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Synthesis and Insect antifeedant Activity of 2-Substituted 2,3-Dihydrofuran-3-ols and Butenolides (Part II).

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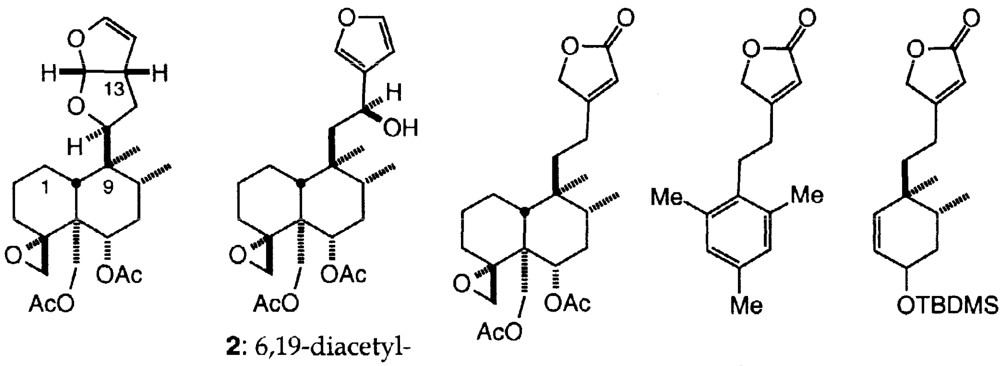
Abstract: The introduction of a hydroxy group at C-13 of the clerodane skeleton is proposed as a strategy to potentially increase the antifeedant activity of simple analogs. This idea is applied to clerodane analogs with furan or butenolide type sidechains and therefore syntheses were developed for several types of 3-alkyl-substituted butenolides, 3-alkyl-substituted-3-hydroxybutenolides and 3-hydroxytetrahydrofuran derivatives. The antifeedant activity was tested on 5th instar larvae of *Pieris brassicae*. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Alkylation; Cyanohydrins; Furanones; Antifeedants

Introduction

Several natural clerodane diterpenoids display high insect antifeedant activity.[1] Especially clerodanes with a perhydrofuro[2,3-b]furan subunit, such as clerodin (**1**), are among the most potent antifeedants known. This subunit has been recognised as an important feature for the biological activity of these natural compounds. For this reason, both we[2a,b] and others[3] have employed this structural element in the search for simplified bioactive analogs.

Figure 1



1: clerodin **2**: 6,19-diacetyl-teumassilin **3**: ajugarin I **4** **5**

However, perhydrofuro[2,3-b]furans are not the only type of biologically active C-9 subunit encountered among natural clerodane antifeedants. A number of clerodanes with monocyclic C-9 sidechains such as a furan ring or a

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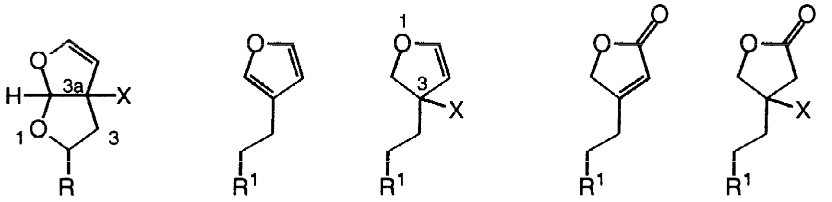
butenolide (*e.g.* **2** or **3**, Figure 1), also exhibit significant antifeedant activity against various pest insect species.[4,5]

Due to their structural simplicity, these monocyclic sidechains are attractive targets in the design of simplified bioactive analogs of natural antifeedants, and indeed, butenolide-based model compounds as **4** [6] and **5** [4a] were found to display antifeedant activity, although usually less than their natural counterpart **3**. Structural modifications that substantially increase this antifeedant activity are therefore required before these simple monocyclic analogs can be considered for application as practical insect control agents.

In the previous article[2c], the introduction of a hydroxy group at position C-13 of the clerodane skeleton (*i.e.* at the C-3a atom of the perhydrofuro[2,3-b]furan ring system **6**) was proposed as a strategy to potentially increase the antifeedant activity of the analog **6a**. Application of this idea to the simple furan-based analog **7a** would lead to compound **7b** (Figure 2). This compound was considered an attractive target structure because of its structural similarity to **6b**.[7-9] A second series of interesting target compounds **8a-c** can be derived from the application of the same type of reasoning to the butenolide-based analog **8a**.

Figure 2



6a: X=H
6b: X=OH

7a

7b: X=OH
7c: X=H

8a

8b: X=OH
8c: X=H

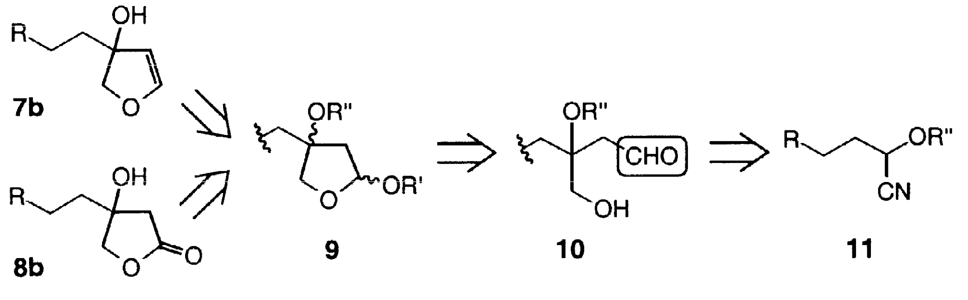
R^1
Ph
$c\text{-}C_6H_{11}$
$n\text{-}C_4H_9$

Investigations on derivatives of the model compounds **4** and **6a** have shown that the antifeedant activity of such bioactive analogs can vary markedly with the nature of the substituent group R, even when only simple *tert*-butyl- or phenyl-groups are used.[3,6] We therefore decided to include a limited range of substituents R^1 (see Figure 2) in our series of test compounds **7** and **8**, in order to examine their effect on the antifeedant properties.

Synthetic Part

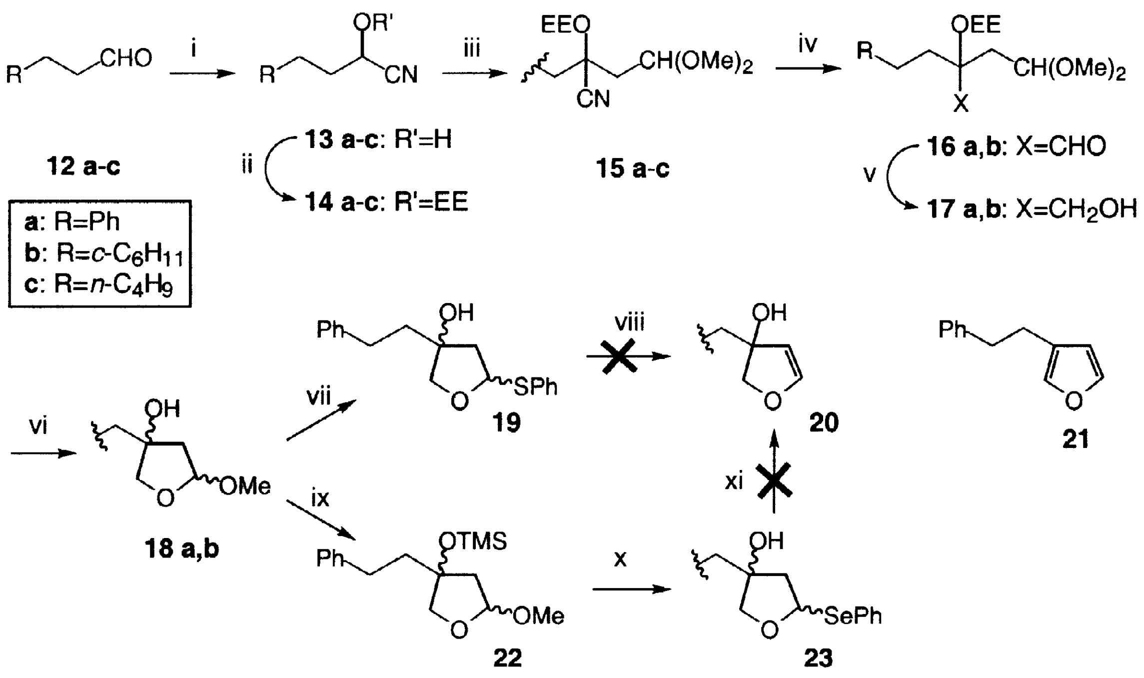
For the preparation of the key target structures **7b** and **8b**, we planned to use a route related to our previous synthesis of the 3a,4,5,6a-tetrahydrofuro[2,3-b]furan-3a-ols **6b**.[2b] In this approach (Scheme 1) the tertiary hydroxy group is introduced *via* alkylation of a suitably protected cyanohydrin **11**.[10] Next, the cyano group is reduced to an alcohol **10**, and cyclization then should yield a central intermediate **9**, from which both **7b** and **8b** should be accessible.

Scheme 1



The protected cyanohydrins **14a-c** were prepared from the corresponding commercially available aldehydes **12a-c** through exchange of hydrogen cyanide from acetone cyanohydrin under basic conditions[11] (Scheme 2) and were protected as the 2-ethoxyethyl (EE) ethers[12] by acid-catalyzed addition to ethyl vinyl ether.

Scheme 2



Reagents and conditions: (i) $Me_2C(OH)CN$ (1.0 eq), Et_3N (cat.), (95-99%); (ii) $EtOCH{=}CH_2$, TFA (cat.), 0°C, (88-100%); (iii) 1) LDA (1.3 eq), THF-HMPA (1:1), -60°C, 0.5 h; 2) $BrCH_2CH(OMe)_2$, -60°C, 2 h, (64-91%); (iv) 1) $LiAlH(OEt)_3$ (1.5-3.0 eq), Et_2O, 0°C, 2.5 h; 2) Glauber's salt, room temperature, 1 h; 3) silicagel, EtOAc, overnight, (64%); (v) $LiAlH_4$ (0.7-1.2 eq), Et_2O, 0°C, 15 min, (92-96%); (vi) TsOH, MeOH, (82%). (vii) PhSH, $BF_3{\bullet}Et_2O$, Et_2O, 0°C, 30 min, (83%); (viii) *m*CPBA, toluene, 0°C; then Et_3N, 110°C, 10 min; (xi) TMSCl, HMDS, pyridine, (74%); (x) PhSeH, $BF_3{\bullet}Et_2O$, Et_2O, 0°C, 30 min, (91%); (xi) *t*-BuOOH (1.1 eq), $Ti(O\textit{i}\text{-}Pr)_4$ (1 eq), *i*-Pr_2NEt, CH_2Cl_2, 0°C, 45 min.

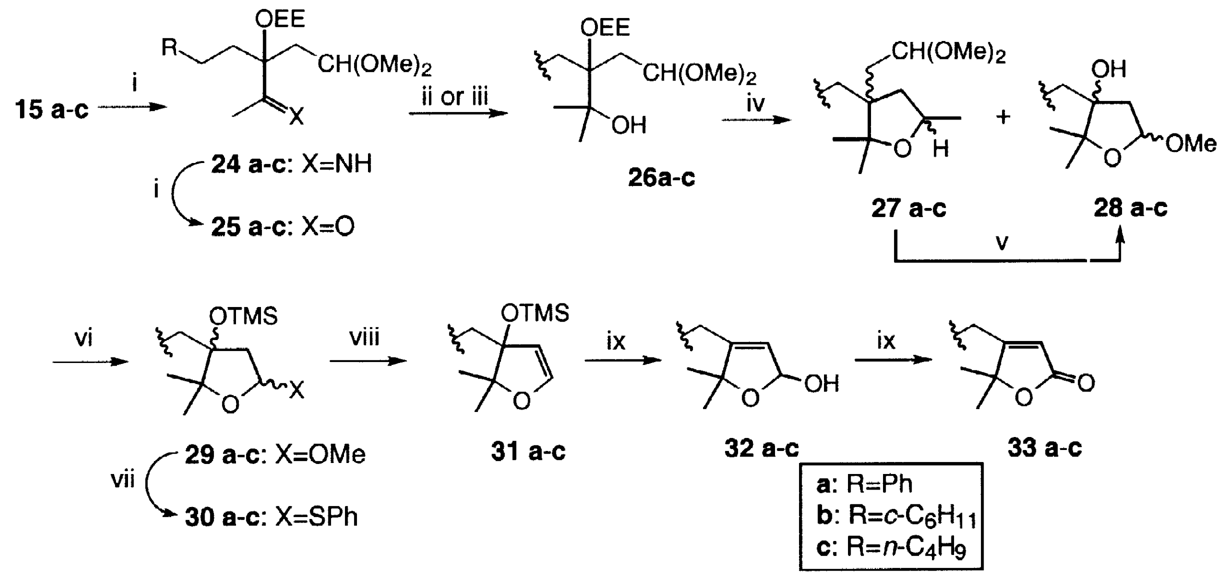
The protected cyanohydrins **14a-c** were alkylated with bromoacetaldehyde dimethylacetal, according to the general procedure developed by Stork *et al.*[13] The cyano group was reduced in two steps to the corresponding alcohol. In our hands,[14] reduction of **15a** with DibalH failed repeatedly, even in refluxing ether but these problems could be circumvented by the use of excess lithium triethoxyaluminumhydride,[15] followed by hydrolysis of the resulting imine intermediates on silicagel. In this way aldehydes **16a,b** could be obtained in a reasonable yield of 64%. Subsequently, **16a,b** were reduced with lithium aluminumhydride to afford the alcohols **17a,b** in 92-96% yield. Finally, simultaneous deprotection and cyclization of **17a,b** under acidic conditions in methanol smoothly afforded **18a,b** in 82% yield as 1 : 2 mixtures of both diastereomeric isomers.

For the introduction of the cyclic enol ether functionality, the phenylsulfenic acid elimination strategy was tried first. Phenylsulfide **19** could be prepared from **18a** in the usual way (Scheme 3), but attempts to convert this compound *via* its sulfoxide into the desired enol ether **20** failed. Usually a complex mixture of products was formed, containing 3-(2-phenylethyl)-furan **21** as the only identifiable component. Apparently **20** is an unstable compound with a strong tendency to aromatize.[7-9]

Then the attention was turned to the elimination of phenylselenic acid from the corresponding phenylselenoxide[16] derivatives and in addition, the hydroxy group of **18a** was protected as a silyl ether in an attempt to lower the tendency of the ring system to aromatize during elimination. However, the TMS group was not stable under the conditions required for phenylselenide introduction, and treatment of **22** with benzeneselenol and boron trifluoride diethyl etherate afforded the phenylseleno-alcohol **23**[17] in 91% yield as a mixture of diastereomers (H-2α : H-2β = 2.6 : 1). In our hands, the oxidation and subsequent elimination of the phenylselenyl group *via* oxidation with *t*-BuOOH in the presence of $Ti(Oi\text{-}Pr)_4$ [9,16] only led to rapid isomerization of **23** to its H-2α isomer, which was recovered in 70% yield and no traces of the 2,3-dihydrofuran-3-ol (**20**) or the corresponding furan were found.

