 1 seemed to be the reagent to be preferred, followed by the sulfone 2. In the sulfone-acetals 3 and 4, as an additional difficulty, an influence of the asymmetric centres in these reagents has to be taken into account.

In the syntheses of 1-4, γ-butyrolactone was used as starting material. By a modification of the procedure of Korte and Machleidt[3] this was converted into a mixture of acetal-esters 5 in 53% yield (Scheme I). The esters 5 were reduced quantitatively to the alcohols 6, and subsequent Swern oxidation[4] resulted in a mixture of the aldehydes 7 and 8. Treatment of this mixture with triethylamine in refluxing benzene gave the rather labile aldehyde 8 in 48% yield. Dithiane 1 was obtained in 55% yield by reaction of aldehyde 8 with 1,3-propanedithiol.[5]

Scheme I



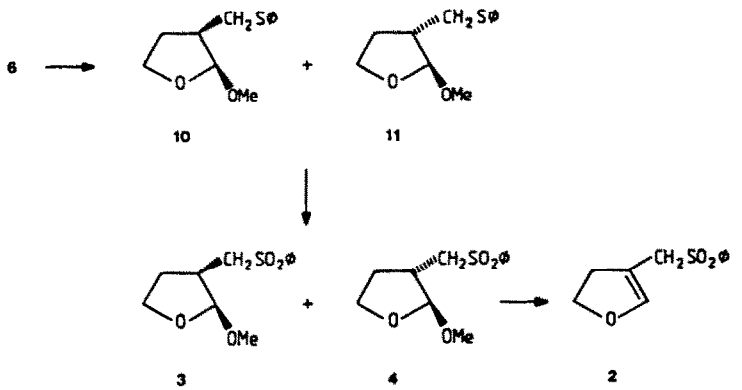
5 6 7



8 1 9

Reaction of the lithiated dithiane 1 with 2,2-dimethylpropanal (pivalaldehyde) in tetrahydrofuran at -78° in the presence of hexamethylphosphoric triamide gave adduct 9 in 80% yield. Attempts at cyclization of 9 to a furo-furan ring, using a number of acidic catalysts, were unsuccessful, and removal of the dithiane moiety with Raney Nickel failed as well.

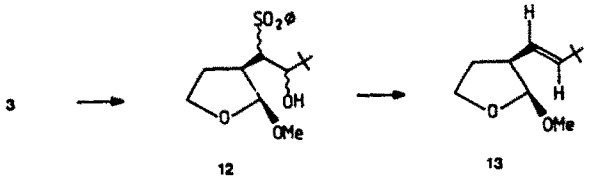
Scheme II



Therefore, attention was focussed on the allylic sulfone 2.[6] The latter was synthesized from the mixture of alcohols 6 in three steps (Scheme II). The alcohols 6 were converted into the sulfides 10 and 11 by reaction with diphenyldisulfide and tri-n-butylphosphine in pyridine.[7] Separation of the diastereoisomeric sulphides was effectuated by means of flash chromatography. Oxidation of the sulphides 10 and 11 with oxone ® in buffered methanol[8] yielded the corresponding sulfones almost quantitatively. The unsaturated sulfone 2 was obtained in yields up to 68% by treatment of sulfone 3 and/or 4 with p-toluenesulfonic acid in benzene. However, it proved to be impossible to isolate any stable product from the reactions carried out between pivalaldehyde and lithiated 2.

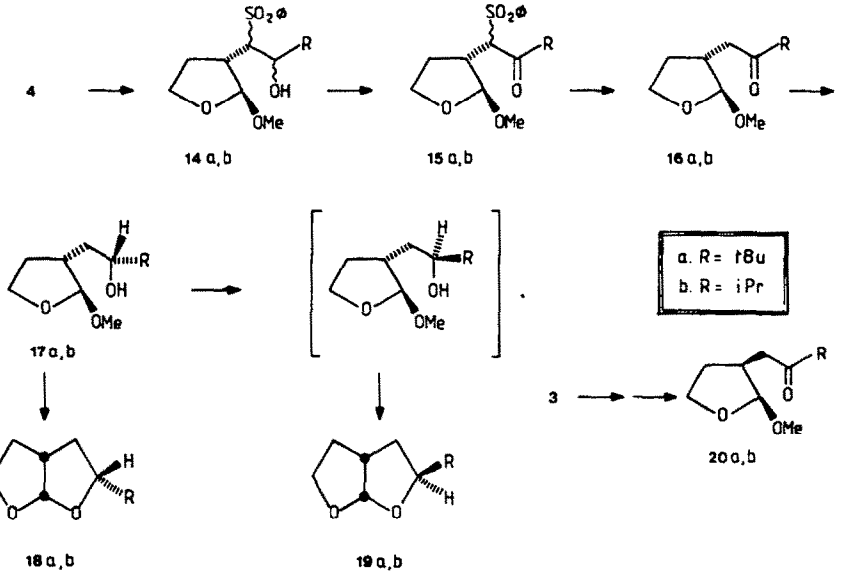
The experiments with dihydrofurans 1 and 2 having been unsuccessful, the sulfone-acetals 3 and 4 remained to be investigated. A disadvantage of the use of these sulfone-acetals was illustrated by the addition of the lithiated sulfone-acetal 3 to pivalaldehyde,[9] which yielded a complex mixture of the stereoisomeric alcohols 12. Apart from that, elimination of the hydroxyl group took place during the reductive desulfonation, and the alkene 13 was obtained in 85% yield (Scheme III).

