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SECONDARY METABOLITES BY CHEMICAL SCREENING[1]-13. ENANTIOSELECTIVE SYNTHESIS OF δ-LACTONES FROM STREPTENOL A, A CHIRAL BUILDING BLOCK FROM STREPTOMYCES

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Abstract: The enantioselective synthesis of all four stereoisomers of the secondary metabolite 3-hydroxy-5-decanolide (**4a**) from Cephalosporium recifei and both enantiomers of massoialactone (**5a**) by starting from one chiral building block, streptenol A (**1a**), a secondary metabolite from Streptomyces sp., is described. The key steps of the reaction sequence involve diastereoselective reduction of **1a** to syn- or anti-triol **2a** and **2b** and the regioselective oxidation of the primary hydroxyl group. This reaction furnishes in one step the δ-lactones **3a** and **3b** and requires no protecting group.

Chemical screening for secondary metabolites[2] in the culture broth of microorganisms leads to natural products with different types of structures and biological activities. This method allows the detection of compounds independent from their biological activity, which can lead to chiral synthons for synthesis. Therefore, this type of screening is a possibility for extending the chiral pool.[3] One of the chiral synthons isolated from Streptomyces sp. DSM 4356 is streptenol A (**1a**),[3] which was also found in Streptomyces fimbriatus[4] and Streptomyces cirratus.[5] Streptenol (**1a**) exhibits an immunostimulating activity.[5]

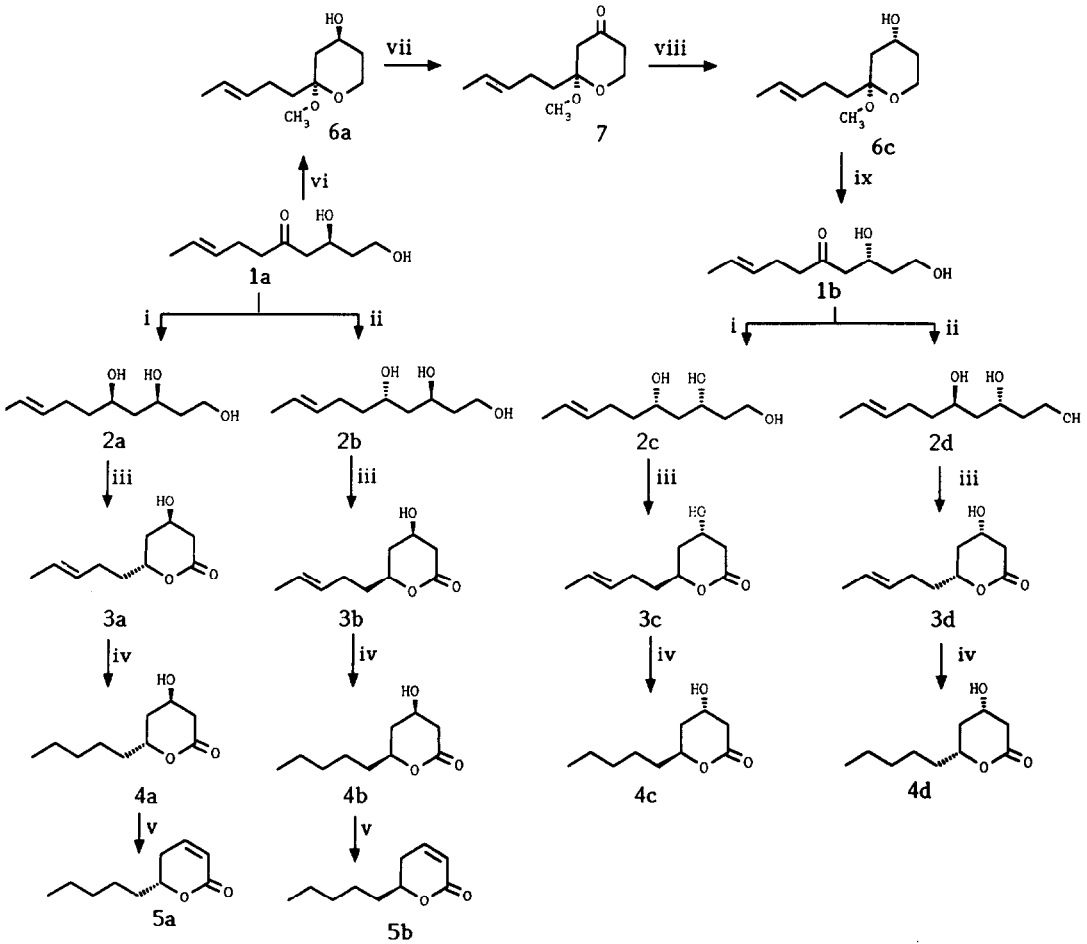
We propose that streptenol A (**1a**) is an excellent starting material for the synthesis of δ-lactones. This study was designed to investigate biologically active members of this family.

δ-Lactones are interesting compounds with widespread distribution in nature and exhibit a variety of biological activities. We were interested in the δ-lactones 3-hydroxy-5-decanolide (**4a**) from Cephalosporium recifei[6] and in massoialactone (**5a**). The lactone **5a** is an ingredient of a number of plant sources, e.g. the bark oil of Cryptocarya massoia,[7] in cane molasses[8] and in the defense secretion of two species of ants of the genus Camponotus.[9] The lactone moiety in compound **4a** is identical to the lactone unit in compactin and mevinolin and might also be a potent inhibitor of the enzyme HMG-CoA reductase.[10] Lactone **5a** could also exhibit further biological activities yet unknown. Investigation of the biological activities of the discussed lactones, should therefore include studies of all four stereoisomers of **4** and both enantiomers of **5**.