In an attempt to obtain a more stable derivative of target structure **7b** it was decided to introduce two alkyl groups at the C-2 position of **7b**, so that the possibility of aromatization to the corresponding furan would be blocked. Addition of methyl lithium (Scheme 3) to nitriles **15a-c** initially yielded the imines **24a-c**, which were sufficiently stable to withstand hydrolysis even in boiling water, but could be hydrolyzed without loss of the protecting group by heating for 24 h in a 10% aqueous NH_4Cl solution to ketones **25a-c** in 79% overall yield. The introduction of a second methyl group via methyl lithium addition to **25a-c** was hampered by the formation of the lithium enolates of **25** as a major side reaction but by recycling the remaining starting material, or by using the less basic $MeCeCl_2$[18] **26a** was obtained in 93-99% yield.

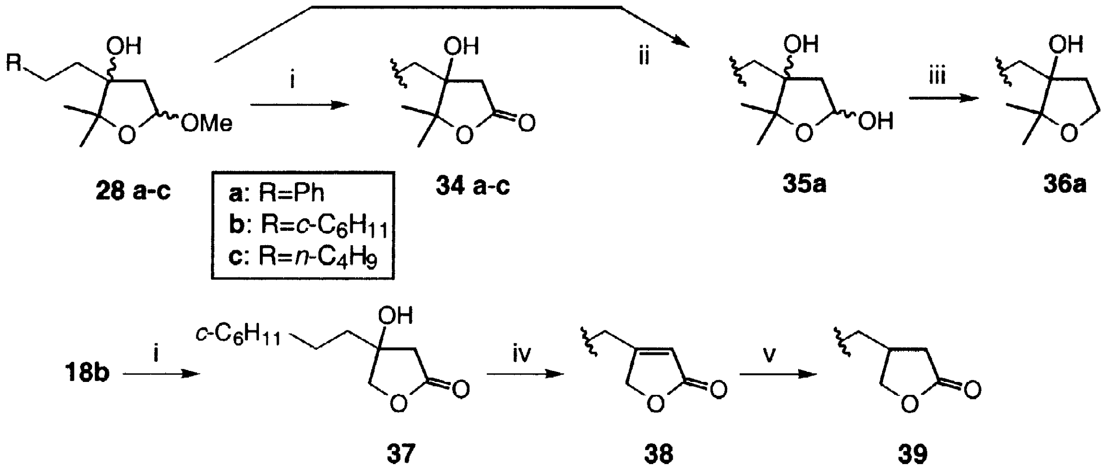
Scheme 3



Reagents and conditions: (i) 1) MeLi (1.6 eq), Et_2O, 0°C, 1.5 h; 2) NH_4Cl, THF-water (1:1), 60-70°C, overnight, (71-79%); (ii) MeLi, ether, 0°C, (33-41% **26**, 41-46% **25**); (iii) $CeCl_3$; MeLi, THF, -78°C, (93-99%); (iv) TsOH (cat.), MeOH, (28-31% **27**, 56-60% **28**); (v) TsOH (cat.), MeOH, 65°C, overnight; (vi) TMSCl, imidazole, DMF, (89-100%); (vii) PhSH, $BF_3{\bullet}Et_2O$ (1.5 eq), Et_2O, 4Å mol. sieves, 0°C, 30 min, (98-100%); (viii) *m*CPBA, toluene, 0°C; then Et_3N, 110°C, 10 min. (ix) 1) 40% HF, THF-water, 10 min; 2) Jones' reagent, 0°C, 30 min (**33**: 46-68% from **31**).

Cyclization of **26a-c** as before with *p*-toluenesulfonic acid in methanol unexpectedly yielded only 56-60% of the desired products **28a-c**. In addition, another cyclization product **27a-c**, resulting from addition of the alcohol upon the acetal center of the EE group, was obtained in 28-31% yield. This side reaction could not be suppressed by different reaction conditions, and complete conversion into **28a-c** could be achieved only after chromatographic separation from **27a-c**, followed by renewed treatment with *p*-toluenesulfonic acid in refluxing methanol. The tertiary hydroxy groups of **28a-c** were protected as their trimethylsilyl ethers in 89-100% yield and subsequently transformed into the corresponding sulfides, yielding 98-100% of **30a-c** as a 1 : 1 mixture of isomers. *In situ* oxidation of **30a-c** to the sulfoxide, followed by thermal elimination as before, yielded crude products which were identified as the desired enol ethers **31a-c** from their ^{1}H NMR spectral data. Upon purification of the crude products *via* chromatography on silicagel or florisil, the enol ethers **3 a-c** were partly transformed into a more polar product **32a-c** that lacked the TMS group.

Scheme 4



Reagents and conditions: (i) Jones' reagent, acetone, 0°C, 10 min, (85-100%); (ii) 4H HCl, THF, 30 min, (67%); (iii) Et_3SiH (4 eq), $BF_3{\bullet}Et_2O$ (2 eq), CH_2Cl_2, -78°C, 1 h, (73%); (iv) $SOCl_2$ (5 eq), pyridine (20 eq), CH_2Cl_2, 0°C, 1 h, (39%); (v) H_2, Pd-C, EtOAc, 6 h (100%).

Desilylation of **31a** with TBAF in THF and subsequent chromatography on silicagel yielded the same rearranged product **32a**. The experiences with **20** and **31a-c** show that the 3-alkyl-2,3-dihydrofuran-3-ol ring system is rather unstable and that rearrangement reactions occur easily. This is probably due to the tertiary nature of the allylic hydroxy group in these compounds, which can easily give a stable cationic intermediate after leaving. Depending on the nature of the C-2 substituents in this intermediate, subsequent reactions can lead to aromatization or to a reaction with a nucleophile, *e.g.* water, leading to **32**. In view of the inherent instability of the key target structure **7b**, further attempts to the synthesis of the other members of the planned test series **7a-c** were abandoned and the butenolides **33a-c** were synthesized instead. *In situ* deprotection of the crude enol ethers **31a-c** with an aqueous 40% hydrofluoric acid solution, followed by oxidation with Jones' reagent, yielded the butenolides **33a-c** in an overall yield of 46-68%.

Jones' oxidation (Scheme 4) of the cyclized products **28a-c** afforded hydroxy-lactones **34a-c** in 85-100% yield. Diol **35a** could be obtained in 67% yield *via* an acid-catalyzed partial hydrolysis of methoxy-acetal **28a** and subsequent reduction with triethylsilane[19] then gave the tetrahydrofuranol **36a** in 73% yield.

The originally planned series of butenolide derivatives **8a-c** could be prepared from the central intermediate **18b**. Direct oxidation of **18b** with Jones' reagent gave rise to hydroxy lactone **37** in very good yield (Scheme 4). The elimination of water from **37** was easily performed with $SOCl_2$[20] and was complete within 1 h but yielded a mixture of **38** and its exocyclic double bond regioisomers. Separation of these products by chromatography proved to be difficult and therefore pure **38** was obtained in only 39% yield. Finally, catalytic hydrogenation in the presence of palladium on activated carbon quantitatively yielded the corresponding lactone **39**.

In conclusion: two different target structures were derived from the introduction of a hydroxy group at C-13 of natural clerodane antifeedants with a sidechain at C-9, containing a perhydrofuran- or a butenolide substituent. The synthesis of a series of 3-alkyl-2,3-dihydrofuran-3-ol derivatives was unsuccessful, due to the instability of this target structure. Instead, a series of test compounds was prepared, centered on the 4-alkyl-4-hydroxylactone moiety, as potentially active model compounds (see Figure 3).

Biological Properties

Two choice assay of the lactone model compounds

The lactone model compounds displayed in Figure 3 were tested in a two-choice assay on *Pieris brassicae* larvae. Half of the compounds showed statistically significant antifeedant activity (Table 1), with **34a** as the most active compound. In view of the applied concentration, however, none of these compounds can be considered as a potent antifeedant for *Pieris brassicae* larvae. It has been suggested[21] that the biological activity of various types of antifeedants might be related to the presence of electrophilic moieties in the molecules. Compound **38** consists of an electrophilic butenolide system, which is also present in natural insect antifeedants such as ajugarin I (**3**).

Figure 3

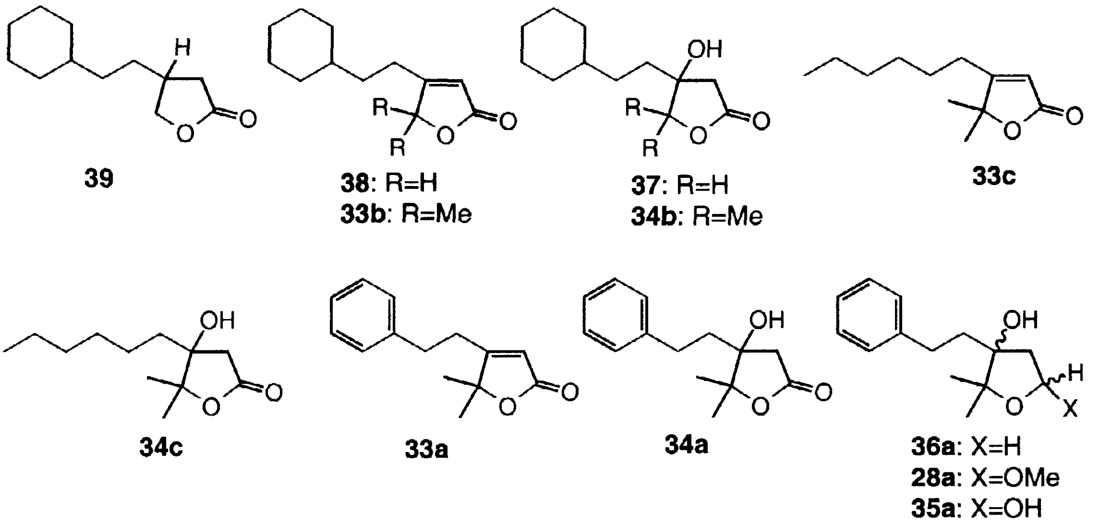


Table 1: Insect antifeedant activities of the lactone model compounds displayed in Figure 3 against 5th instar larvae of the large cabbage white butterfly (Lepidoptera: *Pieris brassicae*) in a two-choice bioassay on cabbage leaf discs (5 mM concentration).[a]

	AI (sem) [b] (%)		AI (sem) [b] (%)		AI (sem) [b] (%)
39	-9.2 (12)	**33c**	9 (9)	**28a**	23 (8) **
38	35 (8) **	**34c**	11 (9)	**35a**	5 (8)
37	-4 (10)	**33a**	33 (10) **		
33b	26 (6) **	**34a**	36 (7) **		
34b	15 (8)	**36a**	28 (10) **		

Notes (a) Adapted from ref. 22.(b) Mean Antifeedant Index AI=[(C-T)/(C+T)]*100; sem=standard error of the mean. (c) Average value from eight experiments. Statistically significant difference between control and treatment areas (Wilcoxon's matched pairs test); p<0.01. (*) p<0.05.

Modification of this butenolide through hydrogenation to **39** or *via* formal addition of water onto the double bond to **37** indeed resulted in complete loss of the antifeedant activity.

Introduction of two methyl groups at carbon atom C-5 gave rise to a series of C-5 dimethylated model compounds. This substitution led to some loss of activity in case of the normal butenolide system (**33** *vs.* **38**), but substantially increased the antifeedant activity of the related 3-hydroxy lactone (**34b**, compared to **37**). Remarkably, for such C-5 dimethylated compounds the presence of the C-3,4 unsaturation in general appears to be of lesser importance, since the 3-hydroxy lactones (**34a**, **34b**, **34c**) were roughly equally active as the corresponding butenolides (**33a**, **33b**, **33c**). However, further degradation of the electrophilic moiety by replacing the lactone in **34a** with a cyclic ether (**36a**) or a cyclic acetal (**28a**) did result in partial loss of activity, while the cyclic half-acetal **35a** was even found to be inactive. The nature of the C-4 alkyl sidechain also had an impact on the activity of the model compounds, generally favouring a phenethyl substituent (**33a**, **34a**) over its cyclohexyl-equivalent (**33b**, **34b**), which in turn was sometimes preferred over a straight-chain alkyl substituent (**33b** *vs.* **33c**), however notice also the higher activity of **34b** *vs.* **34c**.

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Experimental Section

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.

2-Hydroxy-4-phenyl-butanenitrile (13a).

A mixture of 15 ml (0.11 mol) of dihydrocinnamaldehyde **12a**, 10 ml (0.11 mol) of acetone cyanohydrin and 0.2 ml (1.4 mmol) of triethylamine was stirred at room temperature for 2.5 h until tlc-analysis indicated complete disappearance of starting material. The solvent was evaporated and the residue was dissolved in 50 ml of ether, washed with two 15 ml-portions of saturated sodium pyrosulphite solution and two 15 ml-portions of brine, dried with $MgSO_4$, and concentrated under reduced pressure to give 17.5 g (0.11 mol; 99%) of cyanohydrin **13a** as a yellow oil. The crude product was used without purification in the next reaction.

^{1}H NMR ($CDCl_3$, 200 MHz, major peaks): δ 2.19 (m, 2H): H-3; 2.87 (t, J=7.7 Hz, 2H): H-4; 3.76 (br, 1H): OH; 4.44 (t, J=6.3 Hz, 1H): H-2; 7.21-7.41 (m, 5H): Ph H-2 - H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 30.6 (t); 36.5 (t); 60.3 (d): C-2; 120.1 (s): $\underline{C}N$; 126.6 (d): Ph C-4; 128.6 (4 d): Ph C-2, C-3, C-5, and C-6; 139.7 (s): Ph C-1.

2-[(1-Ethoxy)ethoxy]-4-phenyl-butanenitrile (14a).