Scheme III



In order to circumvent both problems, the β-ketosulfone **15a** was synthesized both by oxidation of the hydroxyl group in the adducts **14a**, and by addition of the dilithiated sulfone-acetal **4** to pivaloyl chloride[10] (Scheme IV). Both routes gave yields of about 70%.

Scheme IV



Reductive desulfonation of **15a** with sodium amalgam in buffered methanol[11] yielded ketone **16a**, as expected. Similarly, ketone **16b** was obtained from the trans-sulfone **4**. Starting from the cis-sulfone **3** the corresponding ketones **20a** and **20b** were prepared, following the same procedures.

Upon experimenting with a number of reducing agents on ketones **16a**, **16b**, **20a**, and **20b**, it was found that nearly complete stereoselective reduction of the carbonyl group in **16a** and **16b** could be achieved by reaction with lithium tri-tert-butoxy-aluminohydride in tetrahydrofuran at 0°. Thus, ketone **16a** yielded the alcohol **17a**, after which ring closure to the furo-furan **18a** was achieved by brief treatment of **17a** with acid (yield 95%, calc. from **16a**). Upon determination of the structure of this furo-furan (vide infra), it appeared that the relative stereochemistry of the substituent at C_2 and the acetal proton is opposed to that observed for dihydroclerodin.

Inversion of the configuration at the neopentylic carbon atom C_2 was effectuated via tosylation of the alcohol **17a**, followed by a nucleophilic substitution reaction with potassium superoxide.[12] Consecutively, the furo-furan **19a** was obtained by acid catalyzed cyclization (yield 52%, calc. from ketone **16a**), and proved to possess the same relative stereochemistry as dihydroclerodin (vide infra).

The corresponding 2-isopropyl-perhydrofuro[2,3b]furans **18b** and **19b** were synthesized following the same route as described for **18a** and **19a**, respectively.

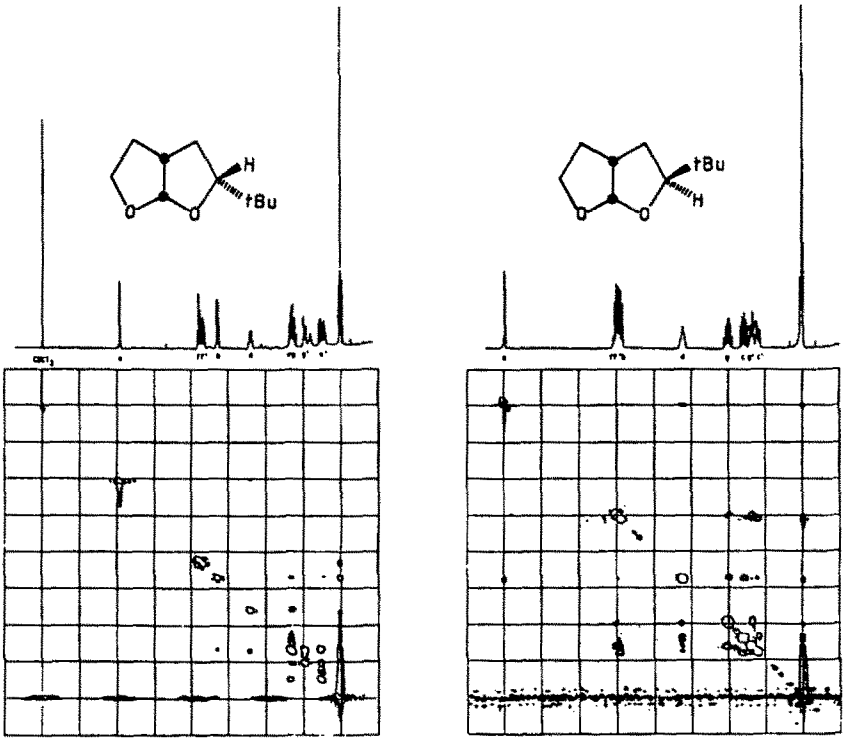
A selectivity, similar to the reactions carried out with the trans compounds **16a** and **16b**, could not be achieved in the reduction of the cis compounds **20a** and **20b**.

Determination of the structures of **18a** and **19a**

The structure of the compounds **18a** and **19a** was elucidated by means of ^{1}H-NMR, viz. by combining the results of double resonance measurements and of the 2D-NOE spectra of the respective compounds.

The 2D-NOE (300 MHz) proton spectra of **18a** and **19a** are shown in Fig. 2 and 3, respectively, in combination with the normal spectra.

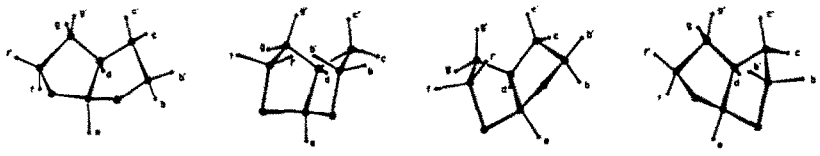
Figures 2 and 3



In cis-fused unsubstituted **21** (see Fig. 4), molecular models show four conformations to be possible. Interconversions between these geometries appear not to occur at room temperature.

Of the four conformations, two (**21a** and **21b**) have C_s symmetry; the remaining two (**21c** and **21d**) possess no symmetry elements, but each is the mirror image of the other. Upon substitution of the proton in the b or b' position, a total of eight possible conformations is obtained.

