Pergamon

Tetrahedron Vol. 51, No. 30, pp. 8247-8258, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00438-6

CHIRAL BUILDING BLOCKS FROM STREPTOMYCES-2.[1] STEREOSELECTIVE TRANSFORMATION OF STREPTENOL A INTO 3-METHYL-δ-LACTONES

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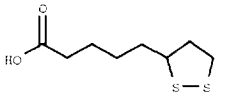
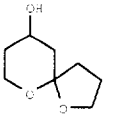
Abstract: The stereoselective synthesis of both enantiomeric forms of 3-alkyl-streptenols A **7 - 9** and ***ent*-7-9** in four steps is described. Hereby, the stereoselective acetalization to the pyrans **2a** and **2b** directed by the solvent and the catalyst used was a key step in the reaction sequence. The 3-alkyl-streptenols represents interesting chiral building blocks which can be used for the synthesis of analogues of HMG-CoA inhibitors, e.g. 3-methyl-δ-lactones.

Chemical screening in the culture broth of microorganisms is an efficient method for detecting secondary metabolites with different types of structures independent from a biological activity.[2] Therefore, chiral building blocks are detectable, for example the streptenols A (**1**),[3-5] B,[3] C[3,6] and D[3,6] which are now readily available by fermentation.

Compound **1** was used as chiral building block in the enantioselective synthesis of all stereoisomers of lipoic acid **A**[7], 9-hydroxy-1,6-dioxaspiro[4.5]decane **B**[7] and of the 3-hydroxy-5-decanolides **C** which can be transformed to the massoialactones **D**.[1]



A



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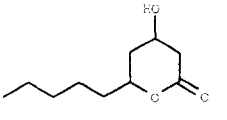

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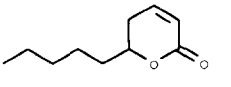


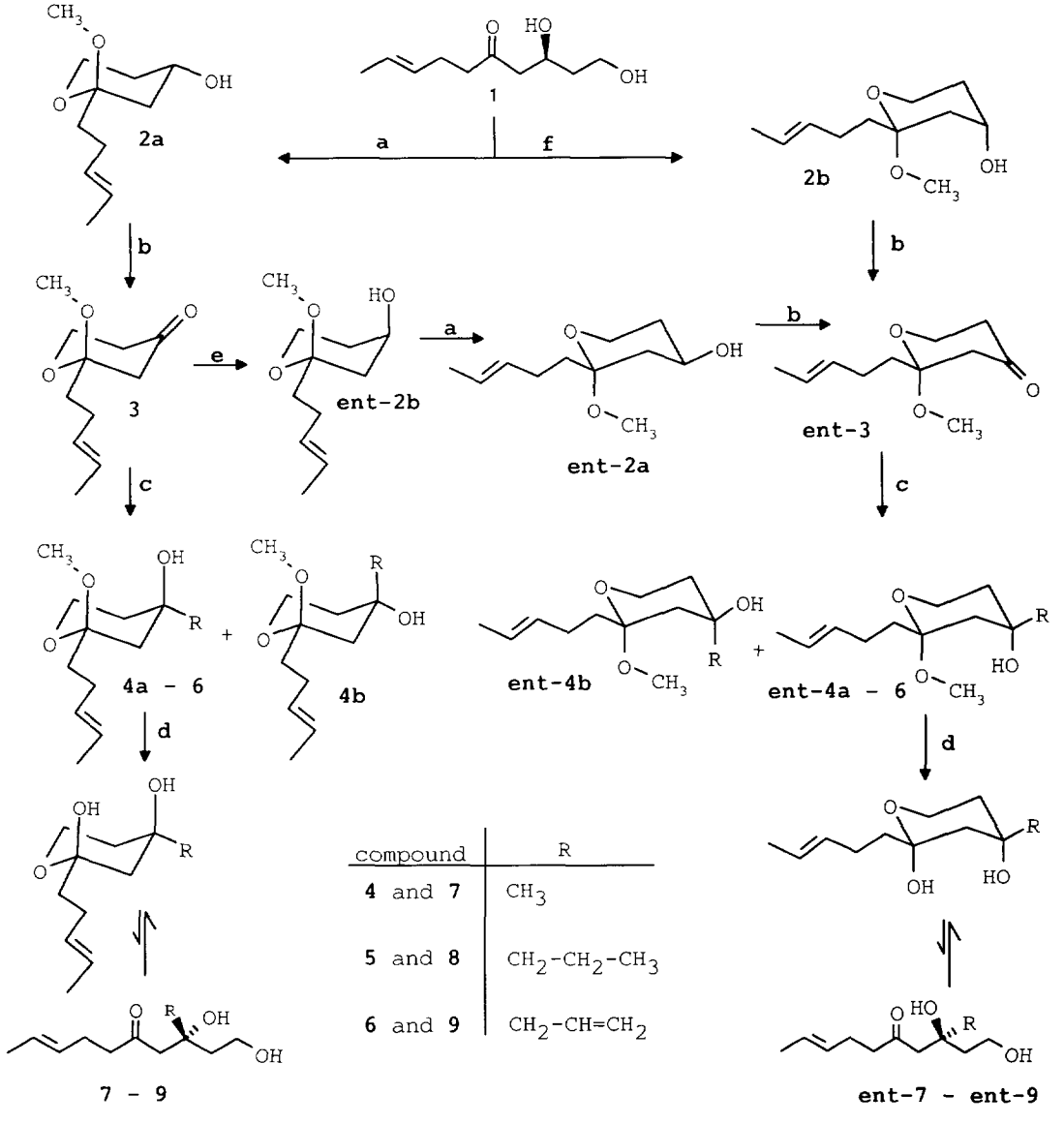
D

In the synthesis of these compounds a key step was the inversion of the chiral centre at C-3 in (3*S*)-streptenol A (**1**) by intramolecular acetalization to the (2*S*,4*S*)-tetrahydropyran **2a**-product, oxidation to the 2*S*-pyrone **3**, stereoselective reduction to the (2*S*,4*R*)-tetrahydropyran *ent*-**2b** and deacetalization which yielded the (3*R*)-streptenol A. This process can be classified as an intramolecular self regeneration of stereogenic centres.[8] The preferentially equatorial attack of sterically hindered hydride donors was in accordance with observations made for the reduction of cyclohexanones with axial positioned alkyl groups in ß-position to the carbonyl group[9] as well as for tertrahydropyrones possessing an axial orientated ß-hydroxyl substituent, e.g. as a methoxy group[1,10-12] or as a part of a spiroketal moiety.[13]

We proposed that this route can also be applied in the synthesis of 3-alkyl derivatives of streptenol A by using alkylmagnesium halogenides as nucleophilic reagents. This gives rise to the possibility to replace the C-3 hydrogen by alkyl groups. Our interest was focused on the preparation of both enantiomers of the 3-alkyl-streptenols. The chiral induction by the nucleophilic attack at the keto group C-4 in **3** is controlled by the

acetal centre at C-2. Therefore, a method directed towards the construction of the (2*R*)-centre in the pyran **2b** would be the key step in the stereoselective synthesis of both enantiomers of the 3-alkyl streptenols. This study was designed to investigate this sequence.

