31. Approaches to the Synthesis of Cytochalasans. Part 6[1])

Synthesis of the C(14)–C(23) Subunit of Cytochalasins A, B, F and Desoxaphomin

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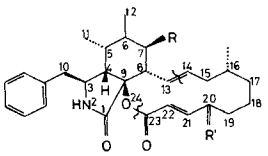
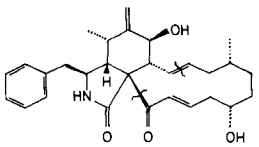
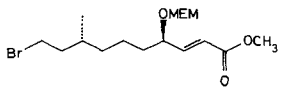
Summary

The synthesis of methyl (4*R*, 8*R*,)-10-bromo-8-methyl-4-(1,3,6-trioxaheptane)-2-deceneoate (**5**), a synthon for the construction of the macrocyclic moieties of the cytochalasins A (**1**), B (**2**), F (**3**) and desoxaphomin (**4**) is described. (*S*)-Glutamic acid (**6**) was transformed to the C_5-epoxide **10** and 3-methylglutaric acid (**11**) to the C_5-bromide **15**. Coupling of both **10** and **15** by a CuI-catalyzed *Grignard* reaction gave the decanol **16** in very high yield. The latter was transformed by several steps to synthon **5**.

The cytochalasans are a family of closely related substances isolated from a variety of moulds and microorganisms. They exhibit a wide range of biological activities which often are used as tools in cell biology [2]. The characteristic structural elements of the cytochalasins A (**1**), B (**2**), F(**3**) and desoxaphomin (**4**) are a bicyclic tetrahydroisoindolinone moiety which is fused to an 11- to 14-membered macrocyclic ring, and its many functional substituents.







5

1 $\Delta^{6,12}$, R=OH, R'=O

2 $\Delta^{6,12}$, R=OH, R'=

3 6,7-Epoxy, R=H, R'=

4

[1]) Part 5: [1].

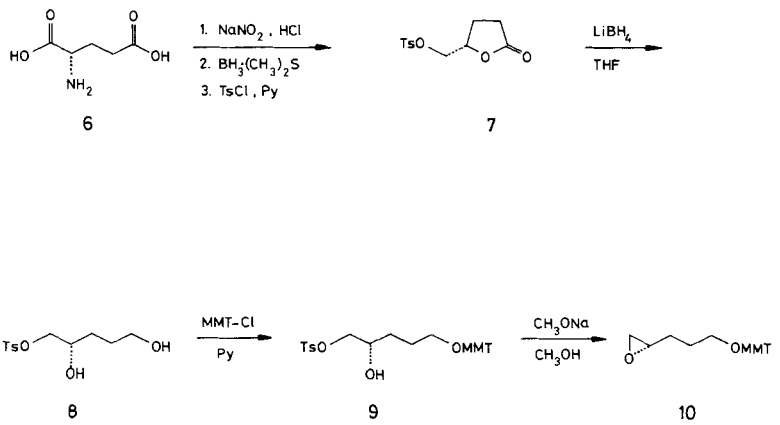
[2]) Part of the planed thesis of *J. A.*

The combination of the unusual biological properties and the unique structural features exhibited by the cytochalasans has led to a strong interest in their synthesis. The *Diels-Alder* reaction has been used to establish the correct relative stereochemistry at C(4), C(5), C(8) and C(9) of the tetrahydroisoindolinone subunit [3]. For the construction of the ring systems present in the cytochalasins A, B and F, appropriate hydroxy-thioesters [4] and an intramolecular *Diels-Alder* reaction [5] have proved to be suitable [6]. Pd-assisted macrocyclization [7] and fragmentation reactions [8] were examined in the course of studies related to the syntheses of the cytochalasins C and D.

Structural modifications of the naturally occurring compounds lead to a better understanding of the relationship between structure and biological activity [9]. Therefore we undertook a synthesis of synthon **5** which corresponds to the C(14)–C(23) subunit and contains two centres of chirality present in the cytochalasins B (**2**), F (**3**) and desoxaphomin (**4**), in such a manner that the same building blocks can be utilized for the preparation of all possible stereoisomers.