Figure 4



21a **21b** **21c** **21d**

The molecular structure of compound **18a**

Assignment of the ^{1}H-signals in the spectrum of compound **18a** was based on direct evidence (as for the t-Bu protons, H_e, H_d, the set H_b, H_f, $H_{f'}$, the set H_c, $H_{c'}$, H_g, $H_{g'}$), on the results obtained upon irradiation of the various multiplets, and on the 2D-NOE spectrum, and is indicated in Fig. 2. The 2D-NOE spectrum shows the protons H_e and H_d to be spatially near, so there can be no doubt about the cis junction of the rings. Also, a strong NOE is observed between H_d and H_c, between H_d and H_g, and between H_b and H_c. NOE's between H_d and $H_{c'}$, between H_d and $H_{g'}$, and between H_b and $H_{c'}$ are conspicuously absent.

Further, upon irradiation of the resonance frequency of H_e, the H_d multiplet turns into a regular quartet (relative intensities 1:3:3:1).

The only condition under which this deceptively simple pattern can occur is when *of the four protons* H_c, $H_{c'}$, H_g, *and* $H_{g'}$ *three have very nearly identical* couplings with H_d, while the fourth coupling constant is zero. Measurements of the torsion angles in a Dreiding molecular model of **21c**, and application of the Karplus relation showed this to be a real possibility. It should be noted that the equality of three of the four coupling constants (the fourth being zero) completely rules out the ring geometries of C_s symmetry, **21a** and **21b**. This is corroborated by the value of the coupling constant J_{de} (5.2 Hz), which appears too small for the torsion angle of zero degrees corresponding to a symmetrical structure. Actually, the value found fits the torsion angle measured in models of **21c** and **21d** very well. Further, the results of the double resonance experiments showed the coupling constants J_{cd}, $J_{c'd}$, and J_{gd} to be nearly equal (ca 9.0 Hz), while $J_{g'd}$ proved to be close to zero, as was confirmed by the simple observation that the $H_{g'}$ multiplet does not change upon irradiation on the H_d multiplet. As in geometry **21d** the coupling constant $J_{c'd}$ would be expected to be zero, this leads to the conclusion that structure **21c** is the correct representation of the geometry of the rings, while the 2D-NOE spectrum proves the t-Bu group to occupy the pseudo equatorial position (a strong NOE between H_b and H_c being present). Compound **18a** thus has structure **21c** (see Fig. 4), with the t-Bu group in the b' position.

It should be noted that the multiplet originating from H_b has the form of a quartet (relative intensities 1:1:1:1); this now can only come about under circumstances in which either $J_{bc} = 2J_{bc'}$ or $J_{bc'} = 2J_{bc}$. Estimation of torsion angles and correlation of the data obtained with the Karplus relation shows that the only condition under which either of these two possibilities (viz. the latter, $J_{bc} = 4.5$ Hz, $J_{bc} = 9.9$ Hz)) can be realized is when compound **18a** has geometry **21c**.

The molecular structure of compound **19a**

Assignment of the ^{1}H-signals in the spectrum of compound **19a** was carried out in the same way as for compound **18a** and is indicated in Fig. 3.

For compound **19a** as well, the 2D-NOE spectrum shows the protons H_e and H_d to be spatially near, proving a cis junction between the rings.

As opposed to the results obtained with compound **18a**, irradiation of the resonance frequency of H_e yields direct evidence that the basic structure of the rings in **19a** his C_s symmetry, witnessing the fact that here the H_d multiplet turns into a triplet-like structure, which could be fully reproduced starting

from the following coupling constants: $J_{cd} = J_{gd} = 9.2$ Hz, $J_{c'd} = 2.2$ Hz, and $J_{g'd} = 3.2$ Hz (the difference between $J_{c'd}$ and $J_{g'd}$ being due to an asymmetry induced in the molecule caused by repulsion between $H_{b'}$ and $H_{f'}$, vide infra). Measurement of the torsion angles in Dreiding models of **21a** and **21b**, and correlation of the values obtained with the Karplus relation shows geometry **21b** to be by far the most probable possibility. This is confirmed by the magnitude of the coupling constants $J_{b'c}$ (9.9 Hz) and $J_{b'c'}$ (6.0 Hz).

In Fig. 3 it is seen that a strong NOE is observed between H_d and $H_{c'}$, between H_d and H_g, and between $H_{b'}$ and $H_{c'}$. The NOE's between H_d and $H_{c'}$ and between H_d and $H_{g'}$ are weak, while a NOE between $H_{b'}$ and H_c is absent. These data inevitably lead to the "closed" symmetric geometry **21b**, the proximity of $H_{b'}$ and $H_{c'}$ showing the t-butyl group to occupy the (least hindered) pseudo equatorial position. The axial position of $H_{b'}$ is confirmed by the values of the coupling constants $J_{b'c}$ and $J_{b'c'}$ (vide supra). However, as noted before, due to a repulsive interaction between $H_{b'}$ and $H_{f'}$ a twist is induced in the molecule, as can be inferred from the fact that in **19a** the coupling constant J_{de} has almost the same value as in **18a** (4.9 and 5.2 Hz, respectively), indicating about the same torsion angles between the respective C-H bonds. Were **19a** to have a fully symmetrical geometry, the torsion angle would be zero and J_{de} consequently would be expected to be larger (and the coupling constants $J_{c'd}$ and $J_{g'd}$ would be equal). This deformation from symmetry can take place in two directions (yielding torsion angles between the bonds to H_d and H_e that have the same absolute magnitude, but opposed signs); however, the values found for the coupling constants $J_{c'd}$ (2.2 Hz) and $J_{g'd}$ (3.2 Hz) show the torsion angle between the bonds to H_d and $H_{c'}$ to be about 30° smaller than the torsion angle between the bonds to H_d and $H_{g'}$. Deformation of the symmetric geometry in this direction will be favoured over the alternative, as in the former case there will be less steric interaction between the t-butyl group and $H_{c'}$.

In summary, compound **19a** is concluded to have structure **21b** (see Fig. 4), with the t-Bu group in the b position.