For the lactone **4a** only one asymmetric synthesis in 7 steps in an overall yield of 26% was described by Knight,[11] where the chirality was introduced by yeast reduction in 76% ee. Stereoisomers **4b** - **4d** were not synthesized up to now. Natural occurring massoialactone (**5a**) was synthesized from **4a** by the elimination of the hydroxyl group.[8,11] Unnatural (+)-massoialactone was prepared by Mori[12] from (*R*)-glycrolaldehyde in 75% ee. Both enantiomers of **5** were synthesized by Pirkle,[13] where the key step involves chromatographic separation of diastereomeric derivatives of racemic intermediates.[14]

The strategy used in our synthesis for the introduction of the second chirality into the diastereomers **2a** and **2b** is the diastereoselective reduction of the ketone in **1a** with metal hydrides by

1,3-asymmetric induction from the stereogenic centre at C-3. Because this reduction determines the chiral centre C-5 in massoialactones **5a** and **5b**, the chirality inducing group OH-3 can be eliminated after lactone formation furnishing the double bond. In fact, only one chiral building block should be used for the synthesis of both enantiomers of **5**.



Scheme I

i. Et_3B, MeOH, $NaBH_4$, -70°C, ii. $NaHB(OAc)_3$, HOAc, CH_3CN, -70°C, iii. $(PPh_3)_3RuCl_2$, benzene iv. Pd/C, H_2. v. p-toluenesulfonic acid vi. LiBr, MeOH, vii. $(C_3H_7)_4NRuO_4$, N-methylmorpholine-N-oxide, viii. L-Selectride, -70°C ix. $FeCl_3$, isopropanol, water.

The 1,3 asymmetric induction by reduction of ß-hydroxy-ketones was studied intensively in the last decade. Excellent syn-selectivity was achieved by prior chelation of the ß-hydroxy-keto moiety with $ZnCl_2$,[15] $FeCl_2$,[16] trialkylboranes in the presence of activators like air[17] or pivalic acid,[18] or alkoxydialkylboranes.[19] Adding $NaBH_4$ to the six-membered-chelate intermediates lead to an intermolecular hydride addition which explains the syn-selectivity. The preparation of the anti-diols was performed by reduction of ß-hydroxy-ketones with $NaHB(OAc)_3$ or $NH_4HB(OAc)_3$, where by ligand exchange of acetate for substrate alcohol a six-membered chair like intermediate is formed. The intramolecular hydride transfer explains the anti-selectivity.[20]

Complexation of **1a** with triethylborane in the presence of methanol and reduction with $NaBH_4$ results in the syn-diol **2a** in good yield and excellent diastereoselectivity (98 : 2). The anti-diol **2b** is achieved by using Evan's method with $NaHB(OAc)_3$ also in good yield and in excellent selectivity (95 : 5). The triol **2b** was first described as a secondary metabolite from the streptenol A production strain Streptomyces sp. DSM 4356 and was named streptenol B.[3] Because of the observed selectivity it is obvious that the C-1 hydroxyl group does not interfer with the different transition states leading to **2a** and **2b**. The diastereomeric purity of **2a** and **2b** determines the enantiomeric purity of **5a** and **5b**, because a preparative chromatographic separation of corresponding diastereomers is not possible at any other step.

In the next step a regioselective oxidation of the primary hydroxyl group in the triols **2a** and **2b** is required, which should directly yield the corresponding lactones. This was described in selected examples by using different ruthenium complexes for the oxidation of 1,4 or 1,5 diols.[21] The reaction of **2a** and **2b** with $(PPh_3)_3RuCl_2$[22] in benzene yields lactones **3a** and **3b** in one step. This reaction proceeds with excellent regioselectivity. TLC control exhibits quantitative conversion of **2a** and **2b** into the corresponding lactones **3a** and **3b**, where no further oxidation of the 3-hydroxyl group can be observed. The 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 directly on silica gel. Using catalytic amounts of the ruthenium complex with N-methylmorpholine-N-oxide[23] as the oxidation reagent decreases the regioselectivity as well as the yields of oxidation products.

The hydrogenation of **3a** finishes the synthesis of the natural product **4a**, $[\alpha]_D^{20}$ +36.9° (c = 0.92, CH_2Cl_2) or $[\alpha]_D^{20}$ + 32.1° (c = 0.92, $CHCl_3$). For the natural product with 3R, 5R stereochemistry **4a** an optical rotation of $[\alpha]_D^{20}$ +27.4° (c = 11.7, $CHCl_3$) was reported and for the synthetic sample Knight calculated $[\alpha]_D^{20}$ + 38.7 (c = 1.4, $CHCl_3$) based on 76% ee.

Diastereoisomer **4b** is obtained in 92% yield from **3b** by hydrogenation, $[\alpha]_D^{20}$ -39.2 (c = 1.4, CH_2Cl_2).

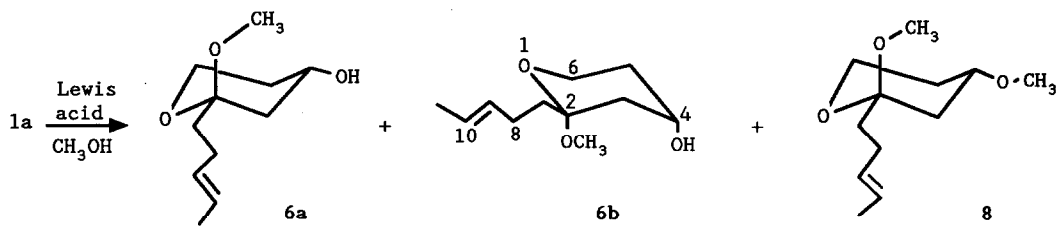
The coupling constants in the ^1H NMR spectra of **4a** and **4b** were studied in detail to verify the stereochemistry. In **4a** and **4b** the alkyl side chain is orientated equatorial, so that the hydroxyl group is positioned axial in **4a**, $J_{4\text{-Hax}/3\text{-Heq}}$ = 3.48Hz, and equatorial in **4b**, $J_{4\text{-Hax}/3\text{-Hax}}$ = 9.30Hz. The full sets of coupling constants indicate a twisted half chair conformation for the lactones **4a** and **4b**. This is also stressed by the slightly reduced W-coupling $^4J_{2\text{-Heq}/4\text{-Heq}}$ = 1.70 Hz in **4a** and $^4J_{2\text{-Heq}/4\text{-Heq}}$ = 1.41Hz in **4b** compared to **6a**, **6b** and **7**.

