A Butyrolactone → 1,3-Diol Strategy for the Obtention of *Tolypothrix* Polyethers – Total Synthesis of the *Tolypothrix* Pentaether from Enantiomerically Enriched *S*-Glycidol[1]☆

Henning Priepke[a] and Reinhard Brückner*[b]

Institut für Organische Chemie der Julius-Maximilians-Universität[a], Am Hubland, D-97074 Würzburg, Germany

Institut für Organische Chemie der Georg-August-Universität[b], Tammannstraße 2, D-37077 Göttingen, Germany

Received February 24, 1997

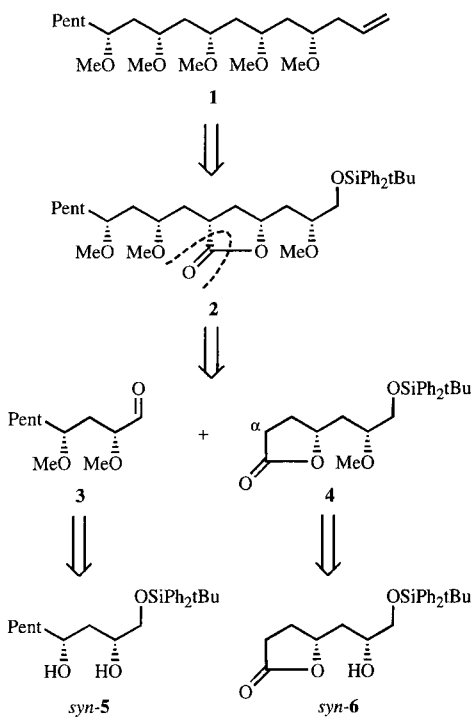
Keywords: 1,3-Diol synthesis / Lactones / Polyethers / 1,3,5,7-...-Polyol synthesis / Rearrangements / *Tolypotrix*

Permethyl ether **1** from *Tolypothrix conglutinata* was synthesized following the retrosynthetic analysis of Scheme 1. According to it, we combined aldehyde **3** [prepared from *S*-glycidol (**7**); cf. Schemes 2, 3] and lactone **4** (also prepared from *S*-glycidol (**7**); cf. the preceding communication[2] and Scheme 4) to the enantiopure and diastereopure trimethoxy lactone **2** (Scheme 5). The C=O group of this lactone was removed through the Criegee rearrangement of a derived lactol peroxonosylate (Scheme 6); thereby, the C–C=O bond of lactone **2** was replaced with complete retention of configuration by one C–OH bond of the resulting *syn*-configured diol **18**. Protecting group manipulations (Schemes 6, 7) and oxidation of the resulting alcohol **21** to aldehyde **31** (Scheme 10) initiated the three final operations: C_2-homologation with Ph_3P=CH-CH=O (→ enal **32**), tosyl hydrazone formation (→ **34**), and reduction/concomitant C=C bond migration. They led to the target ether **1** as a 89:11 mixture with the CH=CH-richer ether **36**.

The preceding paper[2] outlines a strategy for a novel synthesis of the permethyl ether **1** ("*Tolypothrix* pentaether") from *Tolypothrix conglutinata*[3] following a retrosynthetic analysis presented in more detail in Scheme 1 of the present communication. The key step of this approach is the oxidative excission of the indicated sp^2-hybridized carbon atom from the butyrolactone **2**. This transformation would furnish a trimethoxydiol (formula not shown) which appeared convertible into the target ether **1** in very few steps. We intended to prepare lactone **2** by condensation of the aldehyde **3** with the enolate of the α-unsubstituted lactone **4**. Aldehyde **3** should be obtained from the diol *syn*-**5** by a Williamson methylation followed by desilylation, and lactone **4** should arise from the hydroxy lactone *syn*-**6** by another Williamson methylation