The molecular structure of compounds **18b** and **19b**

The structural analysis of the iso-propyl compounds was carried out in the same way as for the tertiary butyl compounds **18a** and **19a**. As the line of reasoning and the results obtained were the same as for the t-Bu derivatives, i.e. compound **18b** proved to have geometry **21c** (with the i-Pr group in the pseudo equatorial b' position), and compound **19b** has geometry **21b** (with the i-Pr group in the pseudo equatorial b position), no details will be given here, except for the following two remarks.

Both in **18b** and in **19b** the rotation of the i-Pr group is (within the ^{1}H-NMR time scale) fully hindered, witnessing the fact that the two methyl groups within the iso-propyl group have clearly different chemical shifts. Therefore, the normal i-Pr coupling pattern is not observed; instead, each of the methyl groups splits into a doublet.

As in the tBu derivative **19a**, the structure of **19b** appears to deviate from C_s symmetry, albeit to a lesser extent. This can be inferred from the facts that a coupling J_{de} of 5.1 Hz is found.

EXPERIMENTAL

Boiling points and melting points are uncorrected. Routine ^{1}H-NMR spectra were recorded on a Varian EM-390 spectrometer. Chemical shifts are reported in ppm downfield relative to tetramethylsilane (δ scale). $CDCl_3$ was used as a solvent unless stated otherwise. The double resonance and 2D-NOE measurements were carried out on a Bruker CXP-300 spectrometer. Mass spectral data and accurate mass measurements were obtained using AEI-MS-902 and VG Micromass 7070F spectrometers. Elemental analyses were carried out using a Carlo Erba Elemental Analyser 1106. Flash chromatography was preformed on silica gel 230-400 mesh. Other silica gel used was 70-230 mesh. Light petroleum refers to petroleum ether b.p. 40-60°C.

Aqueous solutions were usually extracted three times with ether. Combined organic extracts were dried on magnesium sulfate prior to filtration and evaporation of the solvent under reduced pressure.

Methyl 2-methoxy-perhydrofuran-3-carboxylate (5)

To a mechanically stirred suspension of 80% sodium hydride (31.5 g, 1.05 mol) in ether (1 L) was added dropwise a mixture of methyl formate (60 g, 1.0 mol) and γ-butyrolactone (86 g, 1.0 mol). Stirring was continued for 20 h. The solid material was filtered off and washed with hexane and ether, after which it was suspended in dry methanol (300 mL). A solution of hydrogen chloride (67.7 g) in dry methanol (400 mL) was added dropwise and the reaction mixture was stirred for 1 h. After careful neutralization with sodium hydroxide, the reaction mixture was filtered and the filtrate was concentrated carefully. Water was added and the mixture was worked up as usual to afford 93.9 of the crude ester. Vacuum distillation (88-92°C, 13 mm Hg) afforded esters 5 (85.6 g, 53%) as a colourless oil.

^{1}H-NMR: δ 2.1-2.3 (m, 2H), 2.9-3.1 (m, 1H), 3.37 (s, 3H), 3.75 (s, 3H), 3.8-4.2 (m, 2H), 5.1-5.2 (m, 1H).

The mass spectra of both isomers were identical: m/e (%): 159 (0.4), 145 (3), 129 (23), 100 (33), 69 (100), 59 (15).

2-Methoxy-perhydrofuran-3-methanol (6)

Esters 5 (40.0 g, 250 mmol) were dissolved in dry ether (100 mL) and added dropwise to a mechanically stirred suspension of $LiAlH_4$ (6.13 g, 188 mmol) in ether (600 mL). After refluxing for 3 h the mixture was cooled and water (6 mL), 4N sodium hydroxide (6 mL) and water (18 mL) were added successively. The mixture was dried by adding magnesium sulfate directly. After filtration the solvent was evaporated carefully to yield the alcohols 6 (32.8 g, 99%) as a colourless oil.

^{1}H-NMR: δ 1.3-2.5 (m, 3H), 2.9-3.2 (m, 1H), 3.36 (s, 3H), 3.4-3.6 (m, 2H), 3.7-4.0 (m, 2H), 4.9-5.0 (m, 1H). MS: m/e (%): cis: 104 (21), 101 (67), 71 (79), 61 (100), 44 (81), 31 (44); trans: 131 (2), 104 (19), 101 (47), 71 (56), 61 (100), 44 (71), 31 (27).

4,5-Dihydrofuran-3-carbaldehyde (8)

To a stirred solution of oxalylchloride (7.4 mL, 85 mmol) in dry dichloromethane (150 mL) at -78°C under nitrogen, was added dropwise dimethylsulfoxide (13 mL, 185 mmol) in dichloromethane (30 mL). After stirring for 5 min the alcohols 6 (10.2 g, 77 mmol) in dichloromethane (60 mL) were added dropwise. Stirring was continued for 15 more min and triethylamine (54 mL, 390 mmol) was added dropwise. The stirred reaction mixture was slowly warmed to room temperature, water was added and the mixture was extracted three times with dichloromethane. The combined organic extract was washed with brine and dried. The solvent was evaporated and the residue was filtered through a short column of silica gel. The filtrate was concentrated and the residue, still containing some triethylamine, was dissolved in benzene. The solution was refluxed and the condensed vapor was led through a column filled with molecular sieves 4 A. After 48 h the mixture was cooled and concentrated. Flash chromatography on silica gel, eluting with light petroleum/ether (3/1) afforded aldehyde 8 (3.64 g, 48%) as white crystals mp 49-51°C. No satisfactory elemental analysis could be obtained, due to the instability of this compound.