Elimination of the original chirality inducing hydroxyl group at C-3 is carried out as described in literature for conversion of **4a** into **5a** with p-toluenesulfonic acid. Natural (-)-massoialactone (**5a**) is obtained in 77% yield. The optical rotation $[\alpha]_D^{20}$ -112.5° (c = 1, $CHCl_3$) is in good agreement with the value of synthetic **5a** calculated by Knight, $[\alpha]_D^{25}$ -108.4° (c = 2.7, $CHCl_3$)[11] based on 76% ee and determined by Pirkle,[13] $[\alpha]_D^{21.4}$ -110.5° (c = 1, $CHCl_3$). For the natural product **5a** $[\alpha]_D^{25}$ -91.4 (c = 1.035, $CHCl_3$) was described.[11]

Elimination of **4b** yields the unnatural (+)-massoialactone (**5b**) in 70%, $[\alpha]_D^{20}$ +113° (c = 1, $CHCl_3$). Pirkle reported for **5b** $[\alpha]_D^{22.6}$ +109.6° (c = 2, $CHCl_3$).[13]

The discussed synthesis of **4a** and **4b** in three steps in approximately 50% yield and **5a** and **5b** in four steps in approximately 40% yield from **1a** is an economic method, where no protecting group and only one chiral building block is used.

For the synthesis of **4c** and **4d**, enantiomers of **4a** and **4b**, the inversed stereochemistry at C-3 in **1a** is required. Attempts to use the Mitsunobu reaction for the inversion of C-3 in **1a** with an acid as nucleophile leads to a fragmentation of the molecule. Because of this fact another methodology for the inversion sequence is described. The 1-hydroxy-5-oxomoiety in **1a** allows formation of a 1,5 cyclic acetal **6a** where the new created chiral centre is directed by the stereogenic centre at C-3 in **1a** (Scheme II).



SCHEME II

The product distribution of acetals **6a**, **6b** versus ether-acetal **8** depends on the Lewis acid as well as on it's concentration. It turned out that 5% $FeCl_3$ give the dimethyl compound **8**. If 1% $FeCl_3$, 5% $CuCl_2$ or 5% LiBr is used, the desired acetal **6a** is formed as the main product. Isopropanol as more sterically hindered alcohol compared to methanol yields the corresponding acetals, but these products are less stable than **6a** and **6b**. Furthermore, **6b** is less stable than **6a**, which can be explained by the 1,3-diaxial interaction.

The configuration at C-2 of **6a** and **6b** is required for the prediction of the following stereoselective reaction and is therefore determined by ^1H NMR spectroscopy. Acetals **6a** and **6b** both exhibit a chair conformation, where OH-4 is equatorial in **6a** and axial in **6b**. ^1H-^1H coupling constants fit well to a chair conformation (fig. 1). A down field shift of the hydrogen of OH-4 and a large coupling constant $J_{OH\text{-}4}/J_{H\text{-}4}$ is observed in the ^1H NMR spectrum of **6b** as compared to **6a**. The straightforward explanation claims a hydrogen bond between the hydrogen atom of OH-4 and the

axial oxygen atom at C-2 in **6b**. Therefore, the stereochemistry is 2*S* in **6a** and 2*R* in **6b**, and the methoxy group is axial in **6a** as well as in **6b** deduced by ^{13}C NMR.

By using an oxidation and reduction sequence the inversion of the stereochemistry at C-4 in **6a** should be possible. Because of the acid sensitivity of acetal **6a** neutral oxidation conditions are required. Tetrapropylammonium perruthenate/ N-methylmorpholine-N-oxide oxidation[24] of **6a** yields tetrahydropyrone **7**, where the originally inducing stereogenic centre is destroyed. The axial position of the methoxy group in **7** is deduced from the very close similarity of ^{1}H and ^{13}C NMR spectra of **6a**, **6b** and **7**.The inversion should now be possible by an equatorial attack of a hydride anion under kinetic control to **6c**, whereas an axial attack under thermodynamic control should yield the starting material **6a**. Favoured for an equatorial attack are bulky metal hydrides at low temperatures. L-Selectride reduction of **7** yields **6c** exclusively.

Because of the acid labile cyclic acetal, it is recommended to perform work up and column chromatography in the presence of 1% triethylamine. Based on this fact, attempts to use the Mitsunobu reaction for the inversion of C-4 in **6a** failed. The acetal can be easily cleaved with $FeCl_3$ in isopropanol/ water to produce **1b**, which possesses the opposite configuration at C-3 as the natural product **1a**. With this reaction sequence both enantiomers of streptenol A **1** are available for the first time, which is interesting for comparing the immunostimulating activity of both enantiomers. The optical rotation of **1b** is $[\alpha]_D^{20}$ -23° (c = 1, $CHCl_3$), whereas for **1a** $[\alpha]_D^{25}$ +23° (c = 1.05, $CHCl_3$)[4] was found. Optical purity was determined for the acetylated **1a** and **1b** with ^{1}H NMR spectroscopy to be better than 90% ee using $Eu(hfc)_3$ as the chiral shift reagent.

Diastereoselective reduction of **1b** to **2c** and **2d** is performed as decribed for **2a** and **2b**. Using this reaction sequence all four stereoisomers of streptenol B (**2b**) become available. The oxidation of **2c** with the ruthenium complex and following hydrogenation yields **4c**, the enantiomer of the natural product **4a**; $[\alpha]_D^{20}$ -34.9° (c = 2, CH_2Cl_2). The overall yield of this seven step procedure is approximately 30%. The oxidation of **2d** with the ruthenium complex and following hydrogenation results in **4d**, the enantiomer of **4b**, $[\alpha]_D^{20}$ +38.6° (c = 1.5, CH_2Cl_2).

The application of an oxidation and reduction sequence on **4a** and **4b** for the inversion of C-3, should also yield **4c** and **4d**, but we did not study this pathway because of the problems in the chromatographic resolution of the diastereomers. We previously mentioned these problems.