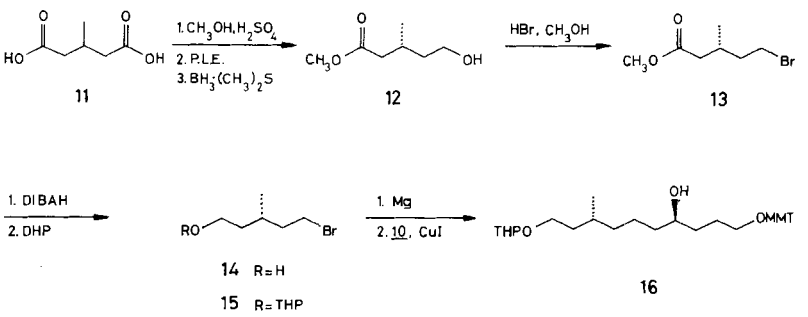
(*S*)-γ-Tosyloxymethyl-γ-butyrolactone (**7**) was chosen as the starting material because it could readily be prepared from (*S*)-glutamic acid (**6**) in an almost optically pure form (e.e. 93%) [10]. Reduction of **7** with $LiBH_4$ in THF gave the (2*S*)-diol **8** (yield 67%) whose primary OH-group was protected by treatment with (4-methoxyphenyl)diphenylchloromethane (MMT) in pyridine. The product **9** obtained was immediately converted to (2*S*)-epoxide (yield 93.3%) with $NaOCH_3$ in MeOH. The (2*S*)-epoxide **10** can serve for a possible later inversion of the configuration of the secondary OH-group by applying well-known procedures [11].

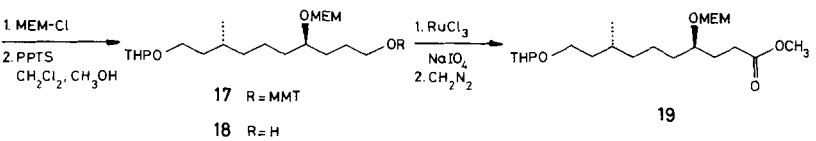
For the preparation of the second C_5-subunit containing a chiral CH_3-group with either (*R*)- or (*S*)-configuration 3-methylglutaric acid (**11**) was very convenient as starting material. The enzymatic hydrolysis of dimethyl 3-methylglutarate with pig liver esterase (PLE) or chymotrypsin generates almost quantitatively the chiral (*R*)-half ester of **11** up to 95% e.e. [12]. Selective reduction of either the methoxycarbonyl or carboxy group is possible. Hence enantioselective transformations can be carried out on both the enantiotopic groups of the original achiral dicarboxylic acid **11**.

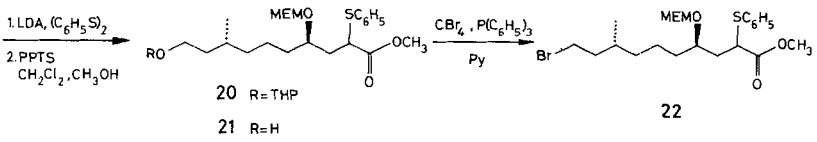


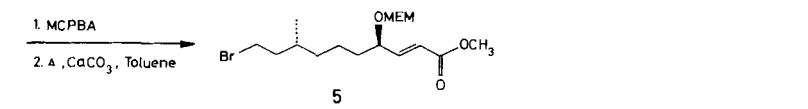
6 7 8 9 10

The dimethyl ester of **11** was treated with PLE. Reduction of the resulting (*R*)-half ester with $BH_3 \cdot (CH_3)_2S$ complex afforded methyl (3*R*)-5-hydroxy-3-methyl-1-pentanoate (**12**) (yield 97%). Compound **12** was converted to the (3*S*)-bromide **13** (yield 95.7%) with HBr in MeOH and the latter was reduced with diisobutylaluminium hydride (DIBAH) in THF at 0° to the (3*S*)-alcohol **14** (93.5%). The free OH-group of **14** was finally protected by the THP-group to give (3*S*)-5-bromo-3-methyl-1-tetrahydropyranyloxypentane (**15**) (88.1%).