A mixture of 17.5 g (0.11 mol) of cyanohydrin **13a**, 50 ml (0.52 mol) of ethyl vinyl ether and 1.0 ml (13 mmol) of trifluoroacetic acid was stirred at 0°C for 20 h. The reaction mixture was then diluted with 50 ml of ether, washed with three 20 ml-portions of saturated aqueous sodium bicarbonate solution and two 20 ml-portions of brine, dried with $MgSO_4$, and concentrated under reduced pressure to yield 25.7 g (0.11 mol; 100%) of a 1.3 : 1 mixture of diastereomeric isomers of cyanohydrin **14a** as a pale yellow oil which was used in the next reaction.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.21 and 1.25 (2 t, J=7.2 Hz; total 3H): $OCH_2C\underline{H}_3$; 1.39 and 1.42 (2 d, J=5.5 Hz; total 3H): $OCH(OEt)C\underline{H}_3$; 2.1-2.3 (dt, 2H): H-3; 2.87 (t, J=7.1 Hz, 2H): H-4; 3.44-3.76 (m, 2H): $OC\underline{H}_2CH_3$; 4.26 and 4.48 (2 t, J=6.6 Hz; total 1H): H-2; 4.84 and 4.95 (2 q, J=5.3 Hz; total 1H): $OC\underline{H}(OEt)CH_3$; 7.22-7.39 (m, 5H): Ph H-2 - H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 14.9 (2 q): $OCH_2\underline{C}H_3$; 19.5 (q): $OCH(OEt)\underline{C}H_3$; 30.8 (2 t): C-3 or C-4; 35.1 and 35.5 (2 t): C-4 or C-3; 61.3 (2 t): $O\underline{C}H_2CH_3$; 62.2 and 62.5 (2 d): C-2; 98.8 and 100.6 (2 d): $O\underline{C}H(OEt)Me$; 118.6 and 119.3 (2 s): $\underline{C}N$; 126.4 (d): Ph C-4; 128.6 (4 d): Ph C-2, C-3, C-5, and C-6; 139.8 (2 s): Ph C-1.

4-Cyclohexyl-2-[(1-ethoxy)ethoxy]-butanenitrile (14b).

Hydrocyanation of 17 ml (0.11 mol) of 3-cyclohexylpropionaldehyde **12b**, according to the procedure described for **13a**, yielded 17.6 g of an oil containing cyanohydrin **13b** and some major impurity. In view of the limited stability of unprotected cyanohydrins the oil was used in the next reaction without purification.

^{1}H-NMR (90 MHz, $CDCl_3$): δ 0.5-1.9 (br m, 15H): H-3, H-4, and *c*-hex H-1 - H-6; 3.3-3.6 (br, 1H): OH; 4.35 (t, J=6.0 Hz, 1H): H-2;

According to the procedure described for **14a**, 17.6 g (105 mmol) of crude cyanohydrin **13b** was reacted with ethyl vinyl ether to give after work up 25.3 g of a yellow oil. Purification by column chromatography on 135 g of silicagel with petrol-EtOAc (15-1) as eluent yielded 22.0 g (92 mmol; 88%) of a partial purified 1 : 1 mixture of diastereomeric isomers of **14b** as an oil, which was used as such in the next reaction. A small sample was again chromatographed on silicagel with petrol-EtOAc (15-1) as eluent to analytical purity.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.7-1.85 (br m, 21H); 3.35-3.70 (m, 2H): $OC\underline{H}_2CH_3$; 4.20 and 4.37 (2 t, J=6.6 Hz; total 1H): H-2; 4.76 and 4.85 (2 q, J=5.1 Hz; total 1H): $OC\underline{H}(OEt)CH_3$. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 15.0 (2 q): $OCH_2\underline{C}H_3$; 19.4 (q): $OCH(OEt)\underline{C}H_3$; 26.3 (3 t); 31.0 (t); 31.5 (t); 32.1 (t); 33.0 (t); 37.0 (d): *c*-hex C-1; 60.8 and 61.3 (2 t): $O\underline{C}H_2CH_3$; 64.4 (d): C-2; 98.7 and 100.3 (2 d): $O\underline{C}H(OEt)Me$; 118.7 and 119.5 (2 s): $\underline{C}N$. MS: *m/e* (%) 212 (3), 96 (2), 83 (3), 81 (3), 74 (4), 73 (100), 67 (3), 55 (5), 45 (16), 41 (2). HRMS: calcd. (M^+-HCN): 212.1776; found: 212.1773.

2-[(1-Ethoxy)ethoxy]-octanenitrile (14c).

Hydrocyanation of 14.8 ml (0.11 mol) of heptanal **12c**, according to the procedure described for **13a**, yielded 14.8 g (0.10 mmol; 95%) of cyanohydrin **13c** as an oil, which was used in the next reaction without purification.

^{1}H-NMR (90 MHz, $CDCl_3$): δ 0.7-1.05 (br t, 3H): H-8; 1.05-1.65 (br m, 8H): H-4 - H-7; 1.65-2.0 (br m, 2H): H-3; 4.25 (br, 1H): OH; 4.45 (t, J=6.0 Hz, 1H): H-2.

According to the procedure described for **14a**, 14.7 g (0.10 mol) of cyanohydrin **13c** was protected as its ethoxyethyl ether, affording after work up 21.9 g (0.10 mol; 100%) of a 1.1 : 1 mixture of diastereomeric isomers of cyanohydrin **14c** as an oil, which was sufficiently pure to be used in the next reaction.

^{1}H NMR ($CDCl_3$, 90 MHz): δ 0.7-1.0 (br t, J=6 Hz, 3H): H-8; 1.0-2.2 (br m, 16H): H-3 - H-7, $OCH(OEt)C\underline{H}_3$, and $OCH_2C\underline{H}_3$; 3.2-3.8 (m, 2H): $OC\underline{H}_2CH_3$; 4.16 and 4.32 (2 t, J=6 Hz; total 1H): H-2; 4.73 and 4.80 (2 q, J=6 Hz; total 1H): $OC\underline{H}(OEt)CH_3$.

2-[(1-Ethoxy)ethoxy]-2-[(2,2-dimethoxy)ethyl]-4-phenyl-butanenitrile (15a).

A solution of 3.6 g (15.4 mmol) of **14a** in 10 ml of anhydrous THF and 20 ml of HMPA was added dropwise in 10 min to 10 ml of a 2M solution of lithium diisopropylamide in THF-hexanes while stirring under a nitrogen atmosphere at -60°C. After 30 min the reaction mixture was treated dropwise with a solution of 3.4 g (20 mmol) of bromoacetaldehyde dimethylacetal in 10 ml of THF. Stirring at -60°C was continued for 2 h while the progress of the reaction was monitored by glc-analysis. The reaction was quenched by addition of 100 ml of water and the resulting mixture was extracted with four 50 ml-portions of ether. The combined extracts were washed with two 50 ml-portions of brine, dried with $MgSO_4$, and concentrated under reduced pressure to give 6.0 g of a yellow oil. Purification *via* chromatography on 90 g of silicagel with petrol-EtOAc (10-1) afforded 4.0 g (12.5 mmol; 81 %) of **15a** as a 1 : 1 mixture of diastereomeric isomers.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.22 (2 q, J=6.3 Hz, 3H): $OCH_2C\underline{H}_3$; 1.37 and 1.39 (2 d, J=3.9 Hz; total 3H): $OCH(OEt)C\underline{H}_3$; 2.00-2.38 (m, 4H): H-1' and H-3; 2.70-2.95 (m, 2H): H-4; 3.35-3.40 (m s, 6H): $OC\underline{H}_3$; 3.57 and 3.65 (2 q, J=6.4 Hz; total 2H): $OC\underline{H}_2CH_3$; 4.65 and 4.71 (2 t, J=5.5 Hz; total 1H): H-2'; 5.05-5.21 (m, 1H): $OC\underline{H}(OEt)Me$; 7.15-7.40 (m, 5H): Ph H-2 - H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 15.1 (q): $OCH_2\underline{C}H_3$; 20.9 (q): $OCH(OEt)\underline{C}H_3$; 30.2 (t); 40.6, (2 t) and 41.2 (2 t); 53.1 (3 q): $O\underline{C}H_3$; 60.8 (2 t): $O\underline{C}H_2CH_3$; 73.9 (s): C-2; 98.2 (2 d): $O\underline{C}H(OEt)Me$; 100.7 (2 d): C-2'; 119.3 (2 s): $\underline{C}N$; 126.2 (d): Ph C-4; 128.4 (2 d): Ph C-2, C-3, C-5, and C-6; 140.5 (2 s): Ph C-1. MS: *m/e* (%) 295 (0.4), 289 (0.2), 282 (0.3), 281 (1.6), 200 (18), 199 (28), 168 (14), 167 (21), 91 (34), 89 (13), 75 (68), 73 (100), 59 (15). HRMS: calcd. (M^+-MeOH): 289.1678; found: 289.1684.

4-Cyclohexyl-2-[(1-ethoxy)ethoxy]-2[(2,2-dimethoxy)ethyl]-butanenitrile (15b).

Alkylation of 5.0 g (20.9 mmol) of **14b** according to the procedure described for **14a** yielded, after purification by chromatography on silicagel with petrol-EtOAc (gradient elution, 99-1 to 97-3) as eluent, 4.4 g (13.5 mmol; 64%) of a 1 : 1 mixture of diastereoisomers **15b** as a colourless oil, which was used as such in the next reaction. A small sample was purified by column chromatography for analytical purposes.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.62-1.10 (br m); 1.10-1.30 (br m); 1.41-1.80 (br m); 1.91 (t, J=4.7 Hz, 1H) and 1.97 (d, J=5.2 Hz, 1H): H-2'; 3.15-3.20 (m, 6H): $OC\underline{H}_3$; 3.27-3.57 (m, 2H): $OC\underline{H}_2CH_3$; 4.46 and 4.53 (2 t, J=5.2 Hz; total 1H): H-2'; 4.87 and 4.95 (2 q, J=4.9 Hz; total 1H): $OC\underline{H}(OEt)Me$. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 14.8 (2 q): $OCH_2\underline{C}H_3$; 20.6 and 20.9 (2 q): $OCH(OEt)\underline{C}H_3$; 26.1 (3 t); 30.9 (2 t); 32.9 (2 t); 36.0 (t); 36.6 (t); 37.3 (2 d): *c*-hex C-1; 40.3 and 40.9 (2 t); 52.8 (4 q): $O\underline{C}H_3$; 60.2 and 60.5 (2 t): $O\underline{C}H_2CH_3$; 74.1 (2 s): C-2; 97.6 (d): C-2'; 100.4 (2 d): $O\underline{C}H(OEt)Me$; 119.2 (2 s): $\underline{C}N$. MS: *m/e* (%) 312 (0.1), 254 (11), 222 (14), 220 (5), 206 (17), 75 (89), 73 (100), 59 (12), 55 (7), 45 (27). HRMS: calcd. (M^+-CH_3): 312.2175; found: 312.2176.

2-[(1-Ethoxy)ethoxy]-2[(2,2-dimethoxy)ethyl]-octanenitrile (15c).

Alkylation of 3.3 g (15.4 mmol) of **14c** according to the procedure described for **14a** yielded after purification *via* chromatography on silicagel with petrol-EtOAc (6-1) as eluent 4.2 g (14.0 mmol; 91%) of a 1 : 1 mixture of diastereoisomers **15c** as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.75-0.90 (br, 3H): H-8; 1.05-1.50 (br m, 14H); 1.70-1.95 (br m) and 2.01-2.12 (m; total 4H): H-1' and H-3; 3.29-3.36 (6 s, 6H): $OC\underline{H}_3$; 3.40-3.75 (m, 2H): $OC\underline{H}_2CH_3$; 4.51, 4.59, and 4.65 (3 t, J=5.4 Hz, total 1H): H-2'; 5.02 and 5.04 (2 q, J=5.1 Hz, total 1H): $OC\underline{H}(OEt)Me$. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 14.0 and 15.1 (2 q): $OCH_2\underline{C}H_3$; 20.9 and 21.2 (2 q): $OCH(OEt)\underline{C}H_3$; 22.5 (t); 23.6 and 23.8 (2 t); 29.0 and 29.1 (2 t); 30.6 (t); 31.5 (t); 38.7 and 39.3 (2 t); 40.6 and 41.2 (2 t); 53.0, 53.1, 53.2, and 53.9 (4 q): $O\underline{C}H_3$; 60.5 and 60.9 (2 t): $O\underline{C}H_2CH_3$; 74.3 (s): C-2; 97.9, 100.6, 100.8, and 103.0 (4 d): C-2' and $O\underline{C}H(OEt)Me$; 119.5 (s): $\underline{C}N$. MS (CI): *m/e* (%): 302 (68), 270 (28), 258 (26), 212 (50), 198 (28), 194 (100), 180 (93), 171 (26). HRMS (CI): calcd. (M+H): 302.2321; found: 302.2328.

3-[(1-Ethoxy)ethoxy]-1,1-dimethoxy-5-phenyl-pentane-3-carbaldehyde (16a).

To an ice-cold solution of 6.7 mmol of lithium aluminumhydride in 20 ml of anhydrous ether (prepared by dilution of a commercial 1.0M solution of $LiAlH_4$ in ether) was added dropwise 1.0 ml (10.0 mmol) of anhydrous ethyl acetate in approx. 5 min while stirring vigorously. The resulting white slurry was stirred for another 30 min before a solution of 1.3 g (4.0 mmol) of nitrile **15a** in 10 ml of ether was added dropwise. Stirring at 0°C was continued, while the progress of the reaction was monitored *via* glc-analysis. After complete disappearance of the starting material (after approx. 1.5 h), the mixture was diluted with 50 ml of ether and the reaction was quenched by addition of 3.5 g (10.8 mmol) of Glaubers' salt. The resulting mixture was stirred at room temperature for 1 h, dried with $MgSO_4$, filtered through a pad of hyflo and concentrated under reduced pressure to give 1.23 g of an oil. The residue was taken up in EtOAc (100 ml), 30 g of silicagel was added and the mixture was stirred overnight at room temperature. The resulting slurry was filtered and concentrated to give 1.21 g of an oil. The crude product was purified by chromatography on 30 g of silicagel with petrol-EtOAc (95-5) as eluent to yield 830 mg (2.6 mmol; 64%) of **16a** as a pale-yellow oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.14 and 1.17 (2 t, J=7.0 Hz; total 3H): $OCH_2C\underline{H}_3$; 1.39 and 1.40 (2 d, J=5.1 Hz; total 3H): $OCH(OEt)C\underline{H}_3$; 1.85-2.25 (m, 4H): H-2 and H-4; 2.45-2.85 (m, 2H): H-5; 3.34-3.56 (m, 8H): $OC\underline{H}_2CH_3$ and $OC\underline{H}_3$ [δ 3.32 and 3.36 (2 s)]; 4.62 (dd, J=6.1, 4.7 Hz) and 4.68 (t, J=5.1 Hz; total 1H): H-1; 4.78 (q, J=5.1 Hz, 0.67 H) and 4.88 (q, J=5.1 Hz, 0.33 H): $OC\underline{H}(OEt)Me$; 7.15-7.35 (m, 5H): Ph H-2 - H-6; 9.51 (s, 0.67H) and 9.57 (s, 0.33H): $C\underline{H}O$. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 14.9 (2 q): $OCH_2\underline{C}H_3$; 20.4 (q): $OCH(OEt)\underline{C}H_3$; 28.6 and 29.1 (2 t); 32.0 (t); 35.2 and 35.4 (2 t); 38.6 (t); 52.6 (2 q) and 53.3 (2 q): $O\underline{C}H_3$; 60.5 and 60.7 (2 t); 81.3 and 82.2 (2 s): C-3; 95.4 and 95.7 (2 d): $O\underline{C}H(OEt)Me$; 100.7 and 101.1 (2 d): C-1; 126.0, 128.2, and 128.4 (3 d): Ph C-2 - C-6; 141.5 (2 s): Ph C-1; 202.1 and 202.4 (2 s): $\underline{C}HO$.