We think that streptenol A (**1a**) is an excellent chiral building block allowing an economic approach to δ-lactones. In the key steps of our reaction sequence diastereoselectivity is controlled by reduction and regioselectivity is achieved by oxidation. The inversion of the stereochemistry at C-3 in **1a** was performed with an intramolecular analog of Seebach's transformation process called self-regeneration of stereogenic centers.[25] The δ-lactones are interesting molecules for biological studies and can be used as intermediates for the synthesis of more complex molecules, e. g. avermectins.[26] Evaluation of the biological activities of the described δ-lactones and their application in the synthesis of natural products are presently under investigation.

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EXPERIMENTAL

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. The coupling constants and their relative signs as well as their signal patterns were estimated and confirmed by simulation of the spectra using the program PANIC from Bruker. 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}. Thin layer chromatography (TLC) was carried out on silica gel plates (Merck F_{254}). Optical rotation was measured with a Perkin Elmer spectrometer 241. The fermentation of **1a** and isolation was carried out as described[3].

(-)-(3*R*,8*E*)-1,3-Dihydroxy-8-decen-5-one (1b)
5 g (25 mmol) **6c** is stirred at room temp. with 50 mg $FeCl_3$ in 50 ml isopropanol and 50 ml water for 30 min. The reaction mixture was adjusted to pH = 7 with sodium hydrogen carbonate solution and concentrated to a syrup. The residue is dissolved in 30 ml CH_2Cl_2 and filtrated over silica gel; yield 4.55 g (97%) of **1b**.

R_f = 0.49 CH_2Cl_2/ CH_3OH (9 : 1); $[\alpha]_D^{20}$ -23° (c = 1, CH_2Cl_2); Analysis for $C_{10}H_{18}O_3$ (186.25): calcd C, 64.5; H, 9.75; found C, 64.2; H, 10.0; ^{1}H NMR δ = 1.6 (m, 5H, 2-H, 10-H), 2.25 (m, 1H, 7-H), 2.5 (t, 1H, J = 7Hz, 6-H), 2.6 (d, 1H, J = 6.5Hz, 4-H), 3.8 (t, 2H, J = 5Hz, 1-H), 4.3 (m, 1H, 3-H), 5.45 (m, 2H, 8-H, 9-H), simulation was not performed; ^{13}C NMR δ = 17.7 (C-10), 26.5 (C-7), 37.9 (C-2), 43.3 (C-6), 49.3 (C-4), 60.7 (C-1), 67.4 (C-3), 126.1 (C-9), 129.2 (C-8), 211.2 (C-5); NMR spectra confirm small amounts of hemiketals in the sample; IR ν = 3100 -3600 (OH), 1705 (C=O).

(+)-(3*S*,5*R*,8*E*)-1,3,5-Trihydroxy-8-decene (2a)
1 g (5.4 mmol) **1a** is stirred in 50 ml tetrahydrofuran at room temp. with 8.6 ml of a 1M triethylborane solution in tetrahydrofuran (8.6 mmol) for 15 min . After cooling to -70°C 4.3 ml methanol and 0.4 g (10.7 mmol) sodium borohydride is added and the reaction mixture is stirred for 3 h at this temperature. After adding 30 ml saturated sodium hydrogencarbonate solution, the mixture is extracted three times with 100 ml ethyl acetate. Drying over sodium sulfate and concentrating, yields a syrup which is reevaporated five times with methanol/ conc. hydrochloric acid (99:1). The residue is chromatographed on silica gel with acetone/ hexane (2 : 3) resulting in the syn-triol **2a** as a colourless oil; yield: 0.82 g (81%).

R_f = 0.40 CH_2Cl_2/ CH_3OH (9 : 1); $[\alpha]_D^{20}$ +4.4° (c=1, CH_2Cl_2); Analysis for $C_{10}H_{20}O_3$ (188.27): calcd C, 63.8; H, 10.7; found C, 63.9; H, 10.7; ^{1}H NMR δ = 1.50 (m, 2H, 6-H), 1.58 (m, 2H, 4-H), 1.63 (m, 3H, 10-H), 1.69, 1.71 (m, 1H, 2-H), 2.07, 2.09 (m, 2H, 7-H), 3.74, 3,81 (m, 2H, 1-H), 3.80 (m, 1H, 5-H), 4.09 (m, 1H, 3-H), 5.42, 5.46 (m, 2H, 8-H, 9-H), simulation was not performed; ^{13}C NMR δ = 17.81 (C-10), 28.44 (C-7), 37.71 (C-6), 38.98 (C-2), 43.03 (C-4), 60.36 (C-1), 71.51 (C-5), 72.01 (C-3), 125.35 (C-9), 130.67 (C-8); IR ν = 3200 - 3600 (OH).

(+)-(3*S*,5*S*,8*E*)-1,3,5-Trihydroxy-8-decene (2b)
To a suspension of 900 mg (23.8 mmol) sodium borohydride in 25 ml tetrahydrofuran within 1 h 4.3 ml acetic acid at -70°C were added and stirred for 1 h. After adding 1 g (5.4 mmol) **1a** dissolved in 5 ml tetrahydrofuran and 20 ml acetic acid the reation mixture is stirred for 2 h at this temperature. The reaction is quenched with 10 ml water and 30 ml of saturated sodium hydrogencarbonate solution. After extraction three times with 100 ml ethyl acetate the organic layer is washed three times with 50 ml water. Drying over sodium sulfate, concentration and following chromatography on silica gel with acetone/ hexane (2 : 3) furnishes the anti-triol **2b** ; yield: 0.78 g (78%).

R_f = 0.37 CH_2Cl_2/ CH_3OH (9 : 1); $[\alpha]_D^{20}$ + 9.5° (c = 1, CH_2Cl_2); Analysis for $C_{10}H_{20}O_3$ (188.27): calcd C, 63.8; H, 10.7; found C, 63.7; H, 10.5; ^{1}H NMR δ = 1.54, 1.62 (m, 2H, 6-H), 1.64 (m, 2H, 4-H), 1.66(m, 3H, 10-H), 1.68, 182 (m, 2H, 2-H), 2.09, 2.11 (m, 2H, 7-H), 3.86, 3.91 (m, 2H, 1-H), 3.98 (m, 1H, 5-H), 4.22 (m, 1H, 3-H), 5.44, 5,48 (m, 2H, 8-H, 9-H), simulation was not performed; ^{13}C NMR δ = 17.86 (C-10), 28.99 (C-7), 37.03 (C-6), 38.29 (C-2), 42.58 (C-4), 61.92 (C-1), 69.15 (C-5), 69.79 (C-3), 125.63 (C-9), 130.74 (C-8); IR ν = 3200 - 3600 (OH).