The resulting chiral 3-alkyl-1,3-dihydroxy-5-oxo compounds are interesting chiral starting materials. This structure unit was found for example in anthraquinone antibiotics,[14-16] in mevalonolactone[16] and in analogs of mevinolin.[17] It is remarkable that 6-alkyl-2-pyrones possessing a 4-hydroxy-4-carboxymethyl moiety, as a



(a) p-toluenesulfonic acid in CH_3OH; (b) $(C_3H_7)_4NRuO_4$, N-methylmorpholine-N-oxide; (c) RMgCl, THF, 20°C; (d) $FeCl_3$, isopropanol, water; (e) L-Selectride, -70°C; (f) $ZnCl_2$, MeOH in CH_2Cl_2

mixture of enantiomers, already exhibited improved properties as HMG-CoA reductase inhibitors, when compared to mevinolin.[17] In contrast, the 4-hydroxy-4-methyl derivatives with an aromatic side chain at C-6 were less active. The discussed compounds as well as corresponding analogs should be easily accessible as enantiomerically pure compounds by synthesis from 3-alkyl-streptenols. Furthermore, because streptenol A (**1**) exhibited immunostimulating-[5] and antihyperlipidemic-activity (inhibitor of the cholesterol biosynthesis),[3] the tertiary substituted derivatives should be interesting targets for studying their biological effects.

Synthesis of the 3*R*-alkyl-streptenols

The enantioselective synthesis of the (3*R*)-alkyl derivatives of streptenol A starts with the intramolecular acetalization of **1** with p-toluenesulfonic acid in methanol which yields the pyran **2a** as the main product (table 1). The oxidation of **2a** with $(C_3H_7)_4NRuO_4$/ methylmorpholine-N-oxide results in the (3*S*)-pyrone **3**. The reaction of **3** with methylmagnesium chloride, propylmagnesium chloride or 2-propenylmagnesium chloride led preferentially, as predicted, by an equatorial attack to the (2*S*,4*R*)-alkyl derivatives **4a** - **4c** in a yield of 60 - 70%, respectively.

Only in the case of the reaction to **4a** the minor (2*S*,4*S*)-compound **4b** was isolated for the purpose of comparison to verify the stereochemistry by NMR analysis. The acetals **4a** and **4b** both exhibit a chair conformation, deduced from the coupling constants of H-6 with 5-H_{ax} which is J = 12.5Hz in **4a** and **4b**. The downfield shift of OH-4 in the ^{1}H NMR spectrum of **4a** is explained by a hydrogen bond between OH-4 and the axial oxygen atom at C-2 or the ring oxygen.[1] Furthermore, this stereochemistry is supported by the chemical shift of CH_3-4 in the ^{1}H NMR- as well as in the ^{13}C NMR spectrum. The methoxy substituent at C-2 causes at the protons of the axially orientated CH_3-4 group in **4b**, when compared to the equatorially positioned methyl group in **4a**, a downfield shift in the ^{1}H NMR spectrum, $\Delta\delta_{\mathbf{4a-4b}}$ = -0.27 ppm, and a high field shift at C-4 in the ^{13}C NMR spectrum, $\Delta\delta_{\mathbf{4a-4b}}$ = 2.27 ppm, which is characteristic for a 1,3 diaxial interaction.[18] Based on these results the stereochemistry of **5** and **6** could be also verified.

The deacetalization is performed with $FeCl_3$ in isopropanol/ water[1] which results in the 3-alkyl streptenols **7** - **9** in yields of 92 - 97 %, respectively. These compounds prefer the cyclic hemiacetal structure, instead of the acylic hydroxy carbonyl form, as observed in **1**. Only up to 10% of the noncyclic compounds is observed. The conformations of the hemiacetal structures **7** - **9** are deduced from the NMR spectra based on the considerations already discussed. For example, in **7** the chemical shift of OH-2 is δ = 3.3 ppm and of OH-4 was δ = 4.37 ppm. These shifts are in good agreement with a intramolecular hydrogen bond between OH-2 and OH-4 which proves the bisaxial position of these oxygen atoms.

Synthesis of the 3*S*-streptenols

For the preparation of the (3*S*)-alkyl derivatives of **1** the (2*R*)-pyrone ***ent*-3** as an intermediate is required. The pyrone ***ent*-3** is accessible either by oxidation of ***ent*-2a** or **2b**. Therefore, a stereoselective reaction to ***ent*-2a** or **2b** is a prerequisite for an efficient synthesis. One approach is based on a stereoselective acetalization of **1** to the pyran **2b**. The control of this reaction can be deduced from the following considerations. In the acid catalyzed acetalization of **1** in methanol in a thermodynamically controlled cyclization the favored isomer at equilibrium is **2a**, (table 1, entries 1- 6). The formation of the configuration at C-2 and therefore the conformation is mainly determined by steric influences, anomeric and related effects and intramolecular hydrogen bonding and other chelation effects.[13] Examination of the NMR spectra for **2a** and **2b** reveals their

conformations.[1] The structure of **2a**, possessing an axial methoxy group and an equatorial hydroxyl group, can be explained by minimized anomeric effects[19,20] and 1,3-diaxial interactions. The minor product **2b** exhibits a conformation where the methoxy and the hydroxyl group both occupy axial positions resulting in a destabilization by 1,3 diaxial interaction. Contributions to the stabilization of this conformation are based on the anomeric effect of the methoxy group and a hydrogen bond between 2-CH_3O and 4-OH. The preferentially formation of **2a** in methanol results obviously from the intermolecular hydrogen bonding of the oxygens with the solvent which overweighs intramolecular effects. Therefore, it could be expected that the intramolecular hydrogen bond gains on importance for the thermodynamic stability of **2b** in nonpolar solvents. If the acetalization of **1** is performed in methylene chloride for example, an influence on the product ratios should be observed.

In order to obtain information on the stabilities of the two possible products in two solvents with distinct differences in polarity molecular dynamics simulations of compounds **2a** and **2b** have been performed in the presence of 50 water molecules or 15 toluene molecules. Using periodic boundary conditions and the valence force field method[21] for evaluating the potential energy the molecular systems have been simulated weakly coupled to a heat bath of 300 K.[21] Assuming that the entropies are the same for **2a** and **2b** and only depent

Table 1: Stereoselective intramolecular acetalization of **1** to **2a** and **2b**

entry	solvent	type	catalyst% by weight	yield (%)	ratio **2a** : **2b**
1	MeOH	H^+	1	90	20 : 1[a,c]
2	MeOH	LiBr	5	90	17 : 1[c]
3	MeOH	$ZrCl_4$	5	90	5 : 1[b]
4	MeOH	$FeCl_3$	1	60	4 : 1[b]
5	MeOH	$ZnCl_2$	5	5	2 : 1
6	MeOH	$CuCl_2$	5	10	2 : 1
7	toluene	H^+	1	50	2 : 1[b,c]
8	toluene	LiBr	5	70	1 : 1[b]
9	toluene	$ZrCl_4$	1	70	1 : 1[b]
10	toluene	$ZnCl_2$	5	50	1 : 3
11	toluene	$CuCl_2$	5	60	1 : 3
12	CH_2Cl_2	H^+	1	50	2 : 1[b,c]
13	CH_2Cl_2	LiBr	5	80	1 : 1[b]
14	CH_2Cl_2	$ZnCl_2$	5	80	1 : 10
15	CH_2Cl_2	$CuCl_2$	5	90	1 : 8