The remaining step consisted in the C–C-coupling of the C_5-units **10** and **15**. Attempts to use a Cu(I)-catalyzed cross-coupling reaction [13] with (*S*)-tosylate **7** and *Grignard* reagent, prepared from the protected (3*S*)-bromide **15**, failed. Therefore the (*S*)-tosylate **7** was converted to the corresponding iodide. The latter was treated with the organo-Cu(I) complex prepared from the *Grignard* derivative of **15** according to *Bergbreiter & Whitesides* [14].

However, the desired product was obtained in a yield of only 11%. To achieve more effective conversion the (2*S*)-epoxide **10**, was allowed to react in the presence of CuI-catalyst [15] with the *Grignard* derivative of **15** in THF at −30° for 1 h and at 0° for 4 h. The desired compound **16** was now obtained in nearly quantitative yield (96%).

Subsequent protection of the secondary OH-group of **16** by treatment with 'methoxyethoxymethyl chloride' (MEM-Cl) in CH_2Cl_2 and deprotection of the tritylated primary OH-group with pyridinium *p*-toluenesulfonate (PPTS) gave compound **18**. The latter was oxidized with $NaIO_4$ and $RuCl_3 \cdot aq$ as catalyst in $CH_3CN/H_2O/CCl_4$ [16] to the corresponding acid which immediately was transformed with CH_2N_2 in ether to the ester **19**. At this stage, there only remained the introduction of the (*E*)-double bond. Following the method of *Trost et al.* [17] a phenylthio group was introduced by treating **19** with lithium diisopropylamide (LDA) at −78° in THF followed by the addition of hexamethylphosphoric triamide and diphenyl disulfide (yield 67.7%). After removal of the THP-group with pyridinium *p*-toluenesulfonate in MeOH the alcohol **21** obtained was converted readily to the bromide **22** [18] (68%). Oxidation of the phenylthio group with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 at −78° followed by elimination at 110° in toluene in the presence of $CaCO_3$ transformed **22** into the desired compound **5** (76.6%). This reaction was highly (*E*)-selective as shown by ^{1}H-NMR spectroscopy.

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Experimental Part

General. Water-sensitive reactions were carried out in an Ar-atmosphere, CH_2Cl_2 and THF were dried by distilling them over P_2O_5 and $LiAlH_4$, respectively. All org. extracts were dried over Na_2SO_4 and evaporated under reduced pressure below 50°. Pig liver esterase (PLE) was purchased from *Boehringer*. Thin layer chromatograms (TLC) were prepared on silica gel *60 F_{254} (Merck)*. The spots were observed by treatment with iodine vapours or by spraying with 5% H_2SO_4 in MeOH. For column chromatography silica gel *60* (0.063–0.2000 mm, *Merck)* was used. Optical rotations were measured with a *Perkin-Elmer* model *141* polarimeter and IR (cm^{-1}) with a *Perkin-Elmer* model *177* grating spectrometer. The 60-MHz ^{1}H-NMR spectra were recorded on a *Varian EM 360* spectrometer, the 90-MHz ^{1}H-NMR and the 22.63-MHz ^{13}C-NMR spectra on a *Bruker WH-90* spectrometer with *Fourier* transform. Chemical shifts are reported in ppm downfield from internal TMS. *Abbreviations:* MMT = (4-methoxyphenyl)diphenylmethyl, MEM = 'methoxyethoxymethyl'(= 2,5-dioxahexyl), THP = tetrahydropyranyl, PPTS = pyridinium *p*-toluenesulfonate, HMPT = hexamethylphosphoric triamide.