^{1}H-NMR: δ 2.80 (br t, J = 10 Hz, 2H), 4.65 (t, J = 10 Hz, 2H), 7.47 (s, 1H), 9.65 (s, 1H). MS: m/e (%): 98 (100), 97 (35), 69 (48), 41 (60), 39 (57).

3-(1,3-Dithian-2-yl)-4,5-dihydrofuran (1)

To a solution of aldehyde 8 (724 mg, 7.4 mmol) in dry chloroform (30 mL) at 0°C under nitrogen, was added 1,3-propanedithiol (750 μL, 7.5 mmol) and boron trifluoride etterate (90 μL, 0.73 mmol). The solution was stirred for 1 h and poured into a diluted solution of sodium bicarbonate. The water layer was extracted with dichloromethane. The combined organic extract was washed with brine, dried, filtered and concentrated.

Flash chromatography on silica gel eluting with light petroleum/ether (10/1) afforded dithiane 1 (762 mg, 55%) as white crystals. An analytical sample was obtained by recrystallization in light petroleum/ether; mp 71-73°C. Elemental analysis: calc. for $C_8H_{12}OS_2$: 51.02% C, 6.42% H; found: 50.57% C, 6.47% H.
^{1}H-NMR: δ 1.7-2.3 (m, 2H), 2.73 (br t, J = 9 Hz, 2H), 2.8-3.0 (m, 4H), 4.37 (t, J = 9 Hz, 2H), 4.80 (br s, 1H), 6.45 (br s, 1H). MS: m/e (%): 188 (100), 155 (22), 114 (25). Calc. for $C_8H_{12}OS_2$: 188.0330; found: 188.0330.

1-(1,3-Dithian-2-yl)-1-(4,5-dihydrofuryl)-3,3-dimethyl-butan-2-one (**9**)
Dithiane 1 (110 mg, 0.59 mmol) and hexamethylphosphoric triamide (100 µL) were dissolved in dry tetrahydrofuran (5 mL) under nitrogen. The solution was cooled to -78°C and 15% n-butyllithium in hexane (420 µL) was added. The mixture was stirred for 15 min and pivalaldehyde (60 µL, 0.55 mmol) in tetrahydrofuran (2 mL) was added. The solution was stirred for 30 min and quenched with aqueous ammonium chloride. The reaction mixture was allowed to warm to room temperature and the usual work up afforded a residue (220 mg), which was purified by flash chromatography on silica gel with light petroleum/ether (9/1) to give dithiane 1 (16 mg) and dithiane 9 (129 mg, 85%).
^{1}H-NMR: δ 1.11 (s, 9H), 1.8-2.1 (m, 3H), 2.6-3.1 (m, 6H), 3.53 (s, 1H), 4.47 (br t, J = 10 Hz, 2H), 6.62 (br s, 1H). MS: m/e (%): 274 (16), 259 (13), 187 (100). Calcd. for $C_{13}H_{22}O_2S_2$: 274.1061; found: 274.1062.

2β-Methoxy-3β-[(phenylthio)-methyl]-perhydrofuran (**10**) and 2α-methoxy-3β-[(phenylthio)-methyl]-perhydrofuran (**11**)
Tri-n-butylphosphine (59 mL, 0.24 mol) was added dropwise to a stirred solution of alcoholmixture **6** (19.5 g, 0.15 mol) and diphenyl disulfide (64.0 g, 0.29 mol) in pyridine (200 mL) at room temperature. The reaction mixture was stirred for 20 h, taken up in ether (700 mL) and washed with 2N sodium hydroxide. The water-layer was extracted twice with ether. The combined organic extracts were washed with brine, dried and concentrated. The residue was dissolved in light petroleum (200 mL) and set aside to crystallize in a refrigerator. The mixture was filtered and the crystals were washed with cold light petroleum. The filtrate was concentrated and chromatographed on silica gel with light petroleum/ether (20/1) and afforded cis sulfide **10** (5.83 g), trans sulfide **11** (10.16 g) and a mixed fraction of **10** and **11** (13.86 g) as colourless oils. The total yield was 29.85 g (90%).
^{1}H-NMR **10**: δ 1.6-2.5 (m, 3H), 3.06 (t, J = 7 Hz, 2H), 3.31 (s, 3H), 3.7-4.1 (m, 2H), 4.81 (d, J = 4 Hz, 1H), 7.1-7.4 (m, 5H). MS: m/e (%): 224 (17), 192 (20), 123 (40), 115 (15), 83 (100), 55 (83). Calc. for $C_{12}H_{16}O_2S$: 224.0871; found: 224.0869.
^{1}H-NMR **11**: δ 1.5-2.4 (m, 3H), 2.9-3.0 (m, 2H), 3.33 (s, 3H), 3.9-4.1 (m, 2H), 4.86 (s, 1H), 7.1-7.4 (m, 5H). MS: m/e (%): 224 (22), 123 (42), 83 (30), 55 (100). Calc. for $C_{12}H_{16}O_2S$: 224.0871; found: 224.0870.