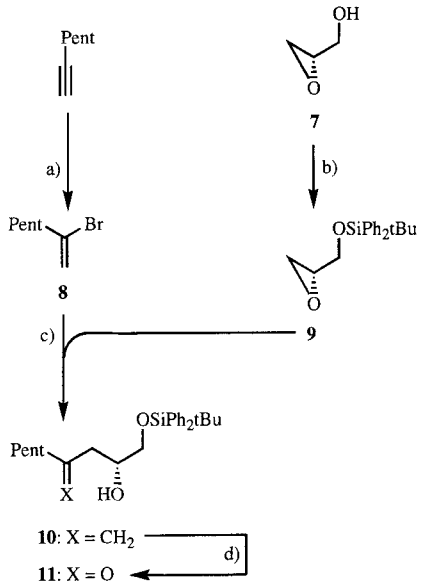
A straightforward route to the required lactone *syn*-**6** has been established.[2] It started from commercially available[4] *S*-glycidol (**7**).[2] It was convenient to utilize the same *S*-glycidol as a starting material for gaining the diol *syn*-**5**. By doing so we could incorporate into the synthesis of the aldehyde **3** a number of the reactions which had already led from *S*-glycidol to the mentioned lactone *syn*-**6**. The other starting compound was the bromoheptene **8** which is accessible from 1-heptyne and HBr by Cousteau's procedure (Scheme 2).[5] This compound was transformed into a Grignard reagent. Upon addition of cat. CuI,[6] the resulting Normant cuprate ring-opened the *tert*-butyldiphenylsilyl glycidyl ether **9**[2] through a regioselective attack at the less hindered epoxide center. The homoallyl alcohol **10** was obtained in 95% yield. Ozonolysis of compound **10** and reductive workup with PPh_3 furnished the β-hydroxy ketone **11** in 90% yield.

Scheme 1



  0947–3440/97/0808–1645 $ 17.50+.50/0

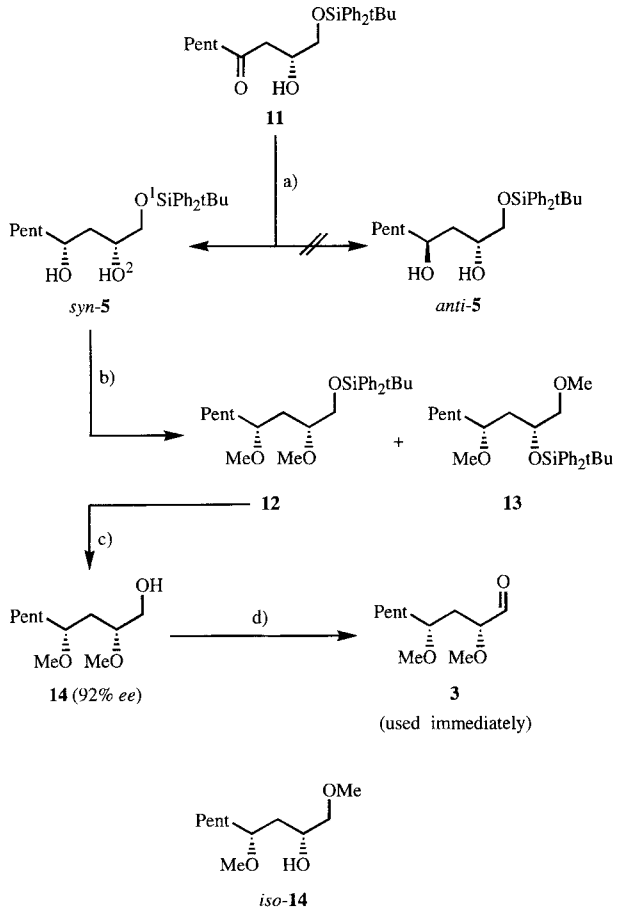
Scheme 2. a) Anhydr. HBr (1.2 equiv.), Et_4NBr (1.2 equiv.), CH_2Cl_2, 1-heptyne, 4.5 h, 40°C; 78%.[5] – b) Ref.[2]; 79%. – c) **8** (1.5 equiv.), Mg (2 equiv.), THF, 35–40°C, 4 h; addition to CuI (0.1 equiv.), THF, −40°C, 15 min; addition of **9**, → 0°C, 2.5 h; 95%. – d) O_3, CH_2Cl_2, −78°C, PPh_3; 90%



By the Narasaka-Prasad chelation-controlled reduction[7] of the C=O bond of hydroxy ketone **11** we proceeded to a single 1,3-diol – compound *syn*-**5** of Scheme 3 – in 92% yield. Highly *syn*-selective reductions of this kind have been exploited often and in many different molecular environments.[8] Thus, the collected precedence can be considered a sound basis for assigning the *syn* configuration to our reduction product and for excluding the alternative stereostructure *anti*-**5**. The di-methylation of diol *syn*-**5** was troublesome. Reactions with MeI and a suspension of KH in THF or treatment with MeI and Ag_2O in DMF did not succeed. Only adding a concentrated THF solution of diol *syn*-**5** to a large excess of KH and Me_2SO_4 suspended/dissolved in another concentrated THF solution worked reasonably well. Under these conditions the desired dimethyl ether **12** formed (76% yield), however, along with up to ca. 6% of the regioisomer **13**. Obviously, the latter was formed after the *tert*-butyldiphenylsilyl group had migrated from O-1 to O-2 in the (di)anion of the substrate diol. Such based-induced migrations in *tert*-butyldiphenylsilylated 1,2-diols are known.[9] Fortunately, the desired dimethyl ether **12** could be liberated almost completely from its isomer **13** by flash chromatography on silica gel.[10] The ensueing reactions were a desilylation and a Swern oxidation. They led via the dimethoxycarbinol **14** (97% yield) to the dimethoxyaldehyde **3** (ca. 88% yield; used as a crude product). By GLC the optical purity of carbinol **14** was 92% *ee* (*vide infra*).