(2S)-2,5-Dihydroxypentyl p-toluenesulfonate (**8**). To a solution of (S)-*γ-tosyloxymethyl-γ-butyrolactone* [7, $[a]_D^{r.t.} = +43.1°$ ($c = 2.45$, $CHCl_3$); [10]: $[\alpha]_D^{20} = +47.0$ ($c = 1.6$, $CHCl_3$)] (10 g, 37 mmol) in 50 ml of abs. THF were added 1.7 g of $LiBH_4$. After stirring for 6 h at r.t. AcOEt- and AcONa-solution were carefully added. The mixture was extracted with Et_2O, washed with brine, dried and evaporated *i.v.* The oily residue was recrystallized (Et_2O) to yield 6.8 g (67%) of colourless crystalline **8**, which was pure according to TLC (AcOEt: $R_f = 0.33$). $[a]_D^{r.t.} = +1.6°$ ($c = 1.87$, $CHCl_3$). IR ($CHCl_3$): 3100–3650, 2940, 1710, 1600. ^{1}H-NMR (60 MHz, $CDCl_3$): 1.2–1.8 (*m*, 4 H, $H_2C(3)$, $H_2C(4)$); 2.4 (*s*, 3 H, $CH_3C_6H_4$); 3.0 (*s*, 2 H, 2 OH); 3.4–4.0 (*m*, 5 H, $H_2C(1)$, H–C(2), $H_2C(5)$); 7.3 and 7.75 (*AB*-system, $J = 8$, $C_6H_4CH_3$).

(2S-5-[(4-Methoxyphenyl) diphenylmethoxy]-1,2-epoxypentane (**10**). To a solution of **8** (6.8 g, 24.7 mmol) in 40 ml of pyridin was added MMT-Cl (10 g, 32.5 mmol). After stirring for 6 h at r.t. the mixture was taken up in Et_2O and washed with $NaHCO_3$ (3 ×), dried and evaporated *i.v.* The yellow, oily residue was purified by column chromatography (Et_2O/petroleum ether 2:1). The pure *(2S)-2-hydroxy-5-[(4-methoxyphenyl)diphenylmethoxy]pentyl* p-*toluenesulfonate* (**9**) thus obtained was immediately dissolved in 50 ml of MeOH and added at 0° to a MeONa-solution (prepared from 1.5 g (62 mg-atom) Na in 50 ml of abs. MeOH). Et_2O was added at 0° after stirring for 15 min. The org. layer was washed with sat. $NaHCO_3$-solution (2 ×) and brine, dried and evaporated *i.v.* The residue, after purification by column chromatography (Et_2O/petroleumether 2:1; $R_f = 0.52$) afforded 8.6 g (93.2%) of **10**. $[\alpha]_D^{r.t.} = -3.6°$ (*c* = 2.85, $CHCl_3$). IR (film): 3050, 2940, 1610, 1510, 1250, 835. ^{1}H-NMR (60 MHz, CCl_4): 1.4–1.7 (*m*, 2 H, $H_2C(4)$); 2.1–2.7 (*m*, 5 H, $H_2C(1)$, H–C(2), $H_2C(3)$); 3.0 (*t*, *J* = 6, 2 H, $H_2C(5)$); 3.75 (*s*, 3 H, $CH_3OC_6H_4$); 6.7 (part of an *AB*-system, *J* = 8, 2 H, C_6H_4–OCH_3); 7.25 (m, 12 H, 2 × C_6H_5, 2 H of C_6H_4–OCH_3).

Methyl (3S)-5-bromo-3-methylpentanoate (**13**). To a solution of 284 g HBr in 220 ml of abs. MeOH was added at 0° within 5 min methyl *(3R)-5-hydroxy-3-methylpentanoate* (**12**, $[\alpha]_D^{r.t.} = +1.95°$ (*c* = 2.6, $CHCl_3$)) (43 g, 294 mmol). The mixture was stirred for 90 min at r.t. and poured on 1.5 kg ice. The cold solution was extracted with Et_2O and the combined org. solutions were washed with brine, dried and evaporated *i.v.* to yield 58.8 g (95.7%) of a yellowish oil pure according to TLC (AcOEt). IR (film): 2960 br., 1740. ^{1}H-NMR (60 MHz, CCl_4): 0.95 (*d*, *J* = 6, 3 H, CH_3–C(3)); 1.5–2.3 (*m*, 5 H, $H_2C(2)$, H–C(3), $H_2C(4)$); 3.3 (*t*, *J* = 7, 2 H, $H_2C(5)$); 3.55 (*s*, 3 H, $COOCH_3$).