Reactions were carried out with 0.1 mmol **1** with the catalyst in 1ml solvent for 30 min; in entries 7 - 15 to the solvents 5µl methanol was added. If not otherwise indicated the yields and ratios are determined by ^1H NMR spectroscopy; a. isolated yield; b. beginning fragmentation; c. p-toluenesulfonic acid was used, although other organic acids can be used instead.

on the solvent, the mean internal energies, resulting from the dynamics runs, directly yielded relative stabilities of the two acetalization products. In water, **2a** was calculated to be more stable than **2b** by 6.5 kcal/mol, whereas in toluene, the energy difference decreased to only 0.6 kcal/mol. These values supported the qualtitative considerations already discussed above and were in good agreement with experimental results. In methanol (table 1, entry 1) the acetalization of **1** with p-toluenesulfonic acid led to **2a** as main product, whereas the reaction in toluene or methylene chloride (table 1, entries 7 and 12) in the presence of methanol resulted in a 2 : 1 mixture of **2a** and **2b**.

Furthermore, if the reaction is carried out under Lewis acid conditions an additional interaction by bidentatet chelation of the cis orientated oxygen atoms in **2b** by the cation could be expected, which should support the preferentially formation of **2b**, especially in nonpolar solvents. Results obtained for the control of the stereocentres in spiro ketals by Lewis acids were less promissing to date.

The influence of chelation in the acetalization of **1** is already observed in methanol (table 1, entries 2 - 6). For example, the application of lithium bromide as chelating cation[22] exhibits only a slight influence on the product ratios in methanol, toluene or methylene chloride if compared to H^+. Cations with higher complexation abilities expresses a distinct effect on the product ratios of **2a** and **2b** in methanol, even though **2a** is still the favored product. Therefore, we studied the acetalization in nonpolar solvents using various Lewis acids (table 1). In methylene chloride and toluene it was recognized, that Lewis acids which are potent catalysts for the acetalization in methanol led to a fragmentation of **2a** and **2b**. This fact might be due to their higher activities of Lewis acids in nonpolar solvents. The conversion of **1** with $FeCl_3$ for example results in a complete decomposition. Zinc chloride and copper chloride turned out to be the best catalysts in the solvent methylene chloride (table 1 entries 14 and 15). Longer reaction times and larger amounts of the catalyst also produces fragmentation products. Treatment of **2a** with $ZnCl_2$ in CH_2Cl_2 also results in **2b**.

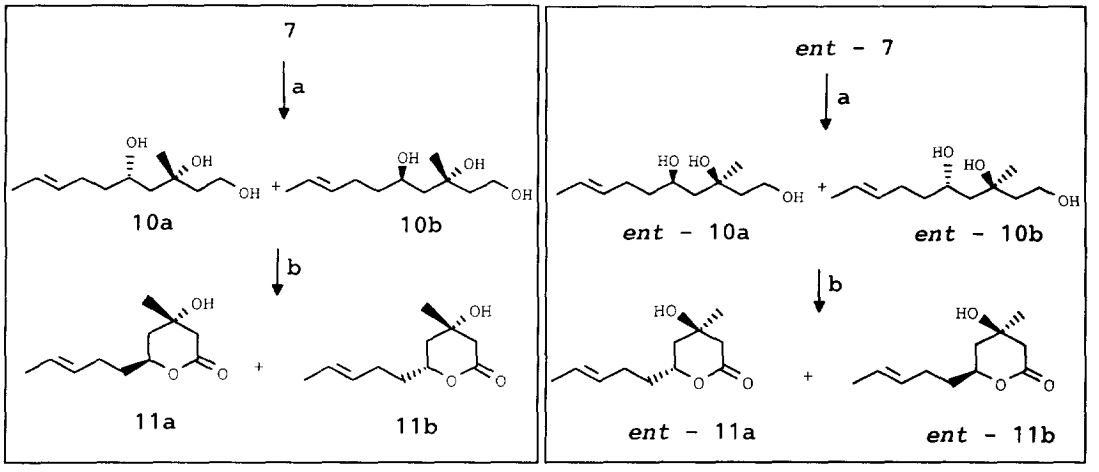
Because of the 1,3-diaxial interaction **2b** is less stable than **2a** and precautions have to be taken in the isolation procedure. Therefore, it is recommended to perform column chromatography in the presence of 0.05 % triethylamine. Nevertheless, some fragmenation of **2a** and especially **2b** during work up and column chromatography could not be avoided. The acetalization of **1** in toluene with $ZnCl_2$ and an 1.1 fold excess of methanol results in 68% of **2b** and 8% of **2a** isolated yield. The subsequent oxidation of **2b** gives the required pyrone ***ent*-3**.

The synthesis of ***ent*-3** could also be achieved from **3**. The reaction sequence starts with the L-Selectride reduction of **3** which yields ***ent*-2b** exclusively.[1] The 1,3-diaxial interaction in ***ent*-2b** gives rise to an isomerization at the acetal centre when treated with H^+ in methanol. In the resulting (2*R*)-pyran ***ent*-2a** the hydroxyl group at C-4 is positioned equatorially, which is in accordance to the already discussed considerations. The advantage of this four step procedure, if compared to the direct acetalization process, is that the less stable ***ent*-2b** does not have to be isolated and can be directly isomerized to the more stable pyran ***ent*-2a**. Oxidation of ***ent*-2a** as described for the preparation of **3** yields the pyrone ***ent*-3**. Although both routes described for the preparation of ***ent*-3** results in a comparable yield of approximately 62%, the procedure via **2b** in two steps was preferred over the five step procedure via ***ent*-2a**.

Reaction of ***ent*-3** with the corresponding alkylmagnesium halogenides to ***ent*-4** -***ent*-6** and deacetalization furnish the synthesis of the (3*S*)-alkyl derivatives of streptenol A ***ent*-7** - ***ent*-9**.