5-Cyclohexyl-3-[(1-ethoxy)ethoxy]-1,1-dimethoxy-pentane-3-carbaldehyde (16b).

According to the procedure described for **16a**, 1.0 g (3.0 mmol) of nitrile **15b** was reduced with 9.0 mmol of $LiAlH(OEt)_3$ in ether to give, after work-up and hydrolysis of the intermediate product on silicagel, 911 mg of a yellow oil. Purification of the crude product by chromatography on 20 g of silicagel with petrol-EtOAc (95-5) as eluent yielded 634 mg (1.9 mmol; 64%) of a 1 : 1 diastereomeric mixture **16b** as an oil.

^{1}H-NMR ($CDCl_3$, 90 MHz): δ 0.4-2.2 (br); 3.1-3.7 (br m, 8H): $OC\underline{H}_3$ [δ 3.3 (s)] and $OC\underline{H}_2CH_3$; 4.4-4.9 (br m, 1H): $OC\underline{H}(OEt)Me$; 9.4 (s, 0.5H) and 9.5 (s, 0.5H): $C\underline{H}O$.

2-[(1-Ethoxy)ethoxy]-2-[(2,2-dimethoxy)ethyl]-4-phenyl-butanol (17a).

To an ice-cold, stirred mixture of 60 mg (1.6 mmol) of lithium aluminumhydride and 5 ml of anhydrous ether was added dropwise a solution of 784 mg (2.4 mmol) of **16a** in 10 ml of ether. After 15 min the reaction was quenched by addition of 1.0 g (3.1 mmol) of Glaubers' salt. The resulting slurry was stirred at room temperature for 30 min, dried with $MgSO_4$, filtered through a pad of hyflo and concentrated under reduced pressure to give 813 mg of an oil. Purification by chromatography on 20 g of silicagel with petrol-EtOAc (gradient elution, 95-5 to 90-10) as eluent afforded 726 mg (2.2 mmol; 92%) of **17a** as a pale-yellow oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.22 (2 t, J=7.1 Hz, 3H): $OCH_2C\underline{H}_3$; 1.34 (d, J=5.3 Hz, 3H): $OCH(OEt)C\underline{H}_3$; 1.75-1.98 (m, 4H): H-3 and H-1'; 2.59-2.74 (m, 2H): H-4; 3.36 (3 s, 6H): $OC\underline{H}_3$; 3.40-3.80 (m, 5H): H-1, OH and $OC\underline{H}_2CH_3$; 4.61 (t, J=4.8 Hz, 1H): H-2'; 4.99 (q, J=5.2 Hz, 1H): $OC\underline{H}(OEt)OMe$; 7.10-7.35 (m, 5H): Ph H-2 - H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 15.2 (q): $OCH_2\underline{C}H_3$; 20.4 (q): $OCH(OEt)\underline{C}H_3$; 29.6 (t); 34.5 and 35.6 (2 t); 37.4 and 37.8 (2 t); 52.7 (2 q): $O\underline{C}H_3$; 59.0 (2 t): $O\underline{C}H_2CH_3$; 65.9 and 66.4 (2 t): C-1; 79.5 and 79.8 (2 s): C-2; 93.2 and 93.8 (2 d): $O\underline{C}H(OEt)Me$; 101.6 and 101.8 (2 d): C-2'; 125.7 (2 d) and 128.3 (d): Ph C-2 - C-6; 142.5 (s): Ph C-1.

4-Cyclohexyl-2-[(1-ethoxy)ethoxy]-2-[(2,2-dimethoxy)ethyl]-butanol (17b).

According to the procedure described for **17a**, 592 mg (1.8 mmol) of aldehyde **16b** was reduced with $LiAlH_4$ to yield 572 mg (1.7 mmol; 96%) of **17b** as a yellow oil. The crude product was sufficiently pure to be used in the next reaction without purification.

2-Methoxy-4-(2-phenylethyl)-tetrahydrofuran-4-ol (18a).

A solution of 491 mg (1.5 mmol) of **17a** and 29 mg (0.15 mmol) of *p*-toluenesulfonic acid monohydrate in 25 ml of anhydrous methanol was stirred at room temperature for 20 h. The purple reaction mixture was concentrated under reduced pressure and the residue was taken up in 50 ml of ether, washed with 10 ml of saturated aqueous sodium bicarbonate solution and 10 ml of brine, dried with $MgSO_4$ and concentrated under reduced pressure to give 297 mg of an oil, consisting of both C-2 epimers of **18a** in a ratio of 1 : 1.6 (least polar isomer : most polar isomer). The crude product was sufficiently pure to be used as such in subsequent reactions. Both isomers could be separated by careful chromatography on silicagel, using petrol-EtOAc (gradient elution, 98-2 to 90-10) as eluent.

Least polar isomer: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.88-1.97 (m, 3H): H-3α [δ 1.92 (dd, J=13.3, 4.4 Hz)] and H-1'; 2.08 (d, J=13.3 Hz, 1H): H-3β; 2.74-2.82 (m, 2H): H-2'; 3.39 (s, 3H): $OC\underline{H}_3$; 3.55 (s, 1H): OH; 3.82 (d, J=9.3 Hz, 1H) and 3.99 (d, J=9.3 Hz, 1H): H-5; 5.07 (d, J=4.4 Hz, 1H): H-2; 7.11-7.33 (m, 5H): Ph H-2 - H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 31.0 (t) and 39.5 (t): C-1' and C-2'; 45.2 (t): C-3; 54.8 (q): $O\underline{C}H_3$; 79.3 (s): C-4; 80.3 (t): C-5; 105.4 (d): C-2; 125.8, 128.3, and 128.4 (3 d): Ph C-2 - C-6; 142.1 (s): Ph C-1.

Most polar isomer: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.85-2.10 (m, 4H): H-3α, H-1' and OH; 2.28 (ddd, J=14.4, 5.8, 1.0 Hz, 1H): H-3β; 2.75 (d, J=10.5 Hz) and 2.78 (dd, J=10.4, 1.1 Hz; total 2H): H-2'; 3.37 (s, 3H): $OC\underline{H}_3$; 3.74 (2 s, 3H): H-5; 5.18 (dd, J=5.8, 3.3 Hz, 1H): H-2; 7.14-7.33 (m, 5H): Ph H-2 - H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 30.9 (t) and 39.4 (t): C-1' and C-2'; 47.3 (t): C-3; 55.3 (q): $O\underline{C}H_3$; 76.7 (t): C-5; 81.0 (s): C-4; 105.3 (d): C-2; 126.0, 128.3, and 128.5 (3 d): Ph C-2 - C-6; 141.8 (s): Ph C-1.

4-(2-Cyclohexylethyl)-2-methoxy-tetrahydrofuran-4-ol (18b).

According to the procedure described for **18a** 572 mg (1.7 mmol) of **17b** was cyclized to give 371 mg of a yellow oil, consisting of both C-2 epimers of **18b** in a 1 : 1.6 ratio. Careful chromatography on 10 g of silicagel with petrol-EtOAc (gradient elution, 98-2 to 90-10) afforded 111 mg (0.49 mmol; 29% yield) of the least polar isomer of (**18b**) and 203 mg (0.89 mmol, 52%) of the most polar isomer.

Least polar isomer: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.70-0.95 (br m, 2H), 1.02-1.48 (br m, 7H) and 1.52-1.75 (br m, 6H): H-1', H-2', and *c*-hex H-1 - H-6; 1.86 (dd, J=13.4, 4.6 Hz, 1H) and 1.99 (d, J=13.4 Hz, 1H): H-3; 3.34 (s, 3H): $OC\underline{H}_3$; 3.41 (s, 1H): OH; 3.77 (d, J=9.2 Hz, 1H) and 3.93 (d, J=9.2 Hz, 1H): H-5; 5.02 (d, J=4.6 Hz, 1H): H-2. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 26.4 (t); 26.7 (t); 32.2 (t); 33.3 (t); 34.9 (t); 38.1 (d): *c*-hex C-1; 45.2 (t): C-3; 54.8 (q): $O\underline{C}H_3$; 80.2 (s): C-4; 80.3 (t): C-5; 105.6 (d): C-2.

Most polar isomer: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.70-1.0 (br m, 2H), 1.02-1.40 (br m, 7H) and 1.51-1.77 (br m, 6H): H-1', H-2' and *c*-hex H-1 - H-6; 1.83 (dd, J=14.3, 3.3 Hz, 1H): H-3α; 2.06 (br, 1H): OH; 2.20 (dd, J=14.3, 5.8 Hz, 1H): H-3β; 2.98 (s, 3H): $OC\underline{H}_3$; 3.70 (s, 2H): H-5; 5.14 (dd, J=5.8, 3.3 Hz, 1H): H-2. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 26.3 (t); 26.6 (t); 32.0 (t); 33.3 (2 t); 34.9 (t); 38.0 (d): *c*-hex C-1; 47.1 (t): C-3; 55.3 (q): $O\underline{C}H_3$; 76.8 (t): C-5; 81.3 (s): C-4; 105.5 (d): C-2.

3-[(1-Ethoxy)ethoxy]-3-[(2,2-dimethoxy)ethyl]-5-phenyl-pentan-2-one (25a).

To an ice-cold, stirred solution of 2.15 g (6.7 mmol) of **15a** in 50 ml of anhydrous ether was added dropwise *via* syringe 6.0 ml (10.7 mmol; 1.6 eq) of a 1.6M solution of methyllithium in ether. Stirring was continued for 90 min while the reaction was monitored *via* tlc-analysis. The reaction was quenched by addition of 25 ml of saturated aqueous ammonium chloride solution. The organic layer was separated and the aqueous layer was extracted with three 25 ml-portions of ether. The combined organic layers were washed with 25 ml of brine, dried with $MgSO_4$, and concentrated under reduced pressure to give 2.26 g (6.5 mmol) of imine **24a**.

^{1}H NMR ($CDCl_3$, 90 MHz): δ 1.0-1.3 (2 t, J=6.0 Hz, 3H): $OCH_2C\underline{H}_3$; 1.3-1.5 (d, J=6.0 Hz, 3H): $OCH(OEt)C\underline{H}_3$; 1.7-2.5 (br m, 9H): H-1, H-4, H-5, and H-1'; 3.1-3.7 (m, 8H): $OC\underline{H}_2CH_3$ and $OC\underline{H}_3$ [δ 3.25-3.30 (3 s, 6H)]; 4.2 and 4.5 (2 t, J=4.5 Hz, 1H): H-2'; 4.7-5.1 (m, 1H): $OC\underline{H}(OEt)Me$; 6.9-7.4 (br m, 5H): Ph H-2 - H-6; 9.3-10.2 (br, 1H): $C(=N\underline{H})Me$. IR ($CHCl_3$) : ν 1640 cm^{-1}.

A mixture of 2.26 g (6.5 mmol) of intermediate imine **24a** in 50 ml of THF and 50 ml of a 10% aqueous ammonium chloride solution was stirred at 60-70°C until tlc-analysis indicated complete hydrolysis of the imine. After 24 h the mixture was extracted with three 25 ml-portions of ether and the combined extracts were washed with 25 ml of brine, dried with $MgSO_4$, and concentrated to yield 2.25 g of a yellow oil. The crude product was purified *via* chromatography on 50 g of silicagel with petrol-EtOAc (5-1) as eluent, affording 1.81 g (5.3 mmol; 79%) of ketone **25a** as an oil.

^1H NMR ($CDCl_3$, 200 MHz, selected peaks): δ 1.12 and 1.16 (2 t, J=6.5 Hz, 3H): $OCH_2C\underline{H}_3$; 1.38 and 1.39 (2 d, J=5.1 Hz, 3H): $OCH(OEt)C\underline{H}_3$; 1.8-2.6 (m, 9H): H-1 [δ 2.24 and 2.26 (2 s, 3H)], H-4, H-5, and H-1'; 3.25, 3.26, 3.28 and 3.30 (4 s, 6H): $OC\underline{H}_3$; 3.42 and 3.46 (2 q, J=7.5 Hz, 2H): $OC\underline{H}_2CH_3$; 4.39 and 4.70 (2 t, J=5.6 Hz, 1H): H-2'; 4.76-4.90 (m, 1H): $OC\underline{H}(OEt)Me$; 7.10-7.29 (m, 5H): Ph H-2 - H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 15.0 (q): $OCH_2\underline{C}H_3$; 20.8 (q): $OCH(OEt)\underline{C}H_3$; 26.6 (q): C-1; 29.2 and 29.4 (2 t); 35.6, 37.2, 37.7, and 38.6 (4 t); 51.8, 52.6, and 53.1 (3 q): $O\underline{C}H_3$; 60.8 and 61.0 (2 t): $O\underline{C}H_2CH_3$; 84.2 and 84.6 (2 s): C-3; 95.3 and 95.7 (2 d): $O\underline{C}H(OEt)Me$; 101.0 (d): C-2'; 125.8 and 126.0 (2 d): Ph C-4; 128.1, 128.2, 128.3, and 128.4 (4 d): Ph C-2, C-3, C-5, and C-6; 141.5 and 142.0 (2 s): Ph C-1; 211.1 (s): C-2. IR ($CHCl_3$) : ν 1710 cm^{-1}. MS (EI): *m/e* (%) 295 (2), 223 (7), 205 (15), 191 (18), 133 (12), 105 (9), 91 (20), 75 (21), 73 (100), 45 (40), 43 (9). MS (CI): *m/e* (%) 308 (10), 307 (100), 294 (6), 293 (31), 263 (7), 235 (9), 231 (8), 217 (4), 185 (5). HRMS (EI): calcd. (M^+-CH_3CO): 295.1909; found: 295.1909.