(3S)-5-Bromo-3-methylpentanol (**14**). To an ice cooled solution of **13** (40 g, 191.3 mmol) in 100 ml of abs. THF were added dropwise in 10 min 470 ml of DIBAH (1M in hexane). After stirring for 4.5 h at 0° and 30 min at r.t. the mixture was quenched with MeOH and ice. The pH-value was adjusted to 3 by dropwise addition of 2N H_2SO_4. The mixture was extracted with Et_2O and the combined org. layers were washed with brine, dried and evaporated *i.v.* to yield 32.4 g (93.5%) of an oil pure according to TLC. (AcOEt: $R_f = 0.6$). $[\alpha]_D^{r.t.} = +11.2°$ (*c* = 2.82, $CHCl_3$). IR (film): 3550–3050 br., 2920. ^{1}H-NMR (60 MHz, CCl_4): 0.9 (*d*, *J* = 6, 3 H, CH_3–C(3)); 1.3–2.0 (*m*, 5 H, $H_2C(2)$, H–C(3), $H_2C(4)$); 3.35 (*t*, *J* = 7, 2 H, $H_2C(1)$); 3.55 (*t*, *J* = 6, 2 H, $H_2C(5)$); 4.4–5.1 (br. *s*, 1 H, OH).

(3S)-5-Bromo-3-methyl-1-(tetrahydropyranyloxy)pentane (**15**). To 32.4 g (178.9 mmol) of **14** was added dropwise at 0° dihydropyrane (50 ml, 523 mmol) and the mixture was allowed to stand 20 h at r.t. The unreacted dihydropyrane was evaporated *i.v.* and the residue was purified by column chromatography (AcOEt/petroleum ether 1:10; $R_f = 0.37$) to yield 41.8 g (88%) of pure **15** IR (film): 2940. ^{1}H-NMR (60 MHz, CCl_4): 0.9 (*d*, *J* = 6, $CH_3C(3)$); 1.2–2.1 (*m*, 11 H, $H_2C(2)$, $H_2C(4)$, H–C(3), $H_2C(3')$, $H_2C(4')$, $H_2C(5')$); 3.1–3.9 (*m*, 6 H, $H_2C(1)$, $H_2C(5)$, $H_2C(6')$); 4.4 (*s*, 1 H, H–C(2')).

(4R,8R)-1-[(4-Methoxyphenyl)diphenylmethoxy]-8-methyl-10-(tetrahydropyranyloxy)-4-decanol (**16**). To 2 g Mg, activated with crystalline I_2 was added after 5 min 6 ml of abs. THF. After heating until the reddish colour had diminished **15** (5.52 g, 20.8 mmol) in 22 ml of abs. THF was added under further heating to reflux within 30 min. After completing the addition of **15** refluxing was continued for 10 min. Then the mixture was cooled to r.t. The *Grignard* reagent thus obtained was added dropwise at −30° to a solution of **10** (6 g, 16 mmol) and freshly purified CuI [19] (0.4 g) in 25 ml of abs. THF. The bluish-black mixture was kept 1 h at −30°, 4 h at 0° and then at r.t. for 14 h. A sat. NH_4Cl-solution was added and the mixture was extracted with Et_2O. The combined org. layers were washed with NH_4Cl-solution (3 ×) and with brine, dried and evaporated *i.v.* to yield a colourless oil which was further purified by column chromatography (AcOEt/petroleum ether 1:4; $R_f = 0.25$), to obtain 8.6 g (96%) of pure **16**. IR (film): 3200–3600, 3040, 2930, 1610, 1510. ^{1}H-NMR (60 MHz, CCl_4): 0.9 (*d*, *J* = 6, 3 H, CH_3–C(8)); 1.0–1.9 (*m*, 19 H, $H_2C(2)$, $H_2C(3)$, $H_2C(5)$, $H_2C(6)$, $H_2C(7)$, H–C(8), $H_2C(9)$, $H_2C(3')$, $H_2C(4')$, $H_2C(5')$); 2.8–4.3 (*m*, 8 H, $H_2C(1)$, H–C(4), HO–C(4), $H_2C(10)$, $H_2C(6')$); 3.7 (*s*, 3 H, CH_3O–C_6H_4); 4.45 (*s*, 1 H, H–C(2')); 6.6 (part of an *AB*-system, *J* = 8, 2 H, C_6H_4-OCH_3): 7.25 (*m*, 12 H, $2C_6H_5$, 2 H of C_6H_4–OCH_3). Anal. calc. for $C_{36}H_{48}O_5$ (560.74): C 77.11, H 8.63; found: C 77.19, H 8.67.