Synthesis of the 3-methyl-δ-lactones

The 3-alkyl streptenols *ent*-**7** - *ent*-**9** represents chiral building blocks which can be used for the synthesis of 3-alkyl lactones with 3*R*,5*R* stereochemistry required for the inhibition of the enzyme HMG CoA-reductase.[23] Therefore, a diastereoselective reduction of *ent*-**7** - *ent*-**9** to the corresponding *syn*-triols and a regioselective oxidation to the δ-lactones is required. This sequence is studied for the 3-methyl streptenol *ent*-**7**. A diastereoselctive reduction for **1** was already described.[1] Excellent *syn* selectivity was achieved by prior chelation of the 3-hydroxy-5-keto compounds with alkoxy boranes and subsequent reduction with $NaBH_4$.[1] The problem in the reduction process of *ent*-**7**, if compared to **1**, is based on the presence of the hemiacetal structure as well as that the inducing centre is a tertiary alcohol. Therefore, reaction of *ent*-**7** with cations results in a chelation of the 2,4-dihydroxy groups which stabilizes the cyclic structure and hinders the reduction of the keto group, especially at lower temperatures and with strong Lewis acids as for example $ZrCl_4$, $FeCl_3$ and Et_2BOMe. In the non cyclic form, which gains on probability at higher temperatures, strong Lewis acids in THF or toluene causes a fragmentation which is accordance with the observations already described. It turned out that the favorable condition is 5% zinc chloride, $NaBH_4$ and performing the reaction at room temperature which gives the desired *syn*-triol *ent*-**10a** and the anti-triol *ent*-**10b** as a 5 : 1 mixture of diastereomers, which could not be separated. The reduction without the Lewis acid yields a 1 : 1 mixture of the stereoisomers. In the next step a regioselective oxidation of the primary hydroxyl group in the triols *ent*-**10a** and *ent*-**10b** is required, which should directly yield the corresponding lactones. This is described already for 1,3,5-trihydroxy compounds derived from streptenol A by using $(PPh_3)_3RuCl_2$[1] as oxidation reagent. The oxidation of *ent*-**10a** and *ent*-**10b** with this reagent in benzene yields the lactones *ent*-**11a** and *ent*-**11b** in one step. This reaction proceeds with excellent regioselectivity. TLC control exhibits quantitative conversion of *ent*-**10a** and *ent*-**10b** into *ent*-**11a** and *ent*-**11b**. The total isolated yield of approximately 70% is explained by the problem of extracting products from the black gum formed from the ruthenium complex during the reaction. The best results are obtained by the evaporation of the benzene and chromatography of the residue, which is dissolved in acetone, directly on silica gel. The lactones *ent*-**11a** and *ent*-**11b** could be easily separated at this step.



(f) $ZnCl_2$, $NaBH_4$ in THF; (b) $[(C_3H_7)_3]_3RuCl_2$ in benzene

The lactones **11a** and **11b** are accessible from **7** via the streptenols **10a** and **10b** by applying the same reaction sequence as described above.

Streptenol A (**1**) is an excellent chiral building block allowing an economic approach to 3-alkyl-δ-lactones. The presented methodology allowed the stereoselective synthesis of both enantiomers of 3-alkyl-streptenol A in four steps and of 3-alkyl-δ-lactones in six steps for the first time starting from one single compound. Furthermore, the two enantiomers of **1** and **3** can be used as starting material in the synthesis of other polyketide derived natural products. The described sequence should not be limited to the variation of the title compound **1**, but should also be applicable to other 1,3-dihydroxy-5-oxo compounds.

The biological activities of the presented derivatives will be described elsewhere. Further application of the pyran acetals **2a**, **2b**, *ent*-**2a** and *ent*-**2b** as synthetic intermediates are presently under investigation.

EXPERIMENTAL

Instrumentation: NMR spectra were recorded on a Bruker AM 360 in $CDCl_3$, if not otherwise indicated, at 303 K with a 5 mm ^{1}H-BB dual probe. Chemical shifts are expressed in ppm with TMS (0 ppm) for ^{1}H- and $CDCl_3$ (77.00 ppm) for ^{13}C- experiments as internal standard. Assignments are based on ^{1}H[^{1}H] decoupling, 2D-^{1}H,^{1}H-COSY and 2D-^{1}H,^{13}C-COSY experiments. IR spectra recorded in $CHCl_3$ on a Perkin-Elmer 197 spectrometer and are expressed in cm^{-1}. Optical rotation was measured with a Perkin Elmer spectrometer 241. ***Materials:*** Thin layer chromatography (TLC) was carried out on silica gel plates (Merck F_{254}). The fermentation and isolation of **1** was carried out as described.[1] The different cations were purchased from Riedel de Haen.

(+)-(2*S*,4*S*,,3'*E*)-4-Hydroxy-2-methoxy-2-(3'-pentenyl)-tetrahydropyran (2a)
10g (54 mmol) Streptenol **1** is dissolved in 500 ml of CH_3OH and is allowed to stir at room temperature with 100 mg p-toluenesulfonic acid for 35 min . The reaction mixture is adjusted to pH 7 with sodium hydrogen carbonate solution and concentrated. Chromatography on silica gel with ethyl acetate/ hexane/ triethylamine (1 : 4 : 0.05) results in **2a** and **2b**; yield 9.7 g (90%) **2a** and 0.32 g (3%) **2b**.
R_f = 0.36 ethyl acetate/ hexane (1 : 2); $[\alpha]_D^{20}$ +82.6° (c = 2.8, CH_2Cl_2); Analalysis for $C_{11}H_{20}O_3$ (200.28): calcd C, 66.0; H, 10.1; found C, 65.8; H, 10.4. The NMR data of **2a** have already been described[1].

(-)-(2*R*,4*R*,3'*E*)-4-Hydroxy-2-methoxy-2-(3'-pentenyl)-tetrahydropyran (*ent*-2a)
1g (5.4 mmol) ***ent*-2b** is allowed to stir with 10 mg p-toluenesulfonic acid in 50 ml of methanol for 1 h. The reaction mixture is adjusted to pH 7 with sodium hydrogen carbonate solution and concentrated. Chromatography on silica gel with ethyl acetate/ hexane / triethylamine (1 : 4 : 0.05) results in **8** as a colourless oil; yield 962 mg (89%).
R_f = 0.36 ethyl acetate/ hexane (1 : 2); $[\alpha]_D^{20}$ -81.3° (c = 3.0, CH_2Cl_2); Analysis for $C_{11}H_{20}O_3$ (200.28): calcd C, 66.0; H, 10.1; found C, 65.6; H, 10.0; The NMR data are identical with those of **2a**, which have already been described.[1]

(-)-(2*R*,4*S*,3'*E*)-4-Hydroxy-2-methoxy-2-(3'-pentenyl)-tetrahydropyran (2b)
15 g (81 mmol) Streptenol **1** is allowed to stir with 750 mg $ZnCl_2$ and 3.6 ml (88.6 mmol) methanol at room temperature in 750 ml methylene chloride for 4 h. The reaction mixture is adjusted to pH 7 with sodium hydrogen carbonate solution and concentrated. Chromatography on silica gel with ethyl acetate/ hexane / triethylamine (1 : 5 : 0.05) results in **2a** and **2b** as colourless oils; yield 10.9 g (67%) **2b** and 1.3 g (8%) **2a**.
R_f = 0.60 ethyl acetate/ hexane (1 : 2); $[\alpha]_D^{20}$ -66.0° (c = 3.0, CH_2Cl_2); Analysisfor $C_{11}H_{20}O_3$ (200.28): calcd C, 66.0; H, 10.1; found C, 65.9; H, 10.1. The NMR data are identical with those of **2a**, which have already been described.[1]