5-Cyclohexyl-3-[(1-ethoxy)ethoxy]-3-[(2,2-dimethoxy)ethyl]-pentan-2-one (25b).

Addition of methyllithium to 1.52 g (4.6 mmol) of **15b** and subsequent hydrolysis of the intermediate imine according to the procedure described for **25a** yielded 1.14 g (3.3 mmol; 71%) of ketone **25b** as an oil after purification *via* chromatography on silicagel with petrol-EtOAc (gradient elution, 7-1 to 5-1) as eluent.

^1H NMR ($CDCl_3$, 200 MHz, major peaks): δ 0.65-1.30 (br m, 14H) and 1.50-1.70 (br, 7H); 1.96-2.06 (m, 1H) and 2.12 (d, J=7.2 Hz, 1H): H-1'; 2.11 and 2.15 (2 s, 3H): H-1; 3.17, 3.19, 3.20, and 3.24 (4 s, 6H): $OC\underline{H}_3$; 3.30-3.41 (m, 2H): $OC\underline{H}_2CH_3$; 4.28 (t, J=5.5 Hz, 0.5H): C-2'; 4.58-4.75 (m, 1.5H): C-2' and $OC\underline{H}(OEt)Me$). ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 14.8 and 14.9 (2 q): $OCH_2\underline{C}H_3$; 20.7 (q): $OCH(OEt)\underline{C}H_3$), 26.2 and 26.5 (2 t); 29.9, 30.0, and 30.2 (3 t); 32.7, 33.1, and 33.3 (3 t); 37.3 and 38.4 (2 t); 37.9 and 38.1 (2 d): *c*-hex C-1; 51.8, 52.2, 52.8, and 53.4 (4 q): $O\underline{C}H_3$; 60.8 and 61.0 (2 t): $O\underline{C}H_2CH_3$; 83.9 and 84.7 (2 s): C-3; 95.2 and 95.5 (2 d): C-2'; 101.0 (2 d): $O\underline{C}H(OEt)Me$; 211.1 and 211.4 (2 s): C-2. IR ($CHCl_3$): ν 1705 cm^{-1}. MS: *m/e* (%) 229 (14), 197 (20), 139 (18), 75 (17), 73 (100), 45 (20). HRMS: calcd. (M^+-OCH_3): 313.2379; found: 313.2387.

3-[(1-Ethoxy)ethoxy]-3-[(2,2-dimethoxy)ethyl]-nonan-2-one (25c).

Addition of methyllithium to 3.9 g (13.0 mmol) of **15c** and subsequent hydrolysis of the intermediate imine according to the procedure described for **25a** yielded after purification *via* chromatography on silicagel with petrol-EtOAc (6-1) as eluent 3.15 g (9.9 mmol; 76%) of ketone **25c** as an oil.

^1H NMR ($CDCl_3$, 200 MHz): δ 0.7-0.9 (br, 3H): H-9; 0.9-1.35 (m, 12H), 1.4-1.8 (m, 2H), and 1.8-2.2 (m, 4H): H-4 - H-8, H-1', $OCH(OEt)C\underline{H}_3$, and $OCH_2C\underline{H}_3$; 2.08 and 2.11 (2 s, 3H): H-1; 3.13, 3.15, 3.17, and 3.20 (4 s, 6H): $OC\underline{H}_3$; 3.33 and 3.36 (2 dq, J=6.5 Hz, 2H): $OC\underline{H}_2CH_3$; 4.26 (t, J=5.0 Hz, 0.5H): C-2'; 4.55-4.72 (m, 1.5H): C-2' and $OC\underline{H}(OEt)Me$. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 13.9 (q): C-9; 14.8 and 14.9 (2 q): $OCH_2\underline{C}H_3$; 20.7 (q): $OCH(OEt)\underline{C}H_3$; 22.4, 22.5, 22.6, and 22.8 (4 t); 26.4 and 26.5 (2 q): C-1; 29.4 and 29.6 (2 t); 31.4 and 31.6 (2 t); 33.3 (t); 35.2 (t); 37.6 (t); 38.6 (t); 51.8, 52.2, 52.8, and 53.2 (4 q): $O\underline{C}H_3$; 60.5 and 60.9 (2 t): $O\underline{C}H_2CH_3$; 84.2 and 84.8 (2 s): C-3; 95.1 and 95.5 (2 d): $O\underline{C}H(OEt)Me$; 101.0 (d): C-2'; 211.4 (s): C-2. IR ($CHCl_3$): ν 1710 cm^{-1}. MS: *m/e* (%) 287 (0.2), 203 (14), 197 (15), 185 (11), 171 (25), 113 (26), 75 (25), 73 (100), 45 (55), 43 (16). HRMS: calcd. (M^+-OCH_3): 287.2222; found: 287.2221.

3-[(1-Ethoxy)ethoxy]-3-[(2,2-dimethoxy)ethyl]-2-methyl-5-phenyl-pentan-2-ol (26a).

a. Addition of MeLi. To an ice-cold, stirred solution of 4.49 g (13.3 mmol) of ketone **25a** in 100 ml of anhydrous ether in a nitrogen atmosphere was added dropwise *via* syringe 10 ml (16 mmol) of an 1.6M solution of MeLi in ether. After 90 min 50 ml of brine was added and the organic layer was separated. The aqueous layer was extracted with three 25 ml-portions of ether. The combined ether extracts were washed with 25 ml of brine, dried with $MgSO_4$ and concentrated under reduced pressure to give 4.26 g of an oil. Careful chromatography on 100 g of silicagel with petrol-EtOAc (gradient elution, 10-1 to 3-1) as eluent yielded, in order of elution, 2.09 g (6.2 mmol, 46%) of the starting material **25a**, 0.58 g of a mixed fraction **25a/26a,** and 1.55 g (4.4 mmol, 33%) of the desired alcohol **26a** as an oil.

b. Addition of $MeCeCl_2$. A solution of this cerium reagent was prepared *in situ* according to the procedures described by Imamoto *et al* and Greeves. Pulverised $CeCl_3 \cdot 7H_2O$ (5.9 g, 15.8 mmol) was heated at 100°C under high vacuum (0.01 mm Hg) for 1 h in a roundbottom flask. The resulting pre-dried solid was finely ground in a mortar and then further dried at 140°C under high vacuum for 2 h to yield anhydrous $CeCl_3$ as a free-flowing white powder. After slow cooling to room temperature in a dry argon atmosphere, the flask was placed on an ice-bath and 40 ml of ice-cold anhydrous THF was added *via* syringe and the resulting suspension was stirred overnight at room temperature under argon. Next, the milky suspension was soniphicated on an ultrasonic bath for 1.5 h. The ultrasonic bath was removed and the $CeCl_3$-suspension was cooled to -78°C while stirring magnetically. *Via* syringe, 9.5 ml (15.2 mmol) of a 1.6M solution of MeLi in ether was added dropwise and after 1 h the mixture was treated dropwise with a solution of 1.69 g (5.0 mmol) of ketone **25a** in 35 ml of anhydrous THF. Stirring at -78°C was continued while the progress of the reaction was monitored by tlc-analysis. After complete conversion of the starting ketone (approx. 30 min) the reaction was quenched by addition of 15 ml of saturated NH_4Cl solution and the resulting mixture was extracted with three 50 ml-portions of ether. The

combined extracts were washed with two 25 ml-portions of brine, dried with $MgSO_4$ and concentrated under reduced pressure to give 1.76 g (4.9 mmol, 99%) of alcohol **26a** as an oil.
^1H NMR ($CDCl_3$, 200 MHz): δ 1.16-1.37 (m, 12H): $C(OH)(C\underline{H}_3)_2$, $OCH(OEt)C\underline{H}_3$ and $OCH_2C\underline{H}_3$; 1.68-2.42 (m, 4H) and 2.55-2.87 (br m; 2H): H-1', H-4, and H-5; 3.32-3.35 (3 s, 6H): $OC\underline{H}_3$; 3.40-3.65 (m, 2H): $OC\underline{H}_2CH_3$; 4.30 and 4.41 (2 s, 1H): OH; 4.65-4.73 (m, 1H): $C\underline{H}(OMe)_2$; 5.00-5.12 (m, 1H): $OC\underline{H}(OEt)Me$; 7.10-7.35 (m, 5H): Ph H-2 - H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 15.0 (q): $OCH_2\underline{C}H_3$; 20.3 (q): $OCH(OEt)\underline{C}H_3$; 25.5 and 25.6 (2 q): $C(OH)(\underline{C}H_3)_2$; 30.8 (t); 34.5 and 35.2 (2 t); 37.7 and 38.0 (2 t); 51.5, 52.5, 52.8, and 53.7 (4 q): $O\underline{C}H_3$; 58.6 and 58.8 (2 t): $O\underline{C}H_2CH_3$; 75.3 (s): C-2; 84.5 (s): C-3; 94.0 and 94.4 (2 d): $O\underline{C}H(OEt)Me$; 101.7 and 102.7 (2 d): C-2'; 125.7 (d): Ph C-3 - C-5; 128.3 (d): Ph C-2 and C-6; 143.2 (s): Ph C-1. MS (EI): *m/e* (%) 295 (0.07), 233 (8), 191 (26), 133 (24), 105 (11), 91 (20), 75 (52), 73 (100), 59 (13), 45 (37), 43 (7). MS (CI): *m/e* (%): 307 (6), 293 (5), 291 (14), 278 (7), 277 (40), 261 (7), 247 (21), 234 (16), 233 (100), 219 (26), 201 (14). HRMS: calcd. (M^+-$C(CH_3)_2OH$): 295.1909; found: 295.1903.

5-Cyclohexyl-3-[(1-ethoxy)ethoxy]-3-[(2,2-dimethoxy)ethyl]-2-methyl-pentan-2-ol (26b).
Addition of methyllithium to 1.12 g (3.3 mmol) of ketone **25b** was carried out according to the procedure described for **26a**. Purification *via* chromatography on 40 g of silicagel with petrol-EtOAc (gradient elution, 10-1 to 3-1) as eluent afforded, in order of elution: 514 mg (1.5 mmol, 45%) of starting ketone **25b** and 493 mg (1.4 mmol; 41%) of alcohol **26b** as an oil.
^1H NMR ($CDCl_3$, 200 MHz): δ 0.72-1.0 (br, 3H); 1.0-1.4 (m, 14H); 1.53-1.82 (br, 9H); 1.85-2.35 (m, 3H); 3.30 (ms, 6H): $OC\underline{H}_3$; 3.38-3.68 (m, 2H): $OC\underline{H}_2CH_3$; 4.30 and 4.35 (2 s, 1H): OH; 4.57 (2 t, J=4.7 Hz, 1H): $C\underline{H}(OMe)_2$; 4.93 and 4.97 (dq, J=5.2 Hz, 1H): $OC\underline{H}(OEt)Me$. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 15.1 (q): $OCH_2\underline{C}H_3$; 20.3 and 20.4 (2 q): $OCH(OEt)\underline{C}H_3$; 25.5 and 25.7 (2 q): $C(OH)(\underline{C}H_3)_2$; 26.4 and 26.7 (2 t); 29.4 (t); 31.7 and 31.9 (2 t); 32.5 (t); 33.4 and 33.5 (2 t); 35.2 (t); 38.6 (t); 38.9 and 39.0 (2 d): *c*-hex C-1; 51.4, 52.4, 52.8, and 53.3 (4 q): $O\underline{C}H_3$; 58.7 (t): $O\underline{C}H_2CH_3$; 75.3 (s): C-2; 84.8 (s): C-3; 94.1 and 94.4 (2 d): $O\underline{C}H(OEt)Me$; 101.7 and 102.6 (2 d): C-2'. IR ($CHCl_3$): ν 3350 cm^{-1} (br).

3-[(1-Ethoxy)ethoxy]-3-[(2,2-dimethoxy)ethyl]-2-methyl-nonan-2-ol (26c).
Addition of methyllithium to 3.0 g (9.4 mmol) of **25c** was carried out according to the procedure described for **26a**. Purification of the crude product (3.0 g) *via* chromatography on 100 g of silicagel with petrol-EtOAc (gradient elution, 10-1 to 3-1) as eluent afforded, in order of elution: 1.24 g (3.9 mmol, 41%) of the starting ketone **25c**, 310 mg of a mixed fraction of **25c** and **26c**, and 1.29 g (3.9 mmol; 41%) of alcohol **26c** as an oil.
^1H NMR ($CDCl_3$, 200 MHz): δ 0.75-0.90 (br t, J=6.6 Hz, 3H): H-9; 1.05-1.45 (m, 19H); 1.45-2.30 (m, 5H); 3.25 (4 s, 6H): $OC\underline{H}_3$; 3.25-3.60 (m, 2H): $OC\underline{H}_2CH_3$; 4.27 (br, 1H): OH; 4.52-4.56 (m, 1H): $C\underline{H}(OMe)_2$; 4.90 and 4.95 (2 q, J=5.0 Hz, 1H): $OC\underline{H}(OEt)Me$. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 14.0 (q): C-9; 15.0 (q): $OCH_2\underline{C}H_3$; 20.2 and 20.3 (2 q): $OCH(OEt)\underline{C}H_3$; 22.6 (t); 24.3 and 24.4 (2 t); 25.3 and 25.6 (2 q): $C(OH)(\underline{C}H_3)_2$; 30.4 (t); 31.7 and 32.0 (2 t); 35.1 and 35.2 (2 t); 38.3 (t); 51.2, 52.2, 52.7, and 53.2 (4 q): $O\underline{C}H_3$; 58.6 (t): $O\underline{C}H_2CH_3$; 75.2 (s): C-2; 84.5 and 84.7 (2 s): C-3; 94.0 and 94.3 (2 d): $O\underline{C}H(OEt)Me$; 101.6 and 102.5 (2 d): C-2'. MS: *m/e* (%) 213 (23), 171 (32), 113 (43), 75 (48), 73 (100), 45 (28). HRMS: calcd. (M^+-H_2O-$OCH(OEt)Me$): 227.2011; found: 227.2012. Anal: calcd. for $C_{18}H_{38}O_5$: C, 64.63; H, 11.45; found: C, 64.36; H, 11.57.