(-)-(3*R*,5*S*,8*E*)-1,3,5-Trihydroxy-8-decene (2c)
1 g (5.4 mmol) **1b** is reduced with triethylborane/ sodium borohydride in the same manner as described for **2a**. The same work up results in **2c** as colourless oil; yield 0.78 g (78%).

$[\alpha]_D^{20}$ -4.2° (c =1, CH_2Cl_2); Analysis for $C_{10}H_{20}O_3$ (188.27): calcd C, 63.8; H, 10.7; found C, 63.6; H, 10.5. The spectral data of **2c** are identical with those of (+)-**2a**.

(-)-(3*S*,5*S*,8*E*)-1,3,5-Trihydroxy-8-decene (2d)
1 g (5.4 mmol) **1b** is reduced with sodium triacetoxyborohydride in the same manner as described for **2b**. The same work up results in **2d** as colourless oil; yield 0.8 g (80%).

$[\alpha]_D^{20}$ -9.2° (c = 1, CH_2Cl_2); Analysis for $C_{10}H_{20}O_3$ (188.27): calcd C, 63.8; H, 10.7; found C, 64.0; H, 10.8. The spectral data of **2d** are identical with those of (+)-**2b**.

(+)-(3*R*,5*R*,8*E*)-3-hydroxy-5-dec-8-enolide (3a)
300 mg (1.59 mmol) **2a** is stirred in 15 ml benzene with 1 g (1.14 mmol) tris(triphenylphosphine)-ruthenium(II)chloride at room temp. for 3 d . The benzene is evaporated and the resulting residue is dissolved in 2 ml acetone. Chromatography of the acetone solution on silica gel with ethyl acetate/ hexane (1 : 1) furnishes the lactone **3a** as colourless oil; yield 200 mg (68%).

R_f = 0.51 ethyl acetate/ hexane (3 : 1); $[\alpha]_D^{20}$ + 54.9° (c = 1, CH_2Cl_2); Analysis for $C_{10}H_{16}O_3$ (184.24): calcd C, 65.2; H, 8.75; found C, 65.4; H, 8.5; ^{1}H NMR δ = 1.64 (m, 4H, J = 5.5Hz, J = 1.5Hz, 4-H, 10-H), 1.78 (m, 2H, 4-H, 6-H), 1.95 (m, 1H, 6-H), 2.15 (m, 2H, 7-H), 2.61 (d,d, 1H, J = -17.2Hz, J = 2.7Hz, 2-Hax), 2.72 (d,d, J = -17.2Hz, J = 4.7Hz, 2-Heq), 4.36 (m, 1H, 3-Heq), 4.7 (m, 1H, 5-Hax), 5.40 (m, 1H, 8-H), 5.45 (m, 1H, 9-H), simulation was not performed; ^{13}C NMR δ = 17.81 (C-10), 27.81 (C-7), 35.39 (C-4), 36.07 (C-6), 38.68 (C-2), 62.76 (C-3), 75.17 (C-5), 126.06 (C-9), 129.75 (C-8), 170.40 (C-1); IR ν = 3200 - 3600 (OH), 1740 (lactone);

(-)-(3*R*,5*S*,8*E*)-3-Hydroxy-5-dec-8-enolide (3b)
300 mg (1.59 mmol) **2b** is oxidized in the same manner as described for the preparation of **3a**. Lactone **3b** is obtained as colourless oil; yield 220 mg (75%).

R_f = 0.49 ethyl acetate/ hexane (3 : 1); $[\alpha]_D^{20}$ -34.7° (c = 1, CH_2Cl_2); Analysis for $C_{10}H_{16}O_3$ (184.24): calcd C, 65.2; H, 8.75; found C, 65.6; H, 8.8; ^{1}H NMR δ = 1.65 (m, 4H, 10-H, 4-Hax), 1.8 (m, 2H, 6-H), 2.2 (m, 3H, 7-H, 4-Heq), 2.5 (d,d, 1H, J = -17.1Hz, J = 7.9Hz, 2-Hax), 2.9 (d,d,d, 1H, J = -17.1Hz, J = 5.9Hz, J = 1.5Hz, 2-Heq), 4.2 (m, 2H, 3-H, 5-H), 5.40, 5.47 (m, 2H, 8-H, 9-H), simulation was not performed; ^{13}C NMR δ = 17.86 (C-10), 27.80 (C-7), 35.36 (C-6), 37.91 (C-4), 39.59 (C-2),

64.00 (C-3), 76.43 (C-5), 126.28 (C-9), 129.57 (C-8), 170.42 (C-1); IR ν = 3200 - 3600 (OH), 1740 (lactone).

(-)-(3*S*,5*S*,8*E*)-3-Hydroxy-5-dec-8-enolide (3c)
300 mg (1.59 mmol) **2c** is oxidized in the same manner as described for the preparation of **3a**. Lactone **3c** is obtained as colourless oil; yield 210 mg (72%).

$[\alpha]_D^{20}$ -52.8° (c = 1, CH_2Cl_2); Analysis for $C_{10}H_{16}O_3$ (184.24): calcd C, 65.2; H, 8.75; found C, 65.4; H, 8.8. The spectral data of **3c** are identical with those of (+)-**3a**.

(+)-(3*S*,5*R*,8*E*)-3-Hydroxy-5-dec-8-enolide (3d)
300 mg (1.59 mmol) **2d** is oxidized in the same manner as described for the preparation of **3a**. Lactone **3d** is obtained as colourless oil; yield 200 mg (68%).

$[\alpha]_D^{20}$ +32.9° (c = 1, CH_2Cl_2); Analysis for $C_{10}H_{16}O_3$ (184.24): calcd C, 65.2; H, 8.75; found C, 65.9; H, 8.5. The spectral data are identical with those of **(-)3b**.