(+)-(2*S*,4*R*,3'*E*)-4-Hydroxy-2-methoxy-2-(3'-pentenyl)-tetrahydropyran (*ent*-2b)
7 g (35 mmol) **3** is allowed to stir in 500 ml of 2-propanol with 12 g (63.2 mmol) L-Selectride at -70°C for 5 h. After quenching the reaction with 10 ml of acetone the mixture is concentrated. Chromatography on silica gel with ethyl acetate/ hexane/ triethylamine (1 : 4 : 0.5) results in ***ent*-2b;** yield 6.45 g (92%).
$[\alpha]_D^{20}$ +64° (c = 3.0, CH_2Cl_2); Analysis for $C_{11}H_{20}O_3$ (200.28): calcd C, 66.0; H, 10.1; found C, 65.8; H, 10.0. The NMR data are identical with those of **2a**, which have been already described.[1]

(+)-(2*S*,3'*E*)-Methoxy-2-(3'-pentenyl)-tetrahydropyran-4-one (3)
10 g (49.9 mmol) **2a** ias allowed to stir with 1.15 g (3.27 mmol) tris(triphenylphosphine) ruthenium(II)chloride and 11.5g N-methyl-morpholine-N-oxide in 300 ml of methylene chloride for 12 h. The reaction mixture is diluted with 300 ml of methylene chloride and is washed three times with 400 ml of a conc. sodium hydrogen carbonate solution and five times with 200 ml of water. The organic layer is dried over sodium sulfate, filtrated with Celite and concentrated which gives ***ent*-3;** yield 9.1 g (90%).
R_f = 0.73 EtOAc/ hexane (1 : 2); $[\alpha]_{20}^D$ +75.9° (c = 1.3, CH_2Cl_2); Analysis for $C_{11}H_{18}O_3$ (198.26): calcd C, 66.65; H, 9.15; found C, 66.5; H, 9.2. The NMR data have already been described[1].

(-)-(2*R*,3'*E*)-Methoxy-2-(3'-pentenyl)-tetrahydropyran-4-one (ent-3)
from **2b**: 10 g (49.9 mmol) **2b** is allowed to stir with . The work up is performed as described for compound **3**. Compound *ent*-**3** is isolated as an colourless oil; yield 8.7 g (92%). R_f = 0.73 ethyl acetate/ hexane (1 : 2); [$\alpha]_{20}^D$ -73.9° (c = 3.0, CH_2Cl_2); Analysis for $C_{11}H_{18}O_3$ (198.26): calcd C, 66.65; H, 9.15; found C, 66.7; H, 9.3. The NMR data were identical with those of **3**, which have already been described.[1]

from ***ent*-2a**: 900 mg (4.5 mmol) **2a** is allowed to stir with 80 mg (0.23 mmol) tris(triphenylphosphine) ruthenium(II)chloride and 800 mg N-methyl-morpholine-N-oxide in 300 ml of methylene chloride for 12 h. The work up is performed as described for compound **3**. Compound *ent*-**3** is isolated as a colorless oil; yield 830 mg (93%).
R_f = 0.73 ethyl acetate/ hexane (1 : 2); $[\alpha]_{20}^D$ -74.2° (c = 3.0, CH_2Cl_2); Analysis for $C_{11}H_{18}O_3$ (198.26): calcd C, 66.65; H, 9.15; found C, 66.5; H, 9.2. The NMR data are identical with those of **3**, which have already been described.[1]

General procedure for the addition of the alkylmagnesium halogenides to 3 and *ent*-3:
2g (10.1 mmol) of **3** or ***ent*-3** is dissolevd in 80 ml of THF and is allowed to stir with 10 ml of a 2M alkylmagnesium halogenide (CH_3MgCl for **4**, $CH_3CH_2CH_2MgCl$ for **5** and CH_2=$CHCH_2MgBr$ for **6**) solution in THF for 4 h at room temperature. After adding 30 ml saturated ammonium chloride solution, the mixture is extracted three times with 100 ml of ethyl acetate. Drying over sodium sulfate and concentrating, yields a syrup which is chromatographed on silica gel with ethyl acetate/ hexane / triethylamine (1 : 6 : 0.05 to 1 : 2 : 0.05) which gives the corresponding tertiary alcohols.

(+)-(2*S*,4*R*,3'*E*)-4-Hydroxy-2-methoxy-4-methyl-2-(3'-pentenyl)-tetrahydropyran (4a) from 3
yield 1.42 g (66%); R_f = 0.49 ethyl acetate/ hexane (1 : 4); $[\alpha]_D^{20}$ +74.2° (c=2, CH_2Cl_2); Analysis for $C_{12}H_{22}O_3$ (214.31): calcd C, 67.3; H, 10.35; found C, 67.6; H, 10.6; ^{1}H NMR δ = 1.15 (s, 3H, 4-CH_3), 1.65 (m, 3H, 5'-H), 3.18 (s, 3H, CH_3-acetal), 3.63 (d,d,d, 1H, J = 11Hz, 5.6Hz, 1.3Hz, 6-Heq), 3.82 (d,d,d, 1H, J = 12.5Hz, 11Hz, 3Hz, 6-Hax), 4.53 (br, 1H, 4-OH), 5.45 (m, 2H, 3'-H, 4'-H); ^{13}C NMR δ = 17.81 (C-5'), 26.31 (C-2'), 30.21 (CH_3-4), 35.83 (C-1'), 37.69 (C-5), 43.16 (C-3), 47.33 (CH_3-acetal), 57.37 (C-6), 66.80 (C-4), 101.08 (C-2), 125.14 (C-4'), 130.31 (C-3'); IR ν = 3500 (OH).

(+)-(2*S*,4*S*,3'*E*)-4-Hydroxy-2-methoxy-4-methyl-2-(3'-pentenyl)-tetrahydropyran (4b) from 3
yield 65 mg (3%); R_f = 0.22 ethyl acetate/ hexane (1 : 4); $[\alpha_D^{20}$ + 70.5° (c = 1, CH_2Cl_2); Analysis for $C_{12}H_{22}O_3$ (214.31): calcd C, 67.3; H, 10.35; found C, 67.6; H, 10.6; ^{1}H NMR δ = 1.42 (s, 3H, 4-CH_3), 1.65 (m, 3H, 5'-H), 3.13 (s, 3H, CH_3-acetal), 3.58 (d,d,d, 1H, J = 11Hz, 12.5Hz, 2.5Hz, 6-Hax), 3.72 (d,d,d, 1H, J = 3.7Hz, 11Hz, 1.8Hz, 6-Heq), 5.42 (m, 2H, 3'-H, 4'-H); ^{13}C NMR δ = 17.85 (C-5'), 26.45 (C-2'),

27.94 (CH_3-4), 36.30 (C-1'), 39.64 (C-5), 46.30 (C-3), 47.23 (CH_3-acetal), 59.28 (C-6), 68.43 (C-4), 100.45 (C-2), 124.97 (C-4'), 130.60 (C-3'); IR ν = 3500 (OH).