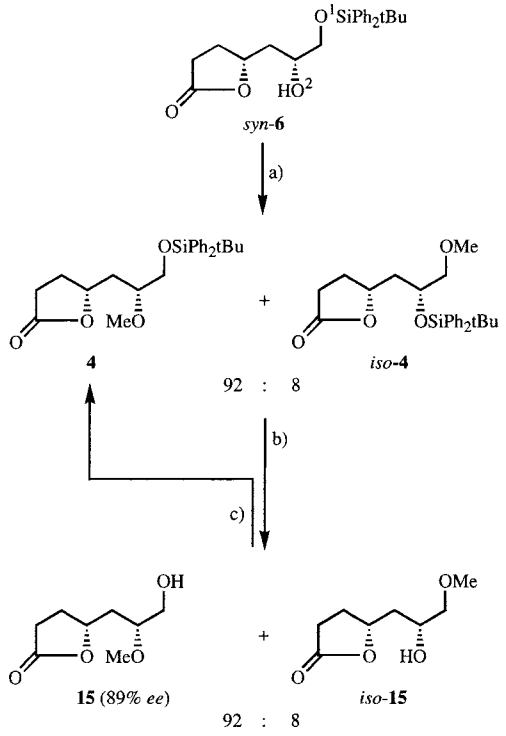
Next, we had to methylate lactone *syn*-**6**[2] (Scheme 4). Under the most efficient conditions – namely treatment at room temperature with large excesses of KH and Me_2SO_4 in THF – the competition of *tert*-butyldiphenylsilyl group migration to O-2 and an ensueing O-1 methylation was even more pronounced than in the analogous methylation *syn*-**5** → **12** (desired) + **13** (undesired) of Scheme 3. The wanted methoxy lactone **4** was invariably accompanied by the undesired regioisomer *iso*-**4**. For minimizing the proportion in which this unwanted isomer contaminated the desired isomer **4** we had to stop the methylation of hydroxy lactone *syn*-**6** before it went to completion. By this modus operandi we recovered 17% of unchanged starting lactone *syn*-**6** and isolated the methylated lactones **4** and *iso*-**4** in a 92:8 ratio and in 61% yield (73% based on recovered starting material).

Scheme 3. a) Et_3B (1.1 equiv.), THF/MeOH (4:1, v:v), room temp., 1 h; → −78°C, addition of **11**, 1 h; addition of $NaBH_4$, 3 h; 92%. – b) *syn*-**5**, Me_2SO_4 (9 equiv.), THF, 0°C, addition of KH (4 equiv.), 1 d; more Me_2SO_4 (4.5 equiv.), → room temp., 1 d; 76% (in another experiment 6% of impure **13** together with 70% **12** were obtained). – c) Bu_4NF (1.2 equiv.); 97%; 2% of regioisomer *iso*-**14** were separated. – d) $(COCl)_2$ (1.1 equiv.), DMSO (2.2 equiv.), THF, −78°C, addition of **14**, 10 min; → room temp., addition of Et_3N; 88% (the crude aldehyde was used.)