Cyclization of alcohol 26a. A solution of 1.71 g (4.8 mmol) of alcohol **26a** and 10 mg (0.06 mmol) of *p*-toluenesulfonic acid monohydrate in 25 ml of methanol was stirred overnight at room temperature. The reaction mixture was poured into 10 ml of saturated aqueous sodium bicarbonate solution and extracted with three 25 ml-portions of ether. The combined extracts were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure to give 1.03 g of an oil. Purification *via* chromatography on 25 g of silicagel with petrol-EtOAc (6-1) as eluent afforded 462 mg of an inseparable mixture, containing the least polar isomer of **28a** and both diastereomers of the unwanted cyclization product **27a** in a ratio of 2 : 1. Further elution yielded 725 mg (2.9 mmol; 60 %) of the most polar isomer of **28a**.

4-[(2,2-Dimethoxy)ethyl]-2,5,5-trimethyl-4-(2-phenylethyl)-1,3-dioxolane (27a).
^1H NMR ($CDCl_3$, 200 MHz): δ 1.05-1.40 (m s, 9H): $OCH(C\underline{H}_3)O$ and $C(C\underline{H}_3)_2$; 2.00-2.25 (m, 4H): H-1' and H-1''; 2.85-3.05 (m, 2H): H-2''; 3.32-3.39 (m s, 6H): $O(C\underline{H}_3)$; 4.55 (dd, J=6.2, 3.1 Hz) and 4.64 (t, J=4.8 Hz, 1H): H-2'; 5.26 (q, J=4.9 Hz, 1H): H-2; 7.14-7.34 (br m, 5H): Ph H-2 - H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 21.5 (q), 22.4 (q), 22.6 (q), 23.8 (q), and 24.4 (q): $OCH(\underline{C}H_3)O$ and $C(\underline{C}H_3)_2$; 30.0 (t), 30.1 (t), and 34.4 (t): C-1' and C-2''; 36.2 (t): C-1'; 52.1 (q), 53.7 (q), and 53.8 (q): $O\underline{C}H_3$; 82.7 (s), 83.8 (s), and 83.9 (s): C-4 and C-5; 102.1 and 102.4 (d): C-2 and C2'; 125.5 (d): Ph C-4; 128.3 (s): Ph C-2, C-3, C-5, and C-6; 142.6 (s): Ph C-1. MS: *m/e* (%) 307 (4), 201 (33), 192 (17), 160 (16), 159 (15), 133 (16), 105 (41), 91 (100), 87 (19), 85 (16), 75 (54), 43 (21), 31 (39). HRMS: calcd. (M^+-H): 307.1909; found: 307.1910.

2-Methoxy-5,5-dimethyl-4-(2-phenylethyl)-tetrahydrofuran-4-ol (28a).
Least polar isomer : ^1H NMR ($CDCl_3$, 200 MHz): δ 1.13 (s, 3H) and 1.34 (s, 3H): $C(C\underline{H}_3)_2$; 1.99-2.25 (br m, 4H): H-1' and H-3; 2.40-2.85 (m, 2H): H-2'; 3.32-3.39 (m s, 3H): $OC\underline{H}_3$; 4.97 (d, J=4.1Hz, 1H): H-2; 7.15-7.35 (m, 5H): Ph H-2 - H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 23.4 (q) and 26.9 (q): $C(\underline{C}H_3)_2$; 31.0 (t), 36.6 (t), and 43.5 (t): C-3, C-1', and C-2'; 54.6 (q): $O\underline{C}H_3$; 80.6 (s) and 88.6 (s): C-4 and C-5; 103.0 (d): C-2; 125.8 (d): Ph C-4; 128.4 (d): Ph C-2, C-3, C-5, and C-6; 142.6 (s): Ph C-1. MS:

m/e (%) 250 (0.3), 192 (77), 160 (50), 159 (23), 133 (20), 105 (35), 104 (13), 92 (15), 91 (72), 87 (100), 59 (15). HRMS: calcd. (M^+): 250.1569; found: 250.1566.

Most polar isomer: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.25 (s, 6H): $C(C\underline{H}_3)_2$; 1.65-1.92 (m, 3H): H-1' and O$\underline{H}$; 2.10 (dd, J=14.3, 4.9 Hz, 1H): H-3α; 2.40 (dd, J=14.3, 6.3 Hz, 1H): H-3β; 2.65 (ddd, J=12.9, 11.1, 6.5 Hz, 1H); H-2'α; 2.90 (ddd, J=13.7, 10.3, 6.6 Hz, 1H): H-2'β; 3.39 (s, 3H): $OC\underline{H}_3$; 5.10 (dd, J=6.3, 4.9 Hz, 1H): H-2; 7.15-7.35 (m, 5H): Ph H-2 -H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 21.5 (q) and 25.9 (q): $C(\underline{C}H_3)_2$; 30.9 (t), 37.1 (t), and 45.9 (t): C-3, C-1', and C-2'; 55.5 (q): $O\underline{C}H_3$; 83.3 (s) and 86.1 (s): C-4 and C-5; 103.3 (d): C-2; 125.9 (d): Ph C-4; 128.3 (d) and 128.5 (d): Ph C-2, C-3, C-5, and C-6; 142.2 (s): Ph C-1. MS: *m/e* (%) 250 (0.8), 192 (71), 160 (50), 159 (23), 133 (25), 105 (35), 104 (13), 92 (15), 91 (72), 87 (100), 59 (15). HRMS: calcd. (M^+): 250.1569; found: 250.1567.

4-(2-Cyclohexylethyl)-2-methoxy-5,5-dimethyl-tetrahydrofuran-4-ol (28b).

According to the procedure described for **28a**, 460 mg (1.3 mmol) of alcohol **26b** was cyclized to yield after purification by chromatography on 10 g of silicagel with petrol-EtOAc (gradient elution, 7-1 to 3-1) as eluent, in order of elution: 115 mg (0.37 mmol, 28%) of 1,3-dioxolane **27b** and 183 mg (0.71 mmol, 56%) of **28b** as an oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.72-0.95 (m, 2H); 1.0-1.85 (m, 20H); 1.97 (dd, J=14.4, 4.9 Hz, 1H): H-3α or H-3β; 2.28 (dd, J=14.4, 6.3 Hz, 1H): H-3β or H-3α; 3.33 (s, 3H): $OC\underline{H}_3$; 5.02 (dd, J=4.9 and 6.3 Hz, 1H): H-2. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 21.5 (q); 26.0, 26.3, and 26.6 (3 q); 31.8 and 32.2 (2 t); 33.3 (t); 38.1 (d); 45.9 (t); 55.4 (q): $O\underline{C}H_3$); 83.4 (s): C-4; 86.1 (s): C-5; 103.3 (d): C-2. MS: *m/e* (%) 207 (28), 139 (6), 123 (10), 102 (25), 95 (5), 87 (25), 69 (5), 55 (12), 43 (5). HRMS: calcd. (M^+-OCH_3): 255.1855; found: 255.1856.

4-hexyl-2-methoxy-5,5-dimethyl-tetrahydrofuran-4-ol (28c).

According to the procedure described for **26a**, 1.1 g (3.3 mmol) of alcohol **26c** was cyclized to yield after purification by chromatography on 20 g of silicagel with petrol-EtOAc (gradient elution, 6-1 to 3-1) as eluent in order of elution: 295 mg (1.0 mmol, 31%) of 1,3-dioxolane **27c** and 431 mg (1.9 mmol, 57%) of **28c** as an oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.72-0.95 (br t, J=6.0 Hz, 3H): hex H-6; 1.1-1.5 (m, 16H); 1.84 (br s, 1H): OH; 1.96 (dd, J=14.3, 4.9 Hz, 1H): H-3α or H-3β; 2.26 (dd, J=14.3, 6.3 Hz, 1H): H-3β or H-3α; 3.31 (s, 3H): $OC\underline{H}_3$; 5.00 (dd, J=4.9, 6.3 Hz, 1H): H-2. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 14.0 (q); 21.5 (q); 22.5 (t); 24.3 (t); 26.0 (q); 29.9 (t); 31.7 (t); 34.9 (t); 45.8 (t); 55.4 (q): $O\underline{C}H_3$); 83.4 (s): C-4; 86.0 (s): C-5; 103.3 (d): C-2. MS: *m/e* (%) 215 (0.5), 199 (3), 172 (16), 115 (12), 113 (16), 102 (27), 87 (100), 85 (14), 70 (16), 59 (15), 55 (13), 43 (30), 41 (13). HRMS: calcd. (M^+-CH_3): 215.1647; found: 215.1644.

2-Methoxy-5,5-dimethyl-4-[(trimethylsilyl)oxy]-4-(2-phenylethyl)-tetrahydrofuran (29a).

To a stirred solution of 970 mg (3.9 mmol) of **28a** in 15 ml of anhydrous DMF was added sequentially 811 mg (11.9 mmol; 3.1 eq) of imidazole and 0.6 ml (4.8 mmol; 1.2 eq) of chlorotrimethylsilane. After stirring overnight the reaction mixture was poured into 100 ml of water and extracted with three 50 ml-portions of petrol. The combined extracts were washed with 25 ml of water, dried with $MgSO_4$ and concentrated under reduced pressure to yield 1.23 g (3.8 mmol; 98%) of silylether **29a** 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 0.2 (s, 9H): $Si(C\underline{H}_3)_3$; 1.29 (s, 6H): $C(C\underline{H}_3)_2$; 1.77-1.97 (m, 2H): H-1'; 2.11 (dd, J=14.7, 4.9 Hz, 1H): H-3α; 2.51 (dd, J=14.7, 6.2 Hz, 1H): H-3β; 2.56-2.85 (m, 2H): H-2'; 3.40 (s, 3H): $OC\underline{H}_3$; 5.08 (dd, J=6.2, 4.9 Hz, 1H): H-2; 7.15-7.37 (m, 5H): Ph H-2 - H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 2.3 (q): $Si(\underline{C}H_3)_3$; 23.1 (q); 26.1 (q); 30.9 (t); 39.4 (t); 46.4 (t); 55.3 (q): $O\underline{C}H_3$; 85.8 (s); 87.2 (s); 103.3 (d): C-2; 125.9 (d): Ph C-4; 128.3 and 128.5 (2 d): Ph C-2, C-3, C-5, and C-6; 142.5 (s): Ph C-1. MS: *m/e* (%) 264 (15), 160 (13), 159 (100), 105 (11), 91 (25), 85 (9), 83 (12), 75 (10), 73 (22). HRMS: calcd. (M^+-CH_3): 307.1729; found: 307.1731.

4-(2-Cyclohexylethyl)-2-methoxy-5,5-dimethyl-4-[(trimethylsilyl)oxy]-tetrahydrofuran (29b).

According to the procedure described for **29a** silylation of 239 mg (0.9 mmol) of **28b** yielded 294 mg of an oil. Purification of the crude product by chromatography on 5 g of silicagel with petrol-EtOAc (25-1) as eluent afforded 270 mg (0.8 mmol; 89%) of **29b** as a colourless oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.1 (s, 9H): $Si(C\underline{H}_3)_3$; 0.70-0.98 (br, 2H); 0.98-1.30 (m, 12H); 1.45-1.75 (m, 7H); 1.96 (dd, J=14.6, 5.0 Hz, 1H): H-3α or H-3β; 2.30 (dd, J=14.6, 6.2 Hz, 1H): H-3β or H-3α; 3.32 (s, 3H): $OC\underline{H}_3$; 4.97 (dd, J=6.2, 5.0 Hz, 1H): H-2. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 2.1 (q): $Si(\underline{C}H_3)_3$; 23.0 (q); 25.9 (q); 26.6 (2 t); 31.7 (t); 33.4 (2 t); 34.2 (t); 38.3 (d): *c*-hex C-1; 46.6 (t); 55.2 (q): $O\underline{C}H_3$; 85.8 (s): C-5; 87.2 (s): C-4; 103.3 (d): C-2.

4-Hexyl-2-methoxy-5,5-dimethyl-4-[(trimethylsilyl)oxy]-tetrahydrofuran (29c).

Silylation of 315 mg (1.4 mmol) of **28c** according to the procedure described for **29a** yielded 413 mg (1.4 mmol; 100%) of silylether **29c** as an oil, which was sufficiently pure to be used in the next reaction.

^1H NMR ($CDCl_3$, 200 MHz): δ 0.0 (s, 9H): $Si(C\underline{H}_3)_3$; 0.65-0.85 (br t, J=6.5 Hz, 3H): hex H-6; 0.95-1.45 (br m, 18H); 1.88 (dd, J=14.7, 5.8 Hz, 1H): H-3α or H-3β); 2.28 (dd, J=14.7, 5.9 Hz, 1H): H-3β or H-3α; 3.24 (s, 3H): $OC\underline{H}_3$; 4.90 (dd, J=5.9, 5.8 Hz, 1H): H-2. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 2.2 (q): $Si(\underline{C}H_3)_3$; 14.0 (q); 22.6 (t); 23.0 (q); 24.1 (t); 26.0 (q); 30.0 (t); 31.8 (t); 36.9 (t); 46.6 (t); 55.3 (q): $O\underline{C}H_3$; 85.9 (s): C-5; 87.2 (s): C-4; 103.4 (d): C-2. HRMS: calcd. (M^+-OCH_3): 271.2093; found: 271.2090.