(+)-(2*S*,4*R*,3'*E*)-4-Hydroxy-2-methoxy-2-(3'-pentenyl)-4-propyl-tetrahydropyran (5) from 3
yield 1.51 g (62%); R_f = 0.71 ethyl acetate/ hexane (1 : 3); $[\alpha]_D^{20}$ + 52.1° (c = 1.7, CH_2Cl_2); Analysis for $C_{14}H_{26}O_3$ (242.36): calcd C, 69.4; H, 10.0; found C, 69.2; H, 9.6; ^{1}H NMR δ = 0.98 (t, 3H, J = 6.5Hz, 3"), 1.65 (m, 3H, 5'-H), 3.21 (s, 3H, CH_3-acetal), 3.67 (d,d,d, 1H, J = 12Hz, 5.5Hz, 1.8Hz, 6-Heq), 3.87 (d,d,d,, 1H, J =12Hz, 11.5Hz, 3.2Hz, 6-Hax), 4.52 (br, 1H, 4-OH), 5.42 (m, 2H, 3'-H, 4'-H); ^{13}C NMR δ = 14.55 (3"), 15.73 (2"), 17.82 (C-5'), 26.35 (C-2'), 35.92 (C-6'), 36.81 (C-5), 41.88 (1"), 45.62 (C-3), 47.33 (CH_3-acetal), 57.32 (C-6), 68.76 (C-4), 101.17 (C-2), 125.16 (C-4'), 130.34 (C-3'); IR ν = 3500 (OH).

(+)-(2*S*,4*R*,3'*E*)-4-Hydroxy-2-methoxy-2-(3'-pentenyl)-4-(2"-propenyl)-tetrahydropyran (6) from 3
yield 1.5 g (62%). R_f = 0.68 ethyl acetate/ hexane (1 : 3); $[\alpha]_D^{20}$ + 65.0° (c = 1.7, CH_2Cl_2); Analysis for $C_{14}H_{24}O_3$ (240.35): calcd C, 69.95; H, 10.1; found C, 70.0; H, 9.9; ^{1}H NMR δ = 1.62 (m, 3H, 5'-H), 3.20 (s, 3H, CH_3-acetal), 3.67 (d,d,d, 1H, J = 12Hz, 5.5Hz, 1.8Hz, 6-Heq), 3.86 (d,d,d,, 1H, J =12Hz, 11.5Hz, 3.2Hz, 6-Hax), 4.95 - 5.12 (m, 2H, 3"-H), 5.42 (m, 2H, 3'-H, 4'-H), 5.84 - 5.96 (m, 1H, 2"-H); ^{13}C NMR δ = 17.94 (C-5'), 26.39 (C-2'), 35.90 (C-1'), 36.11 (C-5), 41.32 (C-1"), 47.44 (C-3), 47.67 (CH_3-acetal), 57.29 (C-6), 68.65 (C-4), 101.25 (C-2), 117.92 (C-3"), 125.22 (C-4'), 130.33 (C-3'), 133.54 (C-2"); IR ν = 3500 (OH).

(-)-(2*R*,4*S*,3'*E*)-4-Hydroxy-2-methoxy-4-methyl-2-(3'-pentenyl)-tetrahydropyran (*ent*-4a) from *ent*-3
yield 1.45 g (67%); R_f = 0.49 ethyl acetate/ hexane (1 : 4); $[\alpha]_D^{20}$ -74.3° (c = 2.5, CH_2Cl_2); Analysis for $C_{12}H_{22}O_3$ (214.31): calcd C, 67.3; H, 10.35; found C, 67.4; H, 10.5; The NMR data are identical with those of **4a**.

(-)-(2*R*,4*S*,3'*E*)-4-Hydroxy-2-methoxy-2-(3'-pentenyl)-4-propyl-tetrahydropyran (*ent*-5) from *ent*-3
yield 1.62 g (66%); R_f = 0.71 ethyl acetate/ hexane (1 : 3); $[\alpha]_D^{20}$ -51.6° (c = 1.5, CH_2Cl_2); Analysis for $C_{14}H_{26}O_3$ (242.36): calcd C, 69.4; H, 10.0; found C, 69.5; H, 9.4; The NMR data were identical with those of **5**.

(-)-(2*R*,4*S*,3'*E*)-4-Hydroxy-2-methoxy-2-(3'-pentenyl)-4-(2"-propenyl)-tetrahydropyran (*ent*-6) from ent-3
yield 1.5 g (62%). R_f = 0.68 ethyl acetate/ hexane (1 : 3); $[\alpha]_D^{20}$ -65.2° (c = 1.7, CH_2Cl_2); Analysis for $C_{14}H_{24}O_3$ (240.35): calcd C, 69.95; H, 10.1; found C, 69.7; H, 9.7; The NMR data are identical with those of **6**.

General procedure for the deacetalization of 4 - 6 and *ent*-4 - *ent*-6
Compound **4**, **5** or **6** (6 mmol) is stirred at room temperature with 20 mg $FeCl_3$ in 30 ml of 2-propanol and 30 ml of water for 30 min. The reaction mixture is adjusted to pH = 7 with sodium hydrogen carbonate solution and concentrated to a syrup. The residue is dissolved in 30 ml of methylene chloride and filtrated over silica gel.

(+)-(2*S*,4*R*,3'*E*)-2,4-Dihydroxy-4-methyl-2-(3'-pentenyl)-tetrahydropyran (7) from 4a
yield 1.1 g (92%); R_f = 0.34 ethyl acetate/ hexane (1 : 2); $[\alpha]_D^{20}$ +31.7° (c = 2, CH_2Cl_2); Analysis for $C_{11}H_{20}O_3$ (200.28): calcd C, 66.0; H, 10.1; found C, 65.5; H, 10.0; ^{1}H NMR δ = 1.2 (s, 3H, 4-CH_3), 1.60 (m, 3H, 5'-H), 3.3 (br, 1H, 2-OH), 3.75 (d,d,d, 1H, J = 12Hz, 5.5Hz, 1.8Hz, 6-Heq), 4.26 (d,d,d,, 1H, J =12Hz, 12.5Hz, 3.Hz, 6-Hax) 4.35 (br, 1H, 4-OH), 5.45 (m, 2H, 3'-H, 4'-H); ^{13}C NMR δ = 17.85 (C-5'), 28.06 (C-2'), 30.83 (CH_3-4), 37.88 (C-1'), 41.93 (C-5), 43.86 (C-3), 56.79 (C-6), 68.71 (C-4), 97.67 (C-2), 125.24 (C-4'), 130.92 (C-3'); NMR spectra confirmed 10% of the noncyclic 5-oxo compound in the sample; ^{13}C NMR δ = 17.8 (C-10), 26.40 (C-7), 26.97 (CH_3-4), 42.42 (C-2), 44.39 (C-6), 51.66 (C-4), 59.37 (C-1),

72.58 (C-3), 126.31 (C-9), 128.91 (C-8), 212.81 (C-5). IR ν = 3100 -3600 (OH), 1705 (C=O).