Unfortunately, the lactones **4** and *iso*-**4** were unseparable by flash chromatography on silica gel.[10] Hence, we had to go through the hardship of desilylating the **4**/*iso*-**4** mixture to an equally 92:8 composed mixture of the underlying alcohols **15** and *iso*-**15** (Scheme 4). They, too, were unseparable by flash chromatography. However, by a reaction between these alcohols, imidazole, and a substoichiometric amount of *tert*-butyldiphenylsilyl chloride, the less hindered

Scheme 4. a) Me_2SO_4 (5 equiv.), THF, KH (1.8 equiv.), 1 d; 61% of a 92:8 mixture of **4**/*iso*-**4** and 17% recovered *syn*-**6**. – b) Bu_4NF (1.2 equiv.), 30 min, 93% (92:8 mixture of **15**/*iso*-**15**). – c) *tert*-$BuPh_2SiCl$ (0.9 equiv.), imidazole, THF, 2 h; 86% (98:2 mixture of **4**/*iso*-**4**)

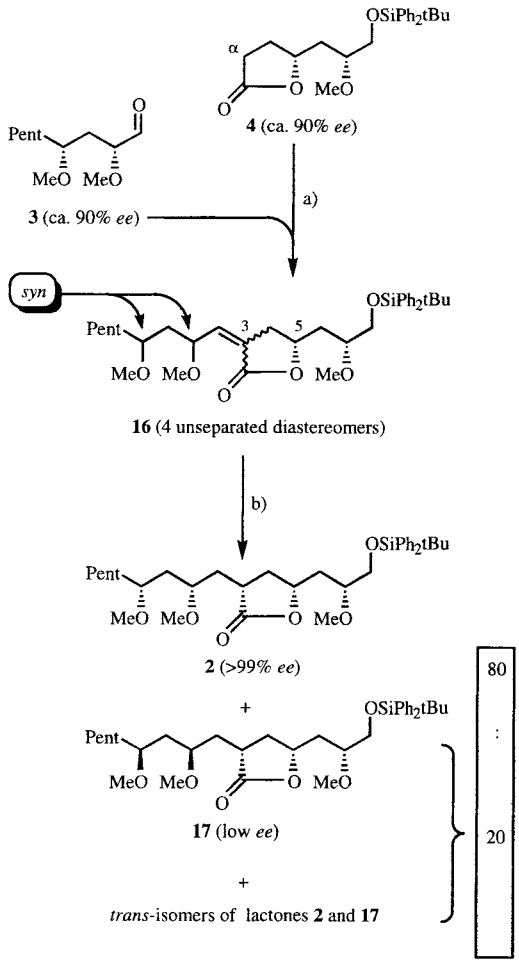


primary alcohol **15** was silylated almost selectively at the expense of the more hindered secondary alcohol *iso*-**15**. In this way the key lactone-intermediate **4** of the present total synthesis was finally obtained essentially free from the isomer *iso*-**4** (86% yield; isomer ratio 98:2).

The enantiomeric purities of the key aldehyde-intermediate **3** (synthesis: Scheme 3) and the key lactone-intermediate **4** (synthesis: Scheme 4) should have been the same and – provided that all reactions were properly done – identical with the enantiomeric purity of their common precursor, i. e. *S*-glycidol (**7**).[4] The *ee*-values of these key intermediates were determined through capillary gas chromatography on a stationary phase of enantiopure 2,6-dimethyl-3-pentyl-ß-cyclodextrin of a derivative being volatile enough at an as far as possible advanced stage. The ultimate precursor of aldehyde **3**, the dimethoxy alcohol **14**, revealed 92% *ee*, and the ultimate precursor of the methoxy(silyloxy)lactone **4**, the methoxy(hydroxy)lactone **15**, 89% *ee*. These values coincide approximately with what the *ee*-value of the starting *S*-glycidol was according to the supplier.[4a] These data, of course, mean that our building blocks **3** and **4** constituted only 96:4 and 94.5:5.5 mixtures, respectively, of desired and undesired enantiomer

The latter circumstance affected severely the ensueing step of the synthesis where these fragment were combined (Scheme 5). As a linking reaction we chose Larson's modification[11] of the Peterson olefination.[12] It consists of the formation of the lithium enolate of an α-unsubstituted butyrolactone – in our case the lactone **4** – with ≥2 equivalents of LDA, the regioselective silylation of the enolate carbon-atom with $Ph_2MeSiCl$, the in-situ deprotonation of the resulting C^{α}-silylated lactone to the C^{α}-silylated lactone enolate, its aldol addition to an aldehyde – in our case aldehyde **3** –, and as the very last step a C=C forming β-elimination of Li^+ $^-OSiPh_2Me$. When we applied the unchanged Larson protocol to the condensation of the lactone **4** with the aldehyde **3**, we could not separate the desired alkylidenelactones **16** from the stoichiometric by-product $(HO)SiPh_2Me$. Therefore, we modified the olefination procedure in the following manner: After all individual reactions had proceeded as far as described above but prior to the aqueous workup we added 1.7 equivalents of Me_3SiCl to the reaction mixture. We thereby silylated the then still negatively charged leaving group Li^+ $^-OSiPh_2Me$ to the siloxane $Me_3Si–OSiPh_2Me$. The latter compound survived the purification of the reaction mixture undamaged. Since it was far less polar then the previous side-product $(HO)SiPh_2Me$ it was removable by flash chromatography from the desired alkylidenelactones **16**.