5,5-Dimethyl-4-[(trimethylsilyl)oxy]-4-(2-phenylethyl)-2-phenylthio-tetrahydrofuran (30a).
A stirred reaction mixture consisting of 800 mg (2.5 mmol) of **29a** in 25 ml of anhydrous ether and 25 beads of 4Å molecular sieve at 0°C was treated dropwise with 0.3 ml (2.9 mmol) of thiophenol, followed by 0.5 ml (4.1 mmol) of boron trifluoride diethyl etherate. Stirring at 0°C was continued for 30 min before the reaction was quenched by addition of 20 ml of 4M aqueous sodium hydroxide solution. After stirring for 10 min at room temperature the organic layer was separated and the aqueous layer was extracted with three 25 ml-portions of ether. The combined organic layers were washed twice with brine, dried with $MgSO_4$ and concentrated under reduced pressure to give 1.17 g of an oil which was purified *via* chromatography on 25 g of silicagel with petrol-EtOAc (95-1) as eluent, affording 1.0 g (2.5 mmol; 100%) of a 1.3 : 1 mixture of C-2 epimers of sulfide **30a** as a colourless oil.
^1H NMR ($CDCl_3$, 200 MHz): δ 0.25 (d, 9H): $Si(C\underline{H}_3)_3$; 1.25, 1.32, and 1.38 (s, 6H): $C(C\underline{H}_3)_2$; 1.75-2.00 (m, 2H); 2.15-2.40 (m, 1H); 2.50-2.80 (m, 3H); 5.45 (t, J=7.4 Hz, 0.43H): H-2α or H-2β, 5.65 (dd, J=9.3, 7.7 Hz, 0.57H): H-2β or H-2α; 7.15-7.40 (m, 8H): Ph H-2 - H-6 and SPh H-3, H-4, and H-5 ; 7.48-7.58 (m, 2H): SPh H-2 and H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 2.5 (3 q): $Si(\underline{C}H_3)_3$; 23.2 (2 q); 25.3 (q); 26.2 (q); 30.7 and 30.9 (2 t); 38.9 and 39.2 (2 t); 43.9 (t); 46.0 (t); 83.2 (s); 83.5 (d): C-2; 85.1 (s); 86.9 (s); 88.8 (s); 126.0 and 126.7 (2 d); 128.3, 128.6, and 128.9 (3 d); 130.7 (2 d); 136.0 and 136.4 (2 s): SPh C-1; 142.2 (s): Ph C-1. MS: *m/e* (%) 400 (0.1), 342 (1), 291 (33), 237 (22), 233 (31), 185 (20), 175 (45), 147 (90), 105 (29), 91 (100), 75 (15), 73 (49). HRMS: calcd. (M^+): 400.1892; found: 400.1893.

4-(2-Cyclohexylethyl)-5,5-dimethyl-4-[(trimethylsilyl)oxy]-2-phenylthio-tetrahydrofuran (30b).
According to the procedure described for **30a**, 270 mg (0.82 mmol) of **29b** was reacted with thiophenol to yield 325 mg (0.80 mmol; 98%) of a 1.2 : 1 mixture of C-2 epimers of sulfide **30b** as an oil, which was sufficiently pure to be used in the next reaction without further purification.
^1H NMR ($CDCl_3$, 200 MHz, major peaks): δ 0.18 (d, 9H): $Si(C\underline{H}_3)_3$; 0.77-1.05 (br, 2H); 1.05-1.40 (br, 12H): $C(C\underline{H}_3)_2$ [δ 1.18 (s), δ 1.24 (s), and δ 1.31 (s)]; 1.52-1.85 (br m, 7H); 2.11-2.32 (m, 1H): H-3α or H-3β; 2.48-2.63 (m, 1H): H-3β or H-3α; 5.39 (dd, J=7.6, 7.6 Hz, 0.46 H): H-2α or H-2β; 5.60 (dd, J=9.0, 6.8 Hz, 0.54 H): H-2β or H-2α; 7.15-7.35 (m, 3H): Ph H-3, H-4, and H-5 ; 7.45-7.55 (m, 2): Ph H-2 and H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 2.4 (2 q): $Si(\underline{C}H_3)_3$; 23.2 (2 q); 25.2 and 26.0 (2 q); 26.4 and 26.7 (2 t); 31.5 and 31.8 (2 t); 33.5 (t); 34.0 and 34.4 (2 t); 38.4 (2 d); 44.0 (t); 46.4 (t); 83.4 (2 d): C-2; 85.3 (s); 86.8 (s); 88.8 (s); 126.6 (d); 128.8 (d); 130.6 (d); 136.1 and 136.6 (2 s).

4-Hexyl-5,5-dimethyl-4-[(trimethylsilyl)oxy]-2-phenylthio-tetrahydrofuran (30c).
According to the procedure described for **30a**, 290 mg (0.96 mmol) of **29c** was reacted with thiophenol to yield 363 mg (0.96 mmol; 100%) of a 1.5 : 1 mixture of C-2 epimers of sulfide **30c** as an oil, which was sufficiently pure to be used in the next reaction without further purification.
^1H NMR ($CDCl_3$, 200 MHz): δ 0.0 (d, 9H): $Si(C\underline{H}_3)_3$; 0.62-0.85 (br m, 3H): hex H-6; 0.9-1.5 (br m, 16H): hex H-1 - H-5 and $C(C\underline{H}_3)_2$ [δ 1.00 (s), δ 1.05(s), and δ 1.13 (s)] ; 1.90-2.17 (m, 1H): H-3α or H-3β, 2.25-2.50 (m, 1H): H-3β or H-3α; 5.22 (t, J=7.4 Hz, 0.58H): H-2α or H-2β; 5.44 (dd, J=11.2, 6.5 Hz, 0.42H): H-2β or H-2α; 6.95-7.20 (m, 3H): Ph H-3, H-4, and H-5 ; 7.25-7.40 (m, 2H): Ph H-2 and H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 2.4 (2 q): $Si(\underline{C}H_3)_3$; 14.1 (q); 22.7 (t); 23.2 (2 q); 24.0 (t); 24.3 (t); 25.2 (q); 26.1 (q); 30.0 (2 t); 31.8 (2 t); 36.6 (t); 37.1 (t); 44.0 (t); 46.3 (t); 83.5 (2 d): C-2; 85.3 (s); 86.9 (s); 88.8 (s); 126.6 (d); 128.8 (d); 130.6 (2 d); 136.1 and 136.7 (2 s). MS: *m/e* (%) 380 (0.3), 271 (42), 237 (29), 213 (54), 155 (25), 127 (100), 85 (27), 73 (62), 71 (32), 43 (23). HRMS: calcd. (M^+): 380.2205; found: 380.2206.

2,2-Dimethyl-3-[(trimethylsilyl)oxy]-3-(2-phenylethyl)-2,3-dihydrofuran (31a).
A solution of 780 mg (3.16-3.39 mmol) of *m*-CPBA (70-75 wt% *m*-CPBA, remainder *m*-CBA and water) in 35 ml of anhydrous toluene was pre-dried in a dropping funnel containing activated 4Å molecular sieves. After 20 min this solution was added dropwise to an ice-cold solution of 1.04 g (2.60 mmol) of sulfides **30a** in 25 ml of toluene. Stirring at 0°C was continued until tlc-analysis indicated complete disappearance of the sulfide. The dropping funnel was replaced by a reflux condensor, 7.8 ml (56 mmol) of triethylamine was added and the flask containing the reaction mixture was placed in an oil bath, pre-heated at 120°C. The mixture was refluxed for approx. 10 min while the disappearance of the sulfoxide intermediate was monitored *via* tlc-analysis. Then, both solvent and triethylamine were removed at the rotary evaporator under reduced pressure and the residual oil was partially purified by chromatography on 75 g of aluminium oxide (activity grade III) with petrol as eluent, affording 714 mg of **31a** and some minor impurities (tlc analysis).
^1H NMR ($CDCl_3$, 90 MHz): δ 0.0 (s, 9H): $Si(C\underline{H}_3)_3$; 1.0 (s, 3H) and 1.2 (s, 3H): $C(C\underline{H}_3)_2$; 1.5-1.8 (m, 2H): H-1'; 2.4-2.7 (m, 2H): H-2'; 4.9 (d, J=3 Hz, 1H): H-4; 6.2 (d, J=3 Hz, 1H): H-5; 6.8-7.2 (m, 5H): Ph H-2 - H-6.

2,2-Dimethyl-3-(2-phenylethyl)-2,5-dihydrofuran-5-ol (32a).

A solution of 600 mg (1.50 mmol) of **30a** in 25 ml of toluene was sequentially oxidised and eliminated as described for **31a** to give 1.3 g of an oil. Chromatography on 20 g of silicagel with petrol-EtOAc (20-1) as eluent yielded 255 mg partially purified product, which was again chromatographed on 6 g of silicagel with petrol-EtOAc (99-1, followed by 10-1) to afford 106 mg (0.49 mmol, 33%) of rearranged **32a** as a viscous oil.

^1H NMR ($CDCl_3$, 200 MHz, selected peaks): δ 1.25 (s, 3H) and 1.35 (s, 3H): $C(C\underline{H}_3)_2$; 2.20-2.33 (m t, J=7.8 Hz, 2H): H-1'; 2.72-3.00 (m, 2H): H-2'; 5.45 (br s, 1H): H-4; 5.88 (br d, J=5.6 Hz, 0.34H): H-5 minor isomer; 6.00 (br s, 0.66H): H-5 major isomer; 7.11-7.34 (m, 5H): Ph H-2 - H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT, major isomer only): δ 26.8 and 27.8 (2 q): $C(\underline{C}H_3)_2$; 28.0 (t); 33.5 (t); 88.6 (s): C-2; 103.7 (d): C-4; 118.4 (d): C-3; 126.0 (d): Ph C-4; 128.2 and 128.4 (2 d): Ph C-2, C-3, C-5, and C-6; 141.5 (s): Ph C-1; 153.0 (s): C-4.

5,5-Dimethyl-4-(2-phenylethyl)-furan-2(5H)-one (33a).

To a stirred solution of 235 mg (810 mmol) of **31a** in 10 ml of THF were added 9 drops of a 40% aqueous hydrofluoric acid solution. After tlc-analysis indicated complete disappearance of the starting material (approx. 15 min) the reaction mixture was cooled on an ice-bath and Jones' reagent was added dropwise until an orange colour persisted. Stirring at 0°C was continued for 30 min before the reaction was quenched by the addition of ethanol. The reaction mixture was extracted with three 15 ml-portions of ether, washed with 10 ml of brine, dried with $MgSO_4$ and concentrated under reduced pressure to yield 220 mg of an oil. The crude product was purified *via* chromatography on 5 g of silicagel with petrol-EtOAc (7-1) as eluent to afford 107 mg (495 mmol, 61%) of butenolide **33a** as an oil.

^1H NMR ($CDCl_3$, 200 MHz): δ 1.42 (s, 6H): $C(C\underline{H}_3)_2$; 2.56 (dt, J=8.5, 1.7 Hz, 2H): H-1'; 2.94 (t, J=8.5 Hz, 2H): H-2'; 5.75 (t, J=1.7 Hz, 1H): H-3; 7.15-7.38 (m, 5H): Ph H-2 - H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 24.8 (q): $C(\underline{C}H_3)_2$; 28.7 (t); 32.9 (t); 87.3 (s): C-5; 114.4 (d): C-3; 126.7 (d): Ph C-4; 128.2 (d): Ph C-3 and C-5; 128.7 (d): Ph C-2 and C-6; 139.2 (s): Ph C-1; 172.4 (s) and 176.5 (s): C-2 and C-4. MS: *m/e* (%) 216 (5), 173 (5), 171 (28), 92 (7), 91 (100), 65 (5). HRMS: calcd. (M^+): 216.1150; found: 216.1150.

4-(2-Cyclohexylethyl)-5,5-dimethyl-furan-2(5H)-one (33b).

According to the procedure described for **31a**, 300 mg (0.74 mmol) of sulfide **30b** was sequentially oxidised and eliminated to give 320 mg of an oil containing some impurities and the trimethylsilyloxy-enolethet **31b**.

^1H NMR ($CDCl_3$, 90 MHz, selected peaks): δ 0.0 (s, 9H): $Si(C\underline{H}_3)_3$; 0.5-1.8 (br m, 21H): $C(C\underline{H}_3)_2$, H-1', H-2' and *c*-hex H-1 - H-6; 4.9 (d, J=3 Hz, 1H): H-4; 6.2 (d, J=3 Hz, 1H): H-5; 6.9-7.6 (m, 5H): Ph H.

A solution of 200 mg of crude **31b** in 10 ml of THF was sequentially desilylated and oxidised as described for **33a**. Purification by repeated chromatography on silicagel with petrol-EtOAc (gradient elution 99-1 to 96-4) as eluent afforded 63 mg (0.28 mmol) of butenolide **33b** in an overall yield of 67% from **30b**.

^1H NMR ($CDCl_3$, 200 MHz): δ 0.78-1.05 (br m, 2H) and 1.05-1.82 (br m, 17H): $C(C\underline{H}_3)_2$ [δ 1.42 (s, 6H)], H-2' and *c*-hex H-1 - H-6; 2.22 (dt, J=1.7, 7.9 Hz, 2H): H-1'; 5.65 (t, J=1.7 Hz, 1H): H-3. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 24.3 (t); 24.9 (q): $C(\underline{C}H_3)_2$; 26.1 (t); 26.4 (t); 33.1 (t); 34.3 (t); 37.3 (d): *c*-hex H-1; 87.3 (s): C-5; 113.6 (d): C-3; 172.2 (s): C-2; 178.2 (s): C-4. MS: *m/e* (%) 222 (12), 207 (17), 179 (38), 163 (12), 162 (20), 161 (29), 135 (21), 127 (101), 111 (38), 96 (28), 65 (47), 81 (44), 67 (42), 55 (48), 43 (62), 41 (38). HRMS: calcd. (M^+): 222.1620; found: 222.1616.

4-Hexyl-5,5-dimethyl-furan-2(5H)-one (33c).

Sulfide **30c** was converted into butenolide **33c** according to the procedure described for **33a**.

^1H NMR ($CDCl_3$, 200 MHz): δ 0.86 (t, J=6.4 Hz, 3H): hex H-6; 1.18-1.45 (br m, 12H): $C(C\underline{H}_3)_2$ [δ 1.41 (s, 6H)], hex H-3 - H-5; 1.50-1.69 (br m, 2H): hex H-2; 2.20 (dt, J=1.7, 7.6 Hz, 2H): hex H-1; 5.65 (t, J=1.7 Hz, 1H): H-3. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 14.0 (q): hex C-6; 22.5 (t); 24.8 (q): $C(\underline{C}H_3)_2$; 26.7 (t); 26.9 (t); 28.9 (t); 31.4 (t); 87.3 (s): C-5; 113.6 (d): C-3; 172.3 (s): C-2; 177.9 (s): C-4. IR ($CHCl_3$): ν 1740, 1630 cm^{-1}. MS: *m/e* (%) 181 (52), 154 (20), 153 (100), 111 (59), 109 (9), 96 (9), 81 (9), 69 (22), 67 (9), 54 (8), 43 (44), 41 (9). HRMS: calcd. (M^+): 196.1463; found: 196.1460.

4-Hydroxy-5,5-dimethyl-4-(2-phenylethyl)-4,5-dihydrofuran-2(3H)-one (34a).