(+)-(2*S*,4*R*,3'*E*)-2,4-Dihydroxy-2-(3'-pentenyl)-4-propyl-tetrahydropyran (8) from 5
yield 1.2 g (89%); R_f = 0.23 ethyl acetate/ hexane (1 : 3); $[\alpha]_D^{20}$ +26.5° (c = 1.5, CH_2Cl_2); Analysis for $C_{13}H_{24}O_3$ (228.33): calcd C, 68.4; H, 10.6; found C, 68.8; H, 10.2; ^{1}H NMR δ = 0.98 (t, 3H, J = 6.5Hz, 3"-H), 1.65 (m, 3H, 5'-H), 3.15 (br, 1H, 2-OH), 3.69 (d,d,d, 1H, J = 12Hz, 5.5Hz, 1.8Hz, 6-Heq), 4.15 (d,d,d,, 1H, J =12Hz, 12.5Hz, 3.Hz, 6-Hax) , 4.4 (br, 1H, 4-OH), 5.42 (m, 2H, 3'-H, 4'-H); ^{13}C NMR δ = 14.46 (C-3"), 15.69 (C-2"), 17.82 (C-5'), 26.07 (C-2'), 36.34 (C-1'), 42.29 (C-5), 42.03 (C-1"), 46.13 (C-3), 56.68 (C-6), 70.80 (C-4), 97.64 (C-2), 125.23 (C-4'), 130.57 (C-3'); IR Anal. Calcd for $C_{13}H_{24}O_3$ (228.33): C, 68.4; H, 10.6. Found: C, 68.8; H, 10.2. Anal. Calcd for $C_{13}H_{24}O_3$ (228.33): C, 68.4; H, 10.6. Found: C, 68.8; H, 10.2. ν = 3200 - 3600 (OH).

(+)-(2*S*,4*R*,3'*E*)-2,4-Dihydroxy-2-(3'-pentenyl)-4-(2"-propenyl)-tetrahydropyran (9) from 6
yield 1.1 g (79%); R_f = 0.26 ethyl acetate/ hexane (1 : 3); $[\alpha]_D^{20}$ +29.0° (c = 1.0, CH_2Cl_2); Analysis for $C_{13}H_{22}O_3$ (226.32): calcd C, 69.0; H, 9.80; found C, 69.3; H, 9.6; ^{1}H NMR δ = 1.58 (m, 3H, 5'-H), 3.05 (br, 1H, 2-OH), 3.65 (d,d,d, 1H, J = 12Hz, 5.5Hz, 1.8Hz, 6-Heq), 4.05 (d,d,d, 1H, J =12Hz, 12.5Hz, 3.2Hz, 6-Hax) , 4.32 (br, 1H, 4-OH), 4.95 - 5.15 (m, 2H, (3"-H), 5.42 (m, 2H, 3'-H, 4'-H), 5.75 - 5.85 (m, 1H, (2"-H); ^{13}C NMR δ = 17.98 (C-5'), 26.15 (C-2'), 36.23 (C-1'), 41.98 (C-1"), 42.42 (C-5), 47.97 (C-3), 56.63 (C-6), 70.30 (C-4), 97.60 (C-2), 119.67 (C-3"), 125.25 (C-4'), 130.97 (C-3'), 132.35 (C-2"); IR ν = 3200 - 3600 (OH).

(-)-(2*R*,4*S*,3'*E*)-2,4-Dihydroxy-4-methyl-2-(3'-pentenyl)-tetrahydropyran (*ent*-7) from *ent*-4a
yield 1.1 g (92%); R_f = 0.34 ethyl acetate/ hexane (1 : 2); $[\alpha]_D^{20}$ -31.1° (c = 2, CH_2Cl_2); Analysis for $C_{11}H_{20}O_3$ (200.28): calcd C, 66.0; H, 10.1; found C, 66.1; H, 9.9. The NMR data are identical with those of **7.**

(-)-(2*R*,4*S*,3'*E*)-2,4-Dihydroxy-2-(3'-pentenyl)-4-propyl-tetrahydropyran (*ent*-8) from *ent*-5
yield 1.2 g (89%); R_f = 0.23 ethyl acetateEtOAc/ hexane (1 : 3); $[\alpha]_D^{20}$ -26.2° (c = 1.5, CH_2Cl_2); Analysis for $C_{13}H_{24}O_3$ (228.33): calcd C, 68.4; H, 10.6; found C, 68.6; H, 10.4. The NMR data are identical with those of **8.**

(-)-(2*R*,4*S*,3'*E*)-2,4-Dihydroxy-4-(2'-propenyl)-2-(3'-pentenyl)-tetrahydropyran (ent-9) from ent-6
yield 1.15 g (84%); R_f = 0.26 ethyl acetate/ hexane (1 : 3); $[\alpha]_D^{20}$ -28.2° (c = 1.0, CH_2Cl_2); Analysis for $C_{13}H_{22}O_3$ (226.32): calcd C, 69.0; H, 9.80; found C, 79.3; H, 9.6; The NMR data are identical with those of **9.**

(3*R*,5*S*,8*E*)-1,3,5-Trihydroxy-3-methyl-8-decene (10a) and (3*R*,5*R*,8*E*)-1,3,5-trihydroxy-3-methyl-8-decene (10b)
To a solution of 1g (5.0 mmol) **7** in 25 ml of THF, 50 mg $ZnCl_2$ and 450 mg (11.9 mmol) sodium borohydride are added and stirred at room temperature for 20 h. The reaction is quenched with 10 ml of water and 1 ml of acetic acid. After extraction three times with 100 ml of ethyl acetate the organic layer is washed three times with 50 ml of water. Drying over sodium sulfate, concentration and chromatography on silica gel with methylene chloride/ methanol (20 : 1) furnished a mixture of the *syn*-triol **10a** and the *anti*-triol **10b**, which could not be sepatrated. The yields of 0.73 g (72%) for **10a** and 0.16g (16%) for **10b** were determined by NMR spectroscopy. The assignments of the NMR signals were performed in the spectra of the mixtures based on 2D NMR analysis.

10a: R_f = 0.60 methylene chloride/ methanol (15 : 1); ^{1}H NMR δ = 1.33 (s, 3H, 3-CH_3), 1.64 (m, 3H, 10-H), 2.10 (m, 2H, 7-H), 3.90 (m, 2H, 1-H), 5.45 (m, 2H, 8-H, 9-H); ^{13}C NMR δ = 17.98 (C-10), 26.83 (4-CH_3), 28.75 (C-7), 38.03 (C-6), 43.79 (C-2), 45.54 (C-4), 59.64 (C-1), 69.30 (C-5), 74.50 (C-3), 125.65 (C-9), 130.73 (C-8).

10b: R_f = 0.58 (15 : 1); ^{1}H NMR δ = 1.29 (s, 3H, 3-CH_3), 1.64 (m, 3H, 10-H), 2.20 (m, 2H, 7-H), 4.1 (m,

2H, 1-H), 5.45 (m, 2H, 8-H, 9-H); ^{13}C NMR δ = 17.98 (C-10), 26.75, (4-CH_3), 28.50 (C-7), 38.03 (C-6), 43.79 (C-2), 46.50 (C-4), 60.02 (C-1), 69.10 (C-5), 73.48 (C-3), 125.60 (C-9), 130.71 (C-8).