Scheme 5. a) LDA (2.5 equiv. with respect to **5**), THF, –78°C, addition of **4** (1.15 equiv.), 40 min; $Me_2SiPhCl$ (1.2 equiv.), –78°C → room temp., 2 h; → –78°C, addition of **5**, → room temp., 16 h; Me_3SiCl (1.7 equiv.), 2 h; 45°C; 70% (mixture of isomers, slightly impure). – b) H_2 (6 bar), Rh (5% on carbon), AcOEt; HPLC separation (80:20 mixture of **2** and **17**/*trans* isomer of **2**/*trans* isomer of **17**); 56% (= 35% total yield from **4**/**5**)



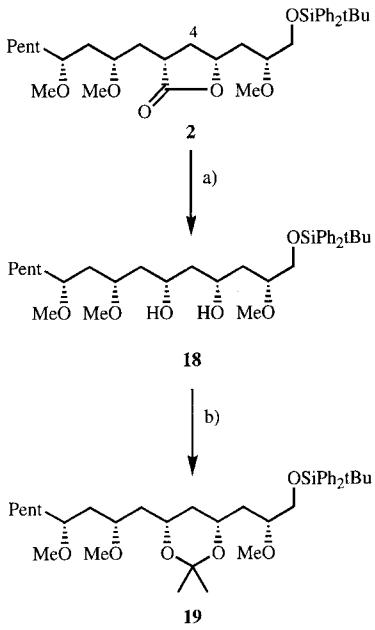
The *plural* form characterizes our product*s* **16** adequately not only because we had obtained them as a 70:30 *E*:*Z* mixture but also because they were sterically inhomogeneous with respect to the relative configurations in the side-chain on C-3 vs. the side-chain on C-5. This complication was an inevitable consequence of the steric inhomogeneity of the underlying building blocks **4** (94.5:5.5 mixture of the shown enantiomer and its mirror image) and **3** (96:4 mixture of the shown enantiomer and its mirror image) provided that there is no mutual kinetic resolution in the Larson olefination by which these building blocks combine. In the total absence of such a mutual kinetic resolution the *E*,*Z* isomers of **16** with a *syn,syn*-arrangement of the three C–OMe bonds would have dominated the *E*,*Z* isomers with a *syn,anti*-orientation of the same C–OMe bonds in a ratio of 91:9. Moreover, the two *syn,syn*-isomers must be almost 100% enantiopure while the *ee*-value of the two *syn,anti*-isomers must be much lower.

We were unable to separate the alkylidenelactones **16** chromatographically. We could not even enrich some of its constituents to an appreciable degree. Gratifyingly, hydrogenation (6 bar) over Rh/C converted the unsaturated lactones **16** into saturated lactones (Scheme 5). They were an 80:20 mixture of the desired *cis*-lactone **2** and three minor lactones which are presumably the following ones: the undesired saturated *cis*-lactone **17**, the *trans*-isomer of lactone **2**, and the *trans*-isomer of lactone **17**. The fact that these minor lactones combined represent 20% of the total lactone yield signifies that the hydrogenation of the unsaturated lactones **16** (ca. 91:9 mixture of *syn,syn*-and *syn,anti*-isomers) had occurred with a *cis,trans*-selectivity of ca. 9:1. This is a typical value for such hydrogenations since *highly cis*-selective hydrogenations of 3-alkylidenebutyrolactones are known[13] but not guaranteed.[14]

From the described mixture of hydrogenated butyrolactones the desired lactone **2** was obtained as a pure compound after preparative HPLC. The overall yield of this lactone with respect to the substrates **4** and **3** of the Larson/Peterson olefination was 35%. Fortunately, the hardship of the HPLC separation was compensated by the advantage that during the remainder of our synthesis we would be working with enantio*pure* compounds.