2β-Methoxy-3β-[(phenylsulfonyl)-methyl]-perhydrofuran (**3**) and 2α-methoxy-3β-[(phenylsulfonyl)-methyl]-perhydrofuran (**4**)
A mixture of sulfides **11** and **12** (23.09 g, 103 mmol) was dissolved in methanol (200 mL) and sodium bicarbonate (50.4 g, 600 mmol) was added. To the resulting suspension, a suspension of oxone ® (123 g, 400 mmol $KHSO_5$) in water (400 mL) was added in 2 h. The solids were filtered off and the filtrate was extracted four times with dichloromethane (150 mL). The combined organic extract was washed with brine, dried, filtered and concentrated. Flash chromatography on silica gel, eluting with light petroleum/ether (1/1) afforded cis sulfone **3** (3.56 g), trans sulfone **4** (7.39 g) and a mixed fraction of **3** and **4** (14.62 g). The total yield was 25.57 g (97%).
^{1}H-NMR **3**: δ 1.5-2.7 (m, 3H), 3.21 (s, 3H), 3.1-3.6 (m, 2H), 3.8-4.0 (m, 2H), 4.75 (d, J = 4 Hz, 1H), 7.5-7.7 (m, 3H), 7.9-8.0 (m, 2H). MS: m/e (%): 256 (0.2), 225 (5), 115 (22), 83 (83), 55 (100). Calc. for $C_{12}H_{16}O_4S$: 256.0770; found: 256.0777.
^{1}H-NMR **4**: δ 1.5-2.7 (m, 3H), 3.0-3.3 (m, 2H), 3.29 (s, 3H), 3.8-4.0 (m, 2H), 4.78 (br s, 1H), 7.6-7.7 (m, 3H), 7.9-8.0 (m, 3H). MS: m/e (%): 225 (2), 115 (22), 83 (46), 55 (100). Calc. for $C_{12}H_{15}O_4S$ (M-H): 255.0691; found: 255.0705.

3-[(Phenylthio)-methyl]-4,5-dihydrofuran (**2**)
A mixture of sulfones **3** and **4** (14.62 g, 57 mmol) and p-toluene-sulfonic acid monohydrate (100 mg) were dissolved in benzene (100 mL). The solution was refluxed and the condensed vapor was led through a column filled with molecular sieves 4 A. After refluxing for 24 h the mixture was cooled, poured into diluted aqueous sodium bicarbonate and worked up as usual. After flash chromatography eluting with light petroleum/ether (1/1) and recrystallization in ether, sulfone **2** (8.65 g, 68%) was obtained as a white solid (mp 94°C). Elemental analysis: calc. for $C_{11}H_{12}O_3S$: 58.91% C, 5.39% H, found: 58.62% C, 5.65% H.
^{1}H-NMR: δ 2.66 (br t, J = 9 Hz, 2H), 3.87 (s, 2H), 4.34 (t, J = 10 Hz, 2H), 6.09 (br s, 1H), 7.5-7.6 (m, 3H), 7.9-8.0 (m, 2H). MS: m/e (%): 224 (5), 83 (100), 55 (11).

(E)-1-(2β-Methoxyperhydrofur-3β-yl)-3,3-dimethyl-1-butene (**13**)
Cis sulfone **3** (995 mg, 3.9 mmol) was dissolved in dry tetrahydrofuran (40 mL) and cooled at -78°C under nitrogen. A solution of 15% n-butyllithium in hexane (2.7 mL) was added to the solution. The mixture was stirred for 15 min and pivalaldehyde (380 μL, 3.5 mmol) in tetrahydrofuran (5 mL) was added dropwise. After stirring for 2 h the reaction mixture was quenched with aqueous ammonium chloride. The mixture was allowed to warm to roomtemperature and worked up as usual. Flash chromatography eluting with light petroleum/ether (1/1) afforded the diastereomeric alcohols **12** (1.222 g, 92%). A sample of this alcoholmixture (717 mg, 2.1 mmol) was dissolved in dry methanol (30 mL) at -15°C. Disodium hydrogen phosphate (1.60 g) and 5% sodium amalgam (5.12 g) were added and the reaction mixture was stirred for 24 h. Ether was added and the suspension was decanted. This procedure was repeated three times. Water was added to the organic solution and the layers were separated. The waterlayer was extracted twice with ether. Further work up as usual afforded alkene **13** (439 mg, 85%) as a colourless oil, which was analyzed without further purification.
^{1}H-NMR: δ 1.02 (s, 9H), 1.7-2.1 (m, 2H), 2.4-2.8 (m, 1H), 3.31 (s, 3H), 3.7-4.1 (m, 2H), 4.72 (d, 1H), 5.33 (dd, J_1 = 7 Hz, J_2 = 16 Hz, 1H), 5.58 (d, J = 16 Hz, 1H). MS: m/e (%): 183 (0.4), 153 (11), 124 (44), 109 (100). Calc. for $C_{11}H_{19}O_2$ (M-H): 183.1385; found: 183.1390. Calc. for $C_{10}H_{17}O$ (M-OMe): 153.1279; found: 153.1278.

1-Phenylsulfonyl-1-(2α-methoxyperhydrofur-3β-yl)-3,3-dimethylbutan-2-one (**15a**)
A. Sulfone **4** (1.08 g, 4.2 mmol) was dissolved in dry tetrahydrofuran (10 mL) at -78°C under nitrogen. A 15% solution of n-butyllithium in hexane (2.9 mL) was added and the solution was stirred for 15 min. Pivalaldehyde (430 μL, 4.0 mmol) in tetrahydrofuran (5 mL) was added dropwise. After stirring for 15 min the reaction mixture was quenched with diluted aqueous ammonium chloride. Work up as usual afforded 1.40 g residue, which was dissolved in dry dichloromethane (25 mL). Pyridinium chlorochromate (200 g, 9.3 mmol) was added and the mixture was stirred for 20 h. The conversion was not yet complete, additional pyridinium chlorochromate (1.0 g, 4.6 mmol) was added and the slurry was stirred for 5 more h. Ether was added and the suspension was filtered through a short silica gel column. Concentration and chromatography on silica gel with light petroleum/ether (2/1) gave β keto sulfones **15a** (0.98 g, 73%).
MS isomer 1: m/e (%): 309 (1.6), 199 (23), 167 (27), 141 (29), 139 (61), 83 (56), 57 (100).
MS isomer 2: m/e (%): 309 (0.8), 199 (17), 167 (32), 141 (29), 139 (61), 83 (65), 57 (100).
B. A 15% solution of n-butyllithium (4.3 mL) in hexane was added dropwise to a solution of sulfone **4** (1.08 g, 4.2 mmol) in dry tetrahydrofuran (5 mL) at 8°C under nitrogen. The mixture was stirred for 20 min and pivaloylchloride (350 μL, 2.8 mmol) in tetrahydrofuran (5 mL) was added dropwise. The mixture was stirred for 2 h and quenched with aqueous ammonium chloride. Work up as usual and flash chromatography as described under A afforded β keto sulfones **15a** (696 mg, 72%).