(3*S*,5*R*,8*E*)-1,3,5-Trihydroxy-3-methyl-8-decene (*ent*-10a) and (3*S*,5*S*,8*E*)-1,3,5-trihydroxy-3-methyl-8-decene (*ent*-10b)

To a solution of 1g (5.0 mmol) *ent*-**7** in 25 ml of THF, 50 mg $ZnCl_2$ and 450 mg (11.9 mmol) sodium borohydride are added and stirred at room temperature for 20 h. The reaction is quenched with 10 ml of water and 1 ml of acetic acid. The work up is performed as described for compounds **10a** and **10b**, which led to a mixture which could not be separated; yield 0.79 g (79%) *ent*-**10a** and 0.16 g (16%) *ent*-**10a**, determined by NMR spectroscopy.

ent-**10a:** R_f = 0.60 methylene chloride/ methanol (15 : 1); the NMR data arre identical with those of **10a.**

ent-**10b:** R_f = 0.58 methylene chloride/ methanol (15 : 1); the NMR data are identical with those of **10b.**

(-)-(3*S*,5*S*,3'*E*)-4-Hydroxy-4-methyl-6-(3'-penteny)-tetrahydropyran-2-one (11a) and (+)-(3*S*,5*R*,3'*E*)-4-hydroxy-4-methyl-6-(3'-penteny)-tetrahydropyran-2-one (11b)

The mixture of compounds **10a** and **10b** (320 mg, 1.58 mmol in a 5 : 1 mixture) are allowed to stir in 15 ml of benzene with 1 g (1.14 mmol) tris(triphenylphosphine)-ruthenium(II)chloride at room temperature for 3 d. The benzene is evaporated and the resulting residue is dissolved in 2 ml of acetone. Chromatography of the acetone solution on silica gel with ethyl acetate/ hexane (1 : 1) furnishes the lactones **11a** and **11b** as colourless oils; yield of 172 mg (55%) **11a** and 34 mg (11%) **11b**.

11a: R_f = 0.66 ethyl acetate/ hexane (3 : 1); $[\alpha]_D^{20}$ -48.9° (c = 1, CH_2Cl_2); Analysis for $C_{11}H_{18}O_3$ (198.26): calcd C, 66.6; H, 9.15; found C, 66.4; H, 9.5; ^{1}H NMR δ = 1.32 (s, 3H, 3-CH_3), 1,58 (m, 1H, 5-Hax), 1.63 (m, 3H, 5'-H), 1.6 - 1.8 (m, 2H, 1'-H), 2.05 (m, 1H, 5-Heq), 2.1 (m, 2H, 2'-H), 2.42 (d, 1H, J = 17Hz, 3-Hax), 2.65 (d,d, 1H, J = -17Hz, 2Hz, 3-Heq), 4.6 (m, 1H, 6-Hax), 5.40 (m, 1H, 3'-H), 5.45 (m, 2H, 3'-H, 4'-H); ^{13}C NMR δ = 17.85 (C-5'), 27.83 (C-2'), 30.32 (CH_3), 35.37 (C-1'), 41.68 (C-5), 44.21 (C-3), 68.28 (C-4), 76.35 (C-6), 125.97 (C-4'), 129.82 (C-3'), 170.71 (C-2); IR ν = 3200 - 3600 (OH), 1740 (lactone);

11b: R_f = 0.58 ethyl acetate/ hexane (3 : 1); $[\alpha]_D^{20}$ +25.5° (c = 1, CH_2Cl_2); Analysis for $C_{11}H_{18}O_3$ (198.26): calcd C, 66.6; H, 9.15; found C, 66.3; H, 9.2; ^{1}H NMR δ = 1.38 (m, 3H, 4-CH_3), 1.58 (m,2H, 1'-H), 1.62 (m, 3H, 5'-H), 1.65 - 1.8 (m, 2H, 1'-H, 5-Hax), 1.94 (d,d,d, J= 14Hz, 4Hz, 1Hz, 5-Heq), 2.1 (m, 2H, 2'-H), 2.4 - 2.6 (m, 2H, 3-H), 4.15 (m, 1H, 6-H_{ax}), 5.45 (m, 2H, 3'-H, 4'-H); ^{13}C NMR δ = 17.87 (C-5'), 27.93 (C-2'), 29. 17 (CH_3), 35.36 (C-1'), 43.28 (C-5), 45.13 (C-3), 68.85 (C-4), 76.44 (C-6), 126.23 (C-4'), 129.53 (C-3'), 170.77 (C-2); IR ν = 3200 - 3600 (OH), 1740 (lactone).

(+)-(3*R*,5*R*,3'*E*)-4-Hydroxy-4-methyl-6-(3'-penteny)-tetrahydropyran-2-one (*ent*-11a) and (-)-(3*R*,5*S*,3'*E*)-4-hydroxy-4-methyl-6-(3'-penteny)-tetrahydropyran-2-one (*ent*-11b)

A mixture of *ent*-**10a** and *ent*-**10b** (250 mg, 1.24 mmol in a 5 : 1 mixture) is oxidized in the same manner as described for the preparation of **11a** and **11b**. Lactones *ent*-**11a** and *ent*-**11b** are obtained as colourless oils; yield 130 mg (53%) *ent*-**11a** and 29 mg (12%) *ent*-**11**.

ent-**11a**: R_f = 0.66 ethyl acetate/ hexane (3 : 1); $[\alpha]_D^{20}$ +48.3° (c = 1, CH_2Cl_2); Analysis for $C_{11}H_{18}O_3$ (198.26): calcd C, 66.6; H, 9.15; found: C, 66.2; H, 9.6. The spectral data of ***ent*-11a** are identical with those of **11a**.

ent-**11b**: R_f = 0.58 ethyl acetate/ hexane (3 : 1); $[\alpha]_D^{20}$ -24.6° (c = 1, CH_2Cl_2); Analysis for $C_{11}H_{18}O_3$ (198.26): calcd C, 66.6; H, 9.15; found: C, 66.5; H, 9.7. The spectral data are identical with those of **11b**.

Acknowledgement: This work is based on the project "chemical-biological screening" originally established by Prof. A. Zeeck, University of Göttingen, and Dr. S. Grabley, Hoechst AG. We would like to thank Dr. J. Wink, Hoechst AG, for fermenation of **1**, Prof. Dr. A. Zeeck, University of Göttingen, Dr. R. Thiericke and Dr. H. Kluge, Hoechst AG, for valuable discussions. Furthermore, we would like to thank R. Schrenk, H. Schneider and R. Schimko for excellent technical assitance. This work was supported by the Bundesministerium für Forschung und Technologie (grant No. 0319311B). The authors are responsible for the contents within this publication.

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(*Received in Germany* 30 *March* 1995; *accepted* 7 *June* 1995)