(+)-(3*R*,5*R*)-3-Hydroxy-5-decanolide (4a)
200 mg (1.1 mmol) **3a** is hydrogenated at room temp.in 20 ml ethyl acetate over 30 mg palladium on carbon at atmospheric pressure for 8 h . After filtration, the catalyst is washed with 20 ml ethyl acetate and the resulting solution is evaporated. Chromatography on silica gel with ethyl acetate/ hexane (1 : 1) furnishes **4a** as colourless oil; yield 190 mg (94%).

R_f = 0.54 ethyl acetate/ hexane (3 : 1); $[\alpha]_D^{20}$ +36.9° (c = 0.92, CH_2Cl_2); Analysis for $C_{10}H_{18}O_3$ (186.25): calcd C, 64.5; H, 9.7; found C, 64.9; H, 10.1; ^{1}H NMR δ = 0.897 (t, 3H, J = 6.90Hz, 10-H), 1.31 (m, 2H, 9-H), 1,32, 1.33 (m, 2H, 8-H), 1.38, 1.53 (m, 2H, 7-H), 1.590, 1.720 (m, 2H, 6-H), 1.741 (d,d,d, 1H, J = -14.43Hz, J = 11.10Hz, J = 3.48Hz, 4-Hax), 1.959 (d,d,d,d, 1H, J = -14.43Hz, J = 3.77Hz, J = 3.11Hz, J = 1.70Hz, 4-Heq), 2.101 (br-d, 1H, J not resolved, 3-OHax) 2.617 (d,d,d, 1H, J = -17.60Hz, J = 3.73Hz, J = 1.70Hz, 2-Heq), 2.728 (d,d, 1H, J = -17.60Hz, J = 5.10Hz, 2-Hax), 4.382 (d,d,d,d,br-d, J = 5.10Hz, J = 3.77Hz, J = 3.73Hz, J = 3.48Hz, J not resolved, 1H, 3-Heq), 4.687 (d,d,d,d, 1H, J = 11.70Hz, J = 7.60Hz , J = 4.88Hz, J = 3.11Hz, 5-Hax); ^{13}C NMR δ = 13.94 (C-10), 22.48 (C-9), 24.51 (C-7), 31.54 (C-8), 35.46 (C-6), 35.99 (C-4), 38.64 (C-2), 62.78 (C-3), 75.87 (C-5), 170.56 (C-1); IR ($CHCl_3$) ν = 3200 - 3600 (OH), 1740 (lactone).

(-)-(3*R*,5*S*)-3-Hydroxy-5-decanolide (4b)
200 mg (1.1 mmol) **3b** is hydrogenated and purified in the same manner as described for **4a**. The lactone **4b** is obtained as colourless oil; yield 188 mg (92%) **4b**.

R_f = 0.53 ethyl acetate/ hexane (3 : 1); $[\alpha]_D^{20}$ -39.2° (c = 1.4, CH_2Cl_2); Analysis for $C_{10}H_{18}O_3$ (186.25): calcd C, 64.5; H, 9.7; found C, 64.5; H, 9.5; ^{1}H NMR δ = 0.895 (t, 3H, J = 6.91Hz, 10-H), 1.32 (m, 4H, 8-H, 9-H), 1.42 (m, 1H, 7-H), 1.51 (m, 1H, 7-H), 1.591 (d,d,d, J = -13.65Hz, J = 11.75Hz, J = 9.30Hz, 1H, 4-Hax), 1.63 (m, 1H, 6-H), 1.73 (m, 1H, 6-H), 2.252 (d,d,d,d, 1H, J = -13.65Hz, J = 5.45Hz, J = 2.98Hz, J = 1.41Hz, 4-Heq), 2.280 (br-d, 1H, J not resolved, 3-OHeq) 2.456 (d,d, 1H, J = -17.12 Hz, J = 7.90 Hz, 2-Hax), 2.899 (d,d,d, 1H, J = -17.12Hz, J = 5.92Hz, J = 1.41Hz, 2-Heq), 4.191 (d,d,d,d, 1H, J = 11.75Hz, J = 7.90Hz, J = 5.92Hz, J = 5.45Hz, 5-Hax), 4.229 (d,d,d,d,br-d, 1H J = 9.30Hz, J = 2.97Hz, J not resolved, 3-Hax); ^{13}C NMR δ = 13.92 (C-10), 22.45 (C-9), 24.49 (C-7), 31.48 (C-8), 35.49 (C-6), 37.89 (C-4), 39.54 (C-2), 63.94 (C-3), 77.28 (C-5), 170.73 (C-1); IR ν = 3200 - 3600 (OH), 1740 (lactone).

(-)-(3*S*,5*S*)-3-Hydroxy-5-decanolide (4c)
200 mg (1.1 mmol) **3c** is hydrogenated and purified in the same manner as described for **4a**. The lactone **4c** is obtained as colourless oil; yield 184 mg (90%).

Analysis for $C_{10}H_{18}O_3$ (186.25): calcd C, 64.5; H, 9.7; found C, 64.6; H, 10.0;. $[\alpha]_D^{20}$ -34.9° (c = 2.0, CH_2Cl_2). The spectral data are identical with those of **4a**.

(+)-(3*S*,5*R*)-3-Hydroxy-5-decanolide (4d)
200 mg (1.1 mmol) **3d** is hydrogenated and purified in the same manner as described for **4a**. The lactone **4d** is obtained as colourless oil; yield 190 mg (94%).

$[\alpha]_{20}^D$ + 38.6° (c = 1.5, CH_2Cl_2) Analysis for $C_{10}H_{18}O_3$ (186.25): calcd C, 64.5; H, 9.7; found C, 64.9; H, 9.4. The spectral data are identical with those of **4b**.

(-)-(5*R*)-2-Decen-5-olide [(-)-massoialactone] (5a)
190 mg (1 mmol) **4a** is refluxed in 30 ml benzene with 80 mg (0.42 mmol) p-toluenesulfonic acid for 5 h. After adding 30 ml water pH = 7 is adjusted with sodium hydrogen carbonate solution. The mixture is extracted three times with 50 ml dichloromethane and the organic layer is washed two times with water. After drying over Na_2SO_4 the solvent is evaporated. Chromatography on silica gel with ethyl acetate/ hexane (1 : 5) results in (-)-massoialactone (**5a**); yield 130 mg (77%).