(4R,8R)-8-Methyl-10-(tetrahydropyranyloxy)-4-(1,3,6-trioxaheptyl)-1-decanol (**18**). To a solution of **16** (4 g, 7.13 mmol) in 15 ml of CH_2Cl_2 were added at r.t. diisopropylethylamine (4 ml) and MEM-Cl (1.5 ml, 12 mmol). After stirring for 3 h at r.t. the mixture was taken up in Et_2O and washed with H_2O, dried and evaporated *i.v.* The residue was taken up in benzene and the solvent was evaporated *i.v.* (This procedure was repeated a second time). The resulting brown oil (5 g) was taken up in 40 ml CH_2Cl_2/MeOH 1:1 and PPTS (200 mg) was added. After stirring for 2 h at r.t. the mixture was taken up in Et_2O and washed with $NaHCO_3$-solution (3 ×) and brine, dried and evaporated *i.v.* The resulting brown oil was purified by column chromatography (Et_2O: $R_f = 0.18$) to yield 2.25 g (84%) of pure **18**. IR (film): 3100–3600, 2940. ^{1}H-NMR (60 MHz, CCl_4): 0.9 (*d*, *J* = 6, 3 H, CH_3–C(8)); 1.0–2.0 (*m*, 19 H, $H_2C(2)$, $H_2C(3)$, $H_2C(5)$, $H_2C(6)$, $H_2C(7)$, H–C(8), $H_2C(9)$,

$H_2C(3')$, $H_2C(4')$, $H_2C(5')$); 2.65 (*s*, 1 H, OH); 3.3 (*s*, 3 H, CH_3O); 3.45 (*m*, 11 H, $H_2C(1)$, H–C(4), $H_2C(10)$, $H_2C(6')$, 2 CH_2O); 4.4 (*s*, 1 H, H–C(2')); 4.5 (s, 2 H, OCH_2O).

Methyl (4 R,*8* R*)-8-methyl-10-(tetrahydropyranyloxy)-4-(1,3,6-trioxaheptyl)-1-decanoate* (**19**). To a suspension of **18** (2.25 g, 6 mmol) in a mixture of 12 ml of CCl_4, 12 ml of CH_3CN and 18 ml of H_2O were added at 0° 3.83 g of $NaIO_4$ and 30 mg of $RuCl_3 \cdot$ aq. After vigorous stirring for 3.5 h at 0° the mixture was taken up in Et_2O, washed with brine, dried and evaporated *i.v.* The crude product was taken up in Et_2O and treated with ethereal CH_2N_2. The reaction mixture was evaporated *i.v.* and purified by column chromatography (Et_2O/petroleum ether 1:1: $R_f = 0.29$) to yield 1.67 g (69%) of pure **19**. IR (film): 2930, 1735. ^{1}H-NMR (60 MHz, CCl_4): 0.9 (*d*, $J = 6$, 3 H, CH_3–C(8)); 1.0–1.9 (*m*, 16 H, $H_2C(3)$, $H_2C(5)$, $H_2C(6)$, $H_2C(7)$, H–C(8), $H_2C(9)$, $H_2C(3')$, $H_2C(4')$, $H_2C(5')$); 2.3 (*t*, $J = 7$, 2 H, $H_2C(2)$); 3.25 (*s*, 3 H, CH_3O); 3.1–3.9 (*m*, 9 H, $H_2C(10)$, $H_2C(6')$, H–C(4), 2 OCH_2): 3.55 (*s*, 3 H, $COOCH_3$); 4.45 (*s*, 1 H, H–C(2')); 4.55 (*s*, 2 H, OCH_2O).