Jones' reagent was added dropwise to a stirred solution of 100 mg (0.40 mmol) of hydroxy acetal **28a** in 10 ml of acetone, cooled on an ice-bath, until an orange colour persisted and glc-analysis indicated complete conversion of the starting material. Stirring at 0°C was continued for 30 min and the reaction was quenched by addition of ethanol. The reaction mixture was extracted with three 15 ml-portions of ether, washed with 10 ml of brine, dried with $MgSO_4$ and concentrated to yield 100 mg of an oil which was purified *via* chromatography on 2.5 g of silicagel with petrol-EtOAc (5-1) as eluent, affording 94 mg (0.40 mmol, 100%) of hydroxy lactone **34a** as an oil.

^1H NMR ($CDCl_3$, 200 MHz): δ 1.34 (s, 3H) and δ 1.45 (s, 3H): $C(C\underline{H}_3)_2$; 1.75-2.02 (m, 2H): H-1'; 2.45-2.98 (m, 5H): H-3α and H-3β [δ 2.57 (d, J=18.0 Hz), δ 2.77 (d, J=18.0 Hz)], H-2', and OH; 7.17-7.30 (m, 5H): Ph H-2 - H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 20.7 and 24.8 (2 q): $C(\underline{C}H_3)_2$; 30.5 (t); 36.8 (t); 41.9 (t): C-3; 79.8 (s): C-5; 90.3 (s): C-4; 126.3 (d): Ph C-4; 128.3 (d):

Ph C-3 and C-5; 128.6 (d): Ph C-2 and C-6; 141.2 (s): Ph C-1; 174.8 (s): C-2. IR ($CHCl_3$): ν 3580, 3450 (br), 1760 cm^{-1}. Anal: calcd. for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74; found: C, 72.07; H, 7.94.

4-Hexyl-4-hydroxy-5,5-dimethyl-4,5-dihydrofuran-2(3H)-one (34c).

According to the procedure described for **34a** lactone **34c** was prepared in 90% yield.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.77-0.90 (br m, 3H): hex H-6; 1.15-1.28 (br m, 8H): hex H-2 - H-5; 1.28 (s, 3H) and 1.38 (s, 3H): $C(C\underline{H}_3)_2$; 1.44-1.60 (br m, 2H): hex H-1; 2.47 (d, J=17.5 Hz, 1H): H-2α; 2.64 (d, J=17.5 Hz, 1H): H-2β; 2.76 (br s, 1H): OH. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 14.0 (q): hex C-6; 20.8 (q); 22.5 (t); 24.0 (t); 24.6 (q); 29.6 (t); 31.6 (t); 34.8 (t); 42.0 (t); 79.8 (s): C-5; 90.5 (s): C-4; 175.3 (s): C-2. MS: *m/e* (%) 128 (58), 116 (19), 86 (68), 84 (99), 71 (57), 59 (32), 58 (74), 49 (100), 43 (31). HRMS: calcd. ($M-CH_3$): 199.1334; found: 199.1337.

5,5-Dimethyl-4-(2-phenylethyl)-tetrahydrofuran-2,4-diol (35a).

A mixture of 455 mg (1.82 mmol) of hydroxy acetal **28a** in 30 ml of THF and 5 ml of 4M aqueous hydrochloric acid solution was stirred at room temperature for 30 min. The reaction mixture was poured into 100 ml of saturated aqueous sodium bicarbonate solution and extracted with four 25 ml-portions of ether. The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure to give 455 mg of an oil which was purified *via* chromatography on 10 g of silicagel with petrol-EtOAc (4-1) as eluent to yield, in order of elution, 50 mg (0.2 mmol, 11%) of starting material **28a** and 287 mg (1.22 mmol, 67%) of hydroxy lactol **35a** as a 6 : 1 mixture of diastereomers.

^{1}H NMR ($CDCl_3$, 200 MHz, selected peaks): δ 1.12 and 1.38 (2 s, total 5.14H): $C(C\underline{H}_3)_2$ major isomer; 1.25 and 1.32 (2 s, total 0.86H): $C(C\underline{H}_3)_2$ minor isomer; 1.62-1.95 (m, 2H); 2.07-2.24 (m, 2H); 2.55-2.75 (m, 1H); 2.82-3.03 (m, 1H); 3.37 (br, 0.86H): OH major isomer; 3.89 (br, 0.14H): OH minor isomer; 4.25 (br, 0.77H): OH major isomer; 5.48 (d, J=4.0 Hz, 0.86H): H-2 major isomer; 5.65 (t, J=5.7 Hz, 0.14H): H-2 minor isomer; 7.15-7.37 (m, 5H): Ph H-2 - H-6.

^{13}C NMR ($CDCl_3$, 50 MHz, DEPT, selected peaks): *Major isomer*: δ 23.3 and 26.8 (2 q): $C(\underline{C}H_3)_2$; 31.0 (t); 36.8 (t); 43.8 (t); 81.5 (s): C-5; 88.7 (s): C-4; 96.6 (d): C-2; 126.0 (d): Ph C-4; 128.4 and 128.5 (2 d): Ph C-2, C-3, C-5, and C-6; 142.3 (s): Ph C-1.

^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): *Minor isomer*: (separated peaks only): 21.5 (q); 26.7 (q); 37.2 (t); 46.4 (t); 83.9 (s); 86.6 (s); 142.1 (s). IR ($CHCl_3$): ν 3575, 3480 (br), 3360 (br) cm^{-1}. MS: *m/e* (%) 218 (14), 178 (59), 160 (80), 134 (15), 133 (26), 105 (38), 104 (22), 92 (44), 91 (100), 85 (32), 73 (51), 59 (35). HRMS: calcd. ($M-H_2O$): 218.1307; found: 218.1303.

2,2-Dimethyl-3-(2-phenylethyl)-tetrahydrofuran-3-ol (36a).

To a stirred solution of 100 mg (0.42 mmol) of diol **35a** in 5 ml of anhydrous CH_2Cl_2 at -78°C was added dropwise 0.1 ml (0.81 mmol) of boron trifluoride diethyl etherate, followed by 0.2 ml (1.25 mmol) of triethylsilane. Stirring was continued for 50 min until tlc analysis indicated complete conversion of the starting material. The reaction mixture was poured into 10 ml of saturated aqueous sodium bicarbonate solution and extracted with three 25 ml-portions of ether. The extracts were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure to give 100 mg of an oil. Purification by chromatography on 2 g of silicagel with petrol-EtOAc (2 : 1) as eluent yielded 67 mg (0.30 mmol, 73%) of **36a**.

^{1}H NMR ($CDCl_3$, 200 MHz, selected peaks): δ 1.11 (s, 3H) and 1.26 (s, 3H): $C(C\underline{H}_3)_2$; 1.68-1.90 (m, 2H); 2.05-2.25 (m, 2H); 2.69 (ddd, J=13.5, 10.6, 6.5 Hz, 1H): H-4α; 2.96 (ddd, J=13.5, 11.4, 6.0 Hz, 1H): H-4β; 3.81-3.99 (m, 2H): H-5; 7.15-7.35 (m, 5H): Ph H-2 - H-6. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 21.1 and 23.9 (2 q): $C(\underline{C}H_3)_2$; 31.1 (t); 37.2 (t); 37.8 (t); 62.9 (t): C-5; 82.2 (s); 84.7 (s); 125.9 (d): Ph C-4; 128.3 and 128.4 (2 d): Ph C-2, C-3, C-5, and C-6; 142.4 (s): Ph C-1. MS: *m/e* (%) 163 (8), 162 (70), 144 (12), 133 (34), 105 (22), 92 (26), 91 (100), 59 (10). HRMS: calcd. ($M-H_2O-CH_3$): 187.1123; found: 187.1120.

4-[2-Cyclohexylethyl]-furan-2(5H)-one (38).

Jones' reagent was added dropwise to a stirred solution of 170 mg (0.75 mmol) of **18b** in 20 ml of acetone until an orange colour persisted and tlc-analysis indicated complete transformation of the starting material. Saturated aqueous sodiumbicarbonate solution was added until a neutral pH was obtained. The resulting mixture was extracted with three 25 ml-portions of ether and the combined extracts were washed with 10 ml of brine, dried with $MgSO_4$ and concentrated under reduced pressure to yield 155 mg of a yellow oil which solidified upon standing at room temperature. Chromatography on 20 g of silicagel with petrol-EtOAc (95-5 to 90-10) as eluent afforded 126 mg (0.59 mmol, 79%) of **4-[2-Cyclohexylethyl]-4-hydroxy-4,5-dihydrofuran-2(3H)-one (37)** as an oil which was sufficiently pure to be used as such in the next reaction.

^{1}H NMR ($CDCl_3$, 90 MHz): δ 0.60-1.45 (br m) and 1.45-2.10 (br m; 15H): H-1', H-2' and *c*-hex H-1 - H-6; 2.55 (br s, 2H): H-3; 2.70 (br s, 1H): OH; 4.03-4.40 (m, 2H): H-5.

A solution of 35 mg (0.16 mmol) of hydroxy-lactone **37**, 0.06 ml (0.8 mmol) of thionylchloride, and 0.13 ml (1.6 mmol) of pyridine in 5 ml of CH_2Cl_2 was stirred on an ice-bath until glc-analysis indicated complete disappearance of the starting material (approx. 60 min). The reaction mixture was concentrated under reduced pressure and the residue was dissolved in 20 ml of ether. The solution was washed with 5 ml of satd. aqueous sodiumbicarbonate soln. and 10 ml of brine, dried with $MgSO_4$ and concentrated under reduced pressure to yield 28 mg of a brown oil. Careful chromatography on 10 g of silicagel with petrol-EtOAc (gradient elution, 98-2 to 96-4) afforded, in order of elution, 5 mg of a mixed fraction, consisting of the desired lactone **38** and two exocyclic double bond regioisomers in 1.6 - 1 ratio (glc-analysis), and 12 mg (0.06 mmol, 39%) of analytically pure butenolide **38**.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.77-1.05 (br m, 2H), 1.05-1.37 (br m, 5H), 1.40-1.51 (m, 2H) and 1.55-1.85 (br m, 4H): H-2' [δ 1.44 (t, J=7.9 Hz) and 1.47 (t, J=7.4 Hz)] and *c*-hex H-1 - H-6; 2.40 (t, J=7.9 Hz, 2H): H-1'; 4.72 (d, J=1.8 Hz, 2H): H-5; 5.81 (quintet, J=1.8 Hz, 1H): H-3. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 26.1 (t); 26.2 (t); 26.4 (t); 33.0 (t); 34.7 (t); 37.3 (d): *c*-hex C-1; 73.1 (t): C-5; 115.2 (d): C-3; 171.0 (s) and 173.1 (s): C-2 and C-4.

4-[2-Cyclohexylethyl]-4,5-dihydrofuran-2(3H)-one (39).

A solution of 10 mg (0.05 mmol) of butenolide **38** in 20 ml of EtOAc, containing 15 mg of 10% Pd/C, was hydrogenated in a Parr apparatus under hydrogen pressure (4 atm) at room temperature. After 6 h, glc-analysis indicated complete transformation of the starting material into a single product. The reaction mixture was filtered and the solvent was evaporated under reduced pressure to yield 10 mg (0.05 mmol, 100%) of lactone **39**.

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.67-1.00 (br m, 2H), 1.0-1.32 (br m, 6H), 1.32-1.50 (br m, 2H) and 1.50-1.85 (br m, 5H): H-1', H-2', *c*-hex H-1 [δ 1.62 (br d, J=7.8 Hz)] and *c*-hex H-2 - H-6; 2.10 (dd, J=16.2, 7.4 Hz, 1H): H-3α; 2.30-2.62 (m, 2H): H-3β [δ 2.54 (dd, J=16.2, 7.8 Hz)] and H-4; 3.85 (dd, J=9.0, 7.0 Hz, 1H): H-5α; 4.35 (dd, J=9.0, 7.3 Hz, 1H): H-5β. ^{13}C NMR ($CDCl_3$, 50 MHz, DEPT): δ 26.3 (t); 26.6 (t); 30.5 (t); 33.3 (t); 34.6 (t): C-3; 35.1 (t); 36.0 (d): C-4; 37.6 (d): *c*-hex C-1; 73.5 (t): C-5; 177.3 (s): C-2.

Notes and References

1. For a comprehensive compilation of insect antifeeding clerodane diterpenes and related compounds, E.A. klein Gebbinck, Ph.D. thesis, Wageningen Agricultural University, 1999, chapter 2.
2. (a) *Ibid*, chapter 5. (b) *Ibid*, chapter 6. (c) E.A. klein Gebbinck, C.T. Bouwman, M. Bourgois, B.J.M. Jansen, and Ae. de Groot, *Tetrahedron* **1999**, **preceding paper**.
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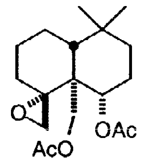
4. (a) W.M. Blaney, M.S.J. Simmonds, S.V. Ley, and P.S. Jones, *Entomol. Exp. Appl.* **1988**, *46*, 267-274. (b) M.S.J. Simmonds, W.M. Blaney, S.V. Ley, G. Savona, M. Bruno, and B. Rodríguez, *Phytochemistry* **1989**, *28*, 1069-1071. A complete account of all antifeedancy reports on **2** or **3**: ref. 1.
5. It has been suggested that the antifeedant activity of clerodin (**1**) and other clerodane antifeedants with a perhydrofuro[2,3-b]furan subunit is a synergetic effect, related to the presence of (elements from) both the decalin fragment and the furofuran fragment in one molecule. (R.B.M. Geuskens, J.M. Luteyn, and L.M. Schoonhoven, *Experientia* **1983**, *39*, 403-404). In analogy, the data collected in Table 2 support the proposal of a similar hypothesis regarding the antifeedant activity of **2** and **3**.

Table 2: Two-choice insect antifeedant activity of *neo*-clerodane diterpenes (**1-3**) and some related model compounds (**5**,**40**) against larvae of the fall armyworm (*Spodoptera frugiperda*) and the African armyworm (*Sp. exempta*).

	(1)	(2)	(3)	(5)	(40)
Sp. frugiperda	78 (4)^{a,b}	94 (2)	47 (7)	12 (7)	15 (6)
Sp. exempta	76 (6)	38 (17)	73 (7)	34 (2)	20 (5)



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Notes: (a) Measured at 100 ppm concentration in a two-choice test on artificial substrate (Glass-fibre/sucrose); (b) Activity reported as AI (sem), with AI = mean Antifeedant Activity = [(C-T)/(C+T)]*100% and sem = standard error of the mean. [Adapted from Ref. 4a,b]

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