R_f = 0.36 ethyl acetate/ hexane (1 : 3); $[\alpha]_D^{20}$ -112.5° (c = 1, $CHCl_3$); Analysis for $C_{10}H_{16}O_2$ (168.24): calcd C, 71.4; H, 9.6; found C, 71.3; H, 9.6; ^{1}H NMR δ = 0.901 (t, 3H, J = 6.9Hz), 1.32 (m, 4H, 8-H, 9-H), 1.41 (m, 1H, 7-H), 1.51 (m, 1H, 7-H), 1.64 (m, 1H, 6-H), 1.80 (m, 1H, 6-H), 2.315 (m, 1H, 4-H), 2.339 (m, 1H, 4-H), 4.419 (m , 1H, 5-H), 6.022 (d,d,d, 1H, J = 9.8Hz, J = 1.1Hz, J = 0.5Hz, 2-H), 6.871 (d,d,d, 1H, J = 9.8Hz, J = 8.9Hz, J = 3.9Hz, 3-H), simulation did not agree sufficently with experimental pattern; ^{13}C NMR δ = 13.94 (C-10), 22.48 (C-9), 24.48 (C-7), 29.40 (C-4), 31.53 (C-8), 34.84 (C-6), 78.00 (C-5), 121.49 (C-2), 144.91 (C-3), 164.54 (C-1); IR ν = 1725 (lactone), 1630 (C=C).

(+)-(5*S*)-2-Decen-5-olide [(+)-massoialactone] (5b)
160 mg (0.86 mmol) **4b** is treated with p-toluenesulfonic acid in 25 ml benzene in the same manner as described for preparation of **5a**. The same work up results in **5b** as colourless oil; yield 100 mg (70%).

$[\alpha]_D^{20}$ +113° (c = 1, $CHCl_3$); Analysis for $C_{10}H_{16}O_2$ (168.24): calcd C, 71.4; H, 9.6; found C, 71.2; H 9.3. The spectral data are identical with those of **5a**.

(+)-(2*S*,4*S*)-4-Hydroxy-2-methoxy-2-(9*E*-pentenyl)-tetrahydropyran (6a) and (-)-(2*R*,4*S*)-4-Hydroxy-2-methoxy-2-(9*E*-pentenyl)-tetrahydropyran (6b)
10 g (54 mmol) **1a** is stirred in 500 ml methanol at room temp. with 500 mg LiBr for 15 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 **6a** and **6b**; yield 9.4 g (87%) **6a** and 0.54 g (5%) **6b**.

6a: R_f = 0.36 ethyl acetate/ hexane (1 : 2); $[\alpha]_D^{20}$ +82.6° (c = 2.8, 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, 10.4; ^{1}H NMR δ = 3.126 (s, 3H, CH_3-acetal), further data are summarized in fig. 1; ^{13}C NMR δ = 17.78 (C-11), 26.38 (C-8), 34.82 (C-5), 35.71 (C-7), 42.18 (C-3), 47.15 (CH_3-acetal), 59.48 (C-6), 64.44 (C-4), 101.10 (C-2), 124.98 (C-10), 130.46 (C-9);

6b: R_f = 0.60 ethyl acetate/ hexane (1 : 2); $[\alpha]_D^{20}$ -66.0° (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%, 66.0; H, 10.7; ^{1}H NMR δ = 3.214 (s, 3H, CH_3-acetal), further data are summarized in fig. 1; ^{13}C NMR δ = 17.73 (C-11), 26.24 (C-8), 31.90 (C-5),