Methyl (2 RS,*4* R,*8* R*)-8-methyl-2-phenylthio-10-(tetrahydropyranyloxy)-4-(1,3,6-trioxaheptyl) decanoate* (**20**). To a solution of cyclohexylisopropylamine (0.8 ml, 4.76 mmol) in 10 ml of abs. THF were added BuLi (3 ml, 1.6M in hexane). After stirring for 10 min, the solution was cooled to −78°. A solution of **19** (1.67 g, 4.13 mmol) in 6 ml of abs. THF was then added over 5 min. After an additional 5 min 1 ml of HMPT was added and the mixture was stirred for 30 min at −78°. Then diphenyldisulphide (1.04 g, 4.76 mmol) in 5 ml of abs. THF was added and the stirring was continued for 30 min at −30° and for 1 h at r.t. The mixture was quenched with NH_4Cl-solution and extracted with Et_2O. The combined org. layers were washed with brine, dried and evaporated *i.v.* The residue, after purification by column chromatography (Et_2O/petroleum ether 1:1; $R_f = 0.23$) afforded 1.44 g (68%) of **20**. IR (film): 3050, 1740, 1580. ^{1}H-NMR (60 MHz, CCl_4): 0.9 (*d*, $J = 6$, 3 H, CH_3–C(7)); 1.0–2.0 (*m*, 17 H, $H_2C(3)$, $H_2C(5)$, $H_2C(6)$, $H_2C(7)$, H–C(8), $H_2C(9)$, $H_2C(3')$, $H_2C(4')$, $H_2C(5')$); 3.25 (*s*, 3 H, CH_3O): 3.55 (*s*, 3 H, $COOCH_3$): 3.0–3.9 (*m*, 10 H, H–C(2), H–C(4), 2OCH_2, $H_2C(10)$, $H_2C(6')$); 4.4 (*s*, 1 H, H–C(2')); 4.5 (*s*, 2 H, OCH_2O); 7.0–7.5 (*m*, 5 H, C_6H_5).

Methyl (2 RS,*4* R,*8* R*)-10-hydroxy-8-methyl-2-phenylthio-4-(1,3,6-trioxaheptyl) decanoate* (**21**). A mixture of 0.7 g (1.36 mmol) of **20** in 30 ml of abs. MeOH and 30 mg of PPTS was stirred for 3 days at r.t. The solvent was evaporated and the crude product was purified by column chromatography (Et_2O; $R_f = 0.26$) to yield 0.428 g (73%) of pure **21**. IR (film): 3100–3600, 2940, 1740, 1580. ^{1}H-NMR (60 MHz, CCl_4): 0.9 (*d*, $J = 6$, 3 H, CH_3–C(8)); 1.0–2.4 (*m*, 12 H, OH, $H_2C(3)$, $H_2C(5)$, $H_2C(6)$, $H_2C(7)$, H–C(8), $H_2C(9)$); 3.25 (*s*, 3 H, CH_3O); 3.55 (*s*, 3 H, $COOCH_3$); 3.1–4.0 (*m*, 8 H, H–C(2), H–C(4), $H_2C(10)$, 2OCH_2); 4.5 (*d*, $J = 2$, OCH_2O): 7.0–7.5 (*m*, 5 H, C_6H_5).