1-(2α-Methoxyperhydrofur-3β-yl)-3,3-dimethylbutan-2-one (**16a**)
To a solution of a mixture of β-keto sulfones **15a** (1.50 g, 4.6 mmol) in tetrahydrofuran (5 mL) and methanol (20 mL) of roomtemperature, was added disodium hydrogen phosphate (2.65 g) and 5% sodium amalgam (8.2 g). The suspension was stirred for 1 h and concentrated. The residue was stirred up in ether and decanted. This procedure was repeated three times. Water was added and the layers were separated. Further work up as usual and flash chromatography on silica gel with light petroleum/ether (5/1) afforded ketone **16a** (884 mg, 96%) as a colourless oil.
^{1}H-NMR: δ 1.10 (s, 9H), 1.2-1.6 (m, 1H), 2.1-2.6 (m, 4H), 3.30 (s, 3H), 3.90 (t, J = 7 Hz, 2H), 4.63 (s, 1H). MS: m/e (%): 200 (0.9), 169 (29), 100 (100), 83 (85), 57 (95). Calc. for $C_{11}H_{20}O_3$: 200.1412; found: 200.1412.

1-(2α-Methoxyperhydrofur-3β-yl)-3-methylbutan-2-one (**16b**)
Ketone **16b** was prepared as described for ketone **16a**, by addition of dilithiated sulfone **4** to methyl isobutyrate and subsequent desulfonation to give ketone **16b** in 60% yield, as a colourless oil.
^{1}H-NMR: δ 1.08 (d, 6H), 1.0-1.6 (m, 2H), 2.1-2.8 (m, 3H), 3.30 (s, 3H), 3.90 (t, J = 7 Hz, 2H), 4.64 (s, 1H). MS: m/e (%): 186 (0.3), 185 (1.6), 155 (48), 143 (58), 126 (25), 111 (33), 100 (49), 83 (100), 71 (92). Calc. for $C_{10}H_{18}O_3$: 186.1256; found: 186.1241. Calc. for $C_{10}H_{17}O_3$ (M-H): 185.1178; found: 185.1172.

1-(2α-Methoxyperhydrofur-3β-yl)-3,3-dimethylbutan-2-ol (**17a**)
Ketone **16a** (884 mg, 4.4 mmol) was dissolved in tetrahydrofuran (5 mL) at 0°. Lithium-tri-tert-butoxyaluminohydride (6.7 mmol) was added and the mixture was stirred for 30 min and diluted with ether (30 mL). Subsequent careful additions of water (1 mL), 4N sodium hydroxide (1 mL) and water (4 mL) to the well stirred reaction mixture were followed by adding magnesium sulfate directly to the

resulting mixture. Filtration and evaporation of the solvents afforded alcohol **17a** (883 mg, 99%) as a colourless oil. The diastereomeric purity was 97%.
^{1}H-NMR (CCl_4): δ 0.83 (s, 9H), 1.3-1.6 (m, 3H), 2.0-2.3 (m, 3H), 3.15 (t, J = 6 Hz, 1H), 3.26 (s, 3H), 3.7-3.9 (m, 2H), 4.62 (d, J = 2 Hz, 1H). MS: m/e (%): 201 (1), 171 (14), 145 (15), 113 (100), 87 (43), 69 (47). Calc. for $C_{11}H_{21}O_3$ (M-H): 201.1491; found: 201.1493.

1-(2α-Methoxyperhydrofur-3β-yl)-3-methylbutan-2-ol (**17b**)
Alcohol **17b** was prepared from ketone **16b** as described for **17a**. Alcohol **17b** was obtained as a colourless oil in 95% yield and with a 93% diastereomeric purity.
^{1}H-NMR (C_6D_6): δ 0.92 (d, 3H), 0.94 (d, 3H), 1.1-2.6 (m, 8H), 3.37 (s, 3H), 3.8-4.0 (m, 2H), 4.86 (d, J = 2 hz, 1H). MS: m/e (%): 187 (2), 157 (38), 133 (50), 113 (94), 73 (100), 69 (68). Calc. for $C_{10}H_{19}O_3$ (M-H): 187.1334; found: 187.1337.

2α-tert-Butyl-2β,3,3aβ,4,5,6aβ-hexahydrofuro-[2,3b]-furan (**18a**)
Ketone **16a** (468 mg, 2.3 mmol) was dissolved in tetrahydrofuran (10 mL) at 0°C. Lithium-tri-tert-butoxyaluminohydride (1.2 g, 4.7 mmol) was added and the mixture was stirred for 2 h. After careful addition of 4N hydrochloric acid (2 mL) the mixture was stirred for 30 min. Work up as usual and flash chromatography on silica gel with light petroleum/ether (6/1) gave furo-furan **18a** (376 mg, 95%) as a colourless oil.
^{1}H-NMR: δ 0.92 (s, 9H), 1.2-1.4 (m, 1H), 1.6-1.7 (m, 1H), 1.9-2.0 (m, 2H), 2.8-2.9 (m, 1H), 3.52 (dd, J = 5 Hz, J_2 = 10 Hz, 1H), 3.8-4.0 (m, 2H), 5.62 (d, J = 5 Hz, 1H).
MS: m/e (%): 169 (0.5), 155 (1), 113 (100), 69 (92). Calc. for $C_{10}H_{17}O_2$ (M-H): 169.1228; found: 169.1227.