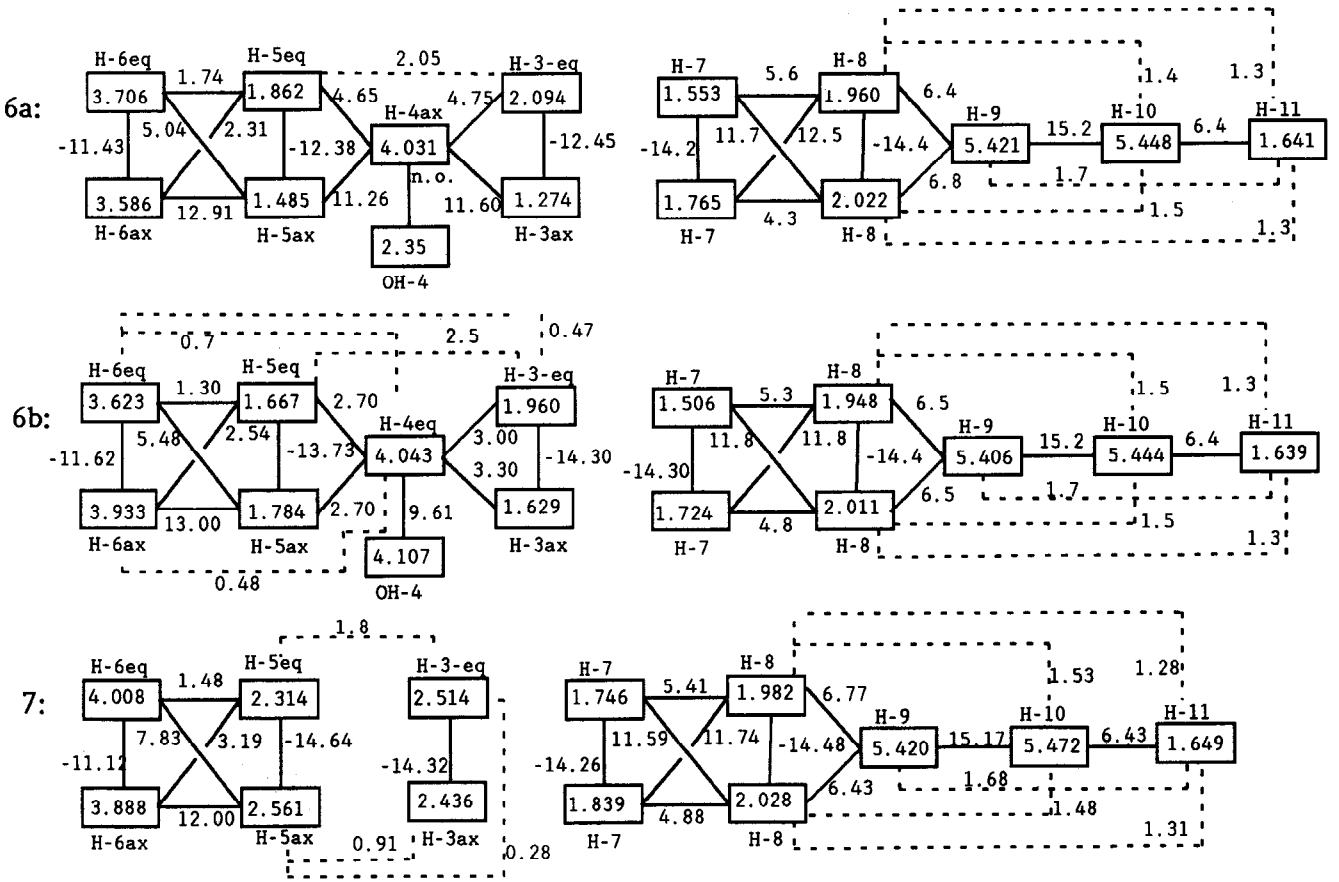

Fig. 1 : ^{1}H NMR chemical shifts and coupling constants of 6a, 6b and 7. (δ-values in the box in ppm; J values at the connecting lines between the boxes in Hz). (n.o. not observed)

35.77 (C-7), 37.41 (C-3), 47.25 (CH_3-acetal), 55.76 (C-6), 63.67 (C-4), 101.00 (C-2), 125.03 (C-10), 130.27 (C-9);

(+)-(2*S*,4*R*)-4-Hydroxy-2-methoxy-2-(9*E*-pentenyl)-tetrahydropyran (6c)
7 g (35 mmol) **7** is stirred in 500 ml isopropanol with 12 g (63.2 mmol) L-Selectride at -70°C for 5 h. After quenching the reaction with 10 ml acetone the mixture is concentrated. Chromatography on silica gel with ethyl acetate/ hexane/ triethylamine (1 : 4 : 0.5) results in **6c**; 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, 66.2; H, 10.0; found C, 66.0; H, 10.1. The spectral data are identical with those of **6b**.

(+)-(2*S*)-Methoxy-2-(9*E*-pentenyl)-4-tetrahydropyrone (7)
7 g (35 mmol) **6a** is stirred with 800 mg (2.28 mmol) tetrapropylammonium perruthenate and 8 g 4-methyl-morpholine-N-oxide in 200 ml CH_2Cl_2 for 8 h. The reaction mixture is diluted with 300 ml CH_2Cl_2 and is washed two times with 400 ml of a sodium hydrogensulfite solution (10%) and five times with water. The organic layer is dried over Na_2SO_4, filtrated with Celite and concentrated; yield 6.7 g (96%) of **7**.
R_f = 0.73 ethyl acetate/ 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, 66.8; H, 9.4; ^{1}H NMR δ = 3.166 (s, 3H, CH_3-acetal), further data are summarized in table 1; ^{13}C NMR δ = 17.76 (C-11), 26.24 (C-8), 35.19 (C-7), 40.89 (C-5), 47.70 (CH_3-acetal), 49.73 (C-3), 59.62 (C-6), 103.16 (C-2), 125.44 (C-10), 129.92 (C-9), 205.33 (C-4);

2,4-Dimethoxy-2-(9*E*-pentenyl)-tetrahydropyran (8)
1 g (5.4 mmol) **1a** is stirred in 50 ml methanol at room temp. with 50 mg $FeCl_3$ for 15 min. Work up and chromatography as described for **6a** furnishes **8**; yield 850 mg (73%).
Analysis for $C_{12}H_{22}O_3$ (214.31): calcd C, 67.25; H, 10.35; found C, 67.5; H, 10.4; ^{1}H NMR (solvent CD_3OD, δ (CHD_2OD) = 3.330 ppm as internal standard) δ = 1.168 (d,d, 1H, J = -12.5Hz, J = 11.06Hz, 3-H ax), 1.333 (d,d,d,d, 1H, J = -12.63Hz, J = 12.63Hz, J = 11.21Hz, J = 5.23Hz, 5-Hax), 1.526 (d,d,d, 1H, J = -14.1Hz, J = 11.5Hz, J = 6.0Hz, 7-H), 1.620 (m 3H, 11-H), 1.735 (d,d,d, 1H, J = -14.1Hz, J = 11.3Hz, J = 5.1Hz, 7-H), 1.950 (m 1H, 8-H), 1.952 (d,d,d,d,d, 1H, J = -12.63Hz, J = 4.60Hz, J = 2.36Hz, J = 2.09Hz, J = 1.83Hz, 5-Heq), 1.93 (m, 1H, 8-H), 2.00 (m, 1H, 8-H), 2.130 (d,d,d, 1H, J = -12.48Hz, J = 4.64Hz, J = 2.09Hz, 3-Heq), 3.112 (s, 3H, CH_3-acetal), 3.313 (s, 3H, CH_3-ether), 3.572 (d,d,d, 1H, J = 12.63Hz, -11.47Hz, J = 2.36Hz, 6-Hax), 3.587 (d,d,d,d, 1H, J = 11.21Hz, J = 11.06Hz, J = 4.64Hz, J = 4.60Hz, 4-Hax), 3.683 (d,d,d, 1H, J = -11.47Hz, J = 5.23Hz, J = 1.83Hz, 46-Heq), 5.42 (m, 1H, 9-H,) 5.46 (m, 1H, 10-H), simulation was only performed for the tetrahydropyran ring; ^{13}C NMR (CD_3OD as solvent and as internal standard δ = 49.00 ppm) δ = 18.03 (C-11), 27.57 (C-8), 32.69 (C-5), 37.07 (C-7), 40.10 (C-3), 47.57 (CH_3-acetal), 55.58 (CH_3-ether), 60.47 (C-6), 74.69 (C-4), 102.34 (C-2), 125.92 (C-10), 131.85 (C-9).

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