Methyl (2 RS,*4* R,*8* R*)-10-bromo-8-methyl-2-phenylthio-4-(1,3,6-trioxaheptyl)decanoate* (**22**). To a mixture of CBr_4 (0.663 g, 2 mmol) pyridine (0.24 ml, 3 mmol) and 5 ml of ether was added Ph_3P (0.500 g, 1.9 mmol). The mixture was stirred for 10 min and **21** (0.428 g, 1 mmol) in 3 ml of Et_2O was added. After stirring over night at r.t. the mixture was taken up in Et_2O and washed with brine, dried and evaporated *i.v.* The crude product was purified by column chromatography (Et_2O/petroleum ether 1:1, $R_f = 0.37$) to yield 332 mg (68%) of pure **22**. IR (film): 2940, 1740, 1580, 1060. ^{1}H-NMR (60 MHz, CCl_4): 0.9 (*d*, $J = 6$, 3 H, CH_3–C(8)); 1.0–2.1 (*m*, 11 H, $H_2C(3)$, $H_2C(5)$, $H_2C(6)$, $H_2C(7)$, H–C(8), $H_2C(9)$); 3.25 (*s*, 3 H, CH_3O); 3.55 (*s*, 3 H, $COOCH_3$); 3.1–3.9 (*m*, 8 H, H–C(2), H–C(4), 2 OCH_2, $H_2C(10)$); 4.5 (*d*, $J = 2$, OCH_2O); 7.0–7.5 (*m*, 5 H, C_6H_5).

Methyl (4 R,*8* R*)-10-bromo-8-methyl-4-(1,3,6-trioxaheptyl)-2-decenoate* (**5**). MCPBA (0.2 g) was added to a solution of **22** (0.332 g, 0.675 mmol) in 15 ml of abs. CH_2Cl_2 at −78°. After stirring for 1 h at −78° the mixture was quenched with Na_2SO_3-solution, then it was taken up in Et_2O, washed with $NaHCO_3$ (2 ×) and once with brine, dried and evaporated *i.v.* The crude product was purified by column chromatography (Et_2O/petroleum ether 3:1, $R_f = 0.15$) to yield the pure sulfoxide. To the solution of this sulfoxide in 10 ml toluene 0.200 g of $CaCO_3$ were added. After refluxing and stirring the mixture for 2 h, toluene was evaporated *i.v.* and the crude product was purified by column chromatography (Et_2O/petroleum ether 1:2; $R_f = 0.17$) to yield 0.198 g (77%) of **5**. $[\alpha]_D^{r.t.} = +45.8$ ($c = 3.08$, $CHCl_3$). IR (film): 2940, 1725, 1660. ^{1}H-NMR (90 MHz, $CDCl_3$): 0.9 (*d*, $J = 6.1$, 3 H, CH_3–C(8)); 1.1–1.9 (*m*, 9 H, $H_2C(5)$, $H_2C(6)$, $H_2C(7)$, H–C(8), $H_2C(9)$); 3.3–3.8 (*m*, 6 H, $H_2C(10)$, 2 OCH_2); 3.4 (*s*, 3 H, CH_3O); 3.7 (*s*, 3 H, $COOCH_3$); 4.3 (*m*, 1 H, H–C(4)); 4.7 (*s*, OCH_2O); 6.0 (*dd*, $J = 15.8$, 1.2, 1 H, H–C(2)); 6.8 (*dd*, $J = 15.7$, 9.4, 1 H, H–C(3)). ^{13}C-NMR (22.63 MHz, $CDCl_3$): 166.6 ($COOCH_3$); 140.1 (C(3)); 121.6 (C(2)); 93.9 (OCH_2O); 75.5 (CH_3O); 71.8 (OCH_2); 67.3 (C(4)); 59.0 (CH_2O); 51.5 ($COOCH_3$); 40.0 (C(5)); 36.4 (C(7)); 35.0 (C(8)): 31.8 (C(5)); 31.6 (C(10)); 22.4 (C(6)); 18.9 (CH_3–C(8). MS 380, 381, 382, 383 (M^+).

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