2α-Isopropyl-2β,3,3aβ,4,5,6aβ-hexahydrofuro-[2,3b]-furan (**18b**)
Furo-furan **18b** was prepared from ketone **16b** as described for **18a**. Furo-furan **18b** was obtained as a colourless oil in quantitative yield.
^{1}H-NMR: δ 0.88 (d, 3H), 0.99 (d, 3H), 1.1-1.4 (m, 2H), 1.6-2.1 (m, 3H), 1.7-3.0 (m, 1H), 3.3-4.0 (m, 3H), 5.63 (d, J = 5 Hz, 1H). MS: m/e (%): 156 (0.1), 155 (3), 113 (92), 69 (100), 56 (34), 55 (34). Calc. for $C_6H_9O_2$ (M-iPr): 113.0603; found: 113.0591.

2β-tert-Butyl-2α,3,3aβ,4,5,6aβ-hexahydrofuro-[2,3b]-furan (**19a**)
Alcohol **17a** (883 mg, 4.4 mmol) and triethylamine (610 µL, 4.4 mmol) were dissolved in dry dichloromethane (20 mL). To this solution 4-dimethylaminopyridine (1.07 g, 8.8 mmol) and p-toluenesulfonyl chloride (1.67 g, 8.8 mmol) were added successively. The reaction mixture was stirred for 20 h and adsorbed on silica gel. Flash chromatography on silica gel with light petroleum/ether (5/1) gave the corresponding tosylate (1.328 g, 3.7 mmol), which was dissolved in dry dimethylsulfoxide (5 mL) and dry 1,2-dimethoxyethane (5 mL). The mixture was kept below 35°C, when 18-crown-6 (2.5 g, 9.5 mmol) and potassium superoxide (18.6 mmol) were added. The cloudy mixture was stirred for 1 h and water, sodium borohydride (1.4 g, 37 mmol) and 4N hydrochloric acid were added carefully! The acidic solution was stirred for 15 min and poured into a saturated solution of sodium bicarbonate. Work up as usual and flash chromatography on silica gel eluting with light petroleum/ether (7/1) yielded furo-furan **19a** (396 mg, 53%) as a colourless oil.
^{1}H NMR: δ 0.87 (s, 9H), 1.5-2.3 (m, 4H), 2.6-3.0 (m, 1H), 3.7-4.0 (m, 3H), 5.68 (d, J = 5 Hz, 1H).
MS: m/e (%): 169 (0.1), 155 (3), 113 (100), 69 (90). Calc. for $C_{10}H_{17}O_2$ (M-H): 169.1228; found: 169.1230.

2β-Isopropyl-2α,3,3aβ,4,5,6aβ-hexahydrofuro-[2,3b]-furan (**19b**)
Furo-furan **19b** was prepared as described for **19a** from alcohol **17b**. Furo-furan **19b** was obtained as a colourless oil in 40% yield.
^{1}H-NMR: δ 0.84 (d, 3H), 0.97 (d, 3H), 1.1-1.3 (m, 2H), 1.6-1.8 (m, 2H), 2.0-2.2 (m, 1H), 2.7-3.0 (m, 1H), 3.5-4.0 (m, 3H), 5.70 (d, J = 5 Hz, 1H).
MS: m/e (%): 156 (0.1), 155 (3), 113 (97), 69 (100), 56 (35), 55 (35). Calc. for $C_6H_9O_2$ (M-iPr): 113.0603; found: 113.0596.

1-(2β-Methoxyperhydrofur-3β-yl)-3,3-dimethylbutan-2-one (**20a**)
Ketone **20a** was prepared as described for ketone **16a**, by addition of dilithiated sulfone 3 to pivalaylchloride and subsequent desulfonation to give ketone **20a** as a colourless oil in 61% overall yield.
^{1}H-NMR: δ 1.14 (s, 9H), 1.5-1.8 (m, 1H), 1.9-3.0 (m, 4H), 3.27 (s, 3H), 3.7-4.1 (m, 2H), 4.90 (d, J = 4 Hz, 1H). MS: m/e (%): 200 (0.7), 199 (0.7), 169 (23), 143 (93), 100 (19), 83 (100), 57 (53). Calc. for $C_{11}H_{20}O_3$: 200.1412; found: 200.1416.

1-(2β-Methoxyperhydrofur-3β-yl)-3-methylbutan-2-one (**20b**)
Ketone **20b** was prepared as described for ketone **16a**, by addition of dilithiated sulfone **3** to methyl-isobutyrate and subsequent desulfonation to give ketone **20b** as a colourless oil in 32% overall yield.
^{1}H-NMR: δ 1.07 (d, 6H), 1.2-2.2 (m, 2H), 2.4-2.9 (m, 3H), 3.23 (s, 3H), 3.6-4.0 (m, 2H), 4.86 (d, J = 4 Hz, 1H). MS: m/e (%): 186 (0.3), 185 (1.8), 155 (40), 143 (50), 126 (21), 111 (35), 100 (47), 83 (100), 71 (93). Calc. for $C_{10}H_{18}O_3$: 186.1256; found: 186.1256.

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