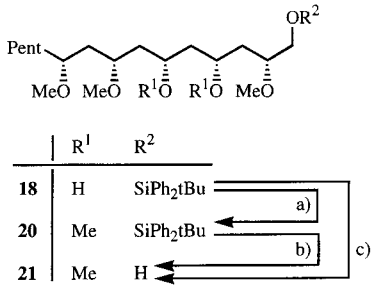
The next step of our synthesis was the oxidative degradation of lactone **2** to the diol **18** (Scheme 6). It was realized in 72% yield by a reaction sequence which Ziegler *et al.* had earlier developed for the degradation of lactones akin to **2** but equipped with an additional ring-substituent on C-4.[15] In the first reaction, the mono-addition of MeLi to lactone **2** gave a lactol in which the OH group was replaced in the second reaction by an OOH group through treatment by 83% H_2O_2 and HOAc. The OOH group was acetylated in step three. A thermolysis in refluxing wet toluene ensued. Finally, the resulting mixture of monoacetylated 1,3-diols was de-acetylated with DIBAL to deliver the diol **18** as a pure diastereomer. Its *syn*-configuration was proven by converting it into the acetonide **19** and performing therein the Rychnovsky/Evans analysis of the ^{13}C-NMR shifts of the carbon atoms of the protecting group.[16] The lines at 19.73

Scheme 6. a) MeLi (3 equiv.), THF, −78°C, 35 min; 83% H_2O_2/THF/HOAc (1:2:0.1, v:v:v), 0°C → room temp., 5.5 h; Et_3N (3.2 equiv.), Ac_2O (3.0 equiv.), DMAP (cat.), CH_2Cl_2, 0°C → room temp., 9 h; solid $NaHCO_3$ (3 equiv.); toluene (saturated with H_2O), 80°C, 5 h; DIBAL (6 equiv.), THF, −78°C, 2.5 h; 72%. – b) CSA (cat.), acetone/2,2-dimethoxypropane (1:1, v:v), 45 min; 78%



and 30.23 ppm for $C_{quat}{}^{13}Me_2$ match the recommended δ-intervals for *cis*-acetonides (19.6±0.35 and 30.0±0.35, respectively) and so does the line at 98.31 ppm for $^{13}C_{quat}Me_2$ with respect to the standard 99.5 ppm shift.

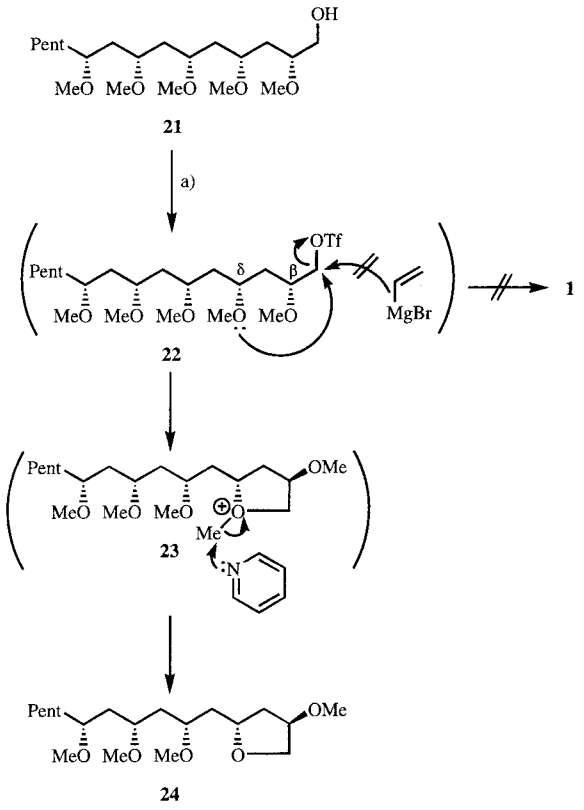
Scheme 7. a) KH (3.6 equiv.), MeI (10 equiv.), THF, 0°C → room temp., 16 h; 81%. – b) Bu_4NF (2.5 equiv.), THF, room temp., 1 h; 83%. – c) (i) KH (3.6 equiv.), MeI (10 equiv.), THF, 0°C, 10 min, then room temp., 2 h; immediately used for (ii) Bu_4NF (1.2 equiv.), THF, room temp., 12 h; 79% over the two steps



Having established the *syn*-configuration of diol **18**, this compound was methylated with KH/MeI (Scheme 7) and the resulting dimethyl ether **20** desilylated. Doing so without purifying the intermediate **20**, the pentamethoxy-alcohol **21** was obtained in 79% yield over the two steps.

Our first attempt to chain-elongate the alcohol **21** used the triflate **22** derived from this alcohol by treatment with triflic anhydride and pyridine in CH_2Cl_2 (Scheme 8). After TLC indicated that this reaction had come to an end, we treated the crude product with a large excess of vinylmagnesium bromide. We hoped that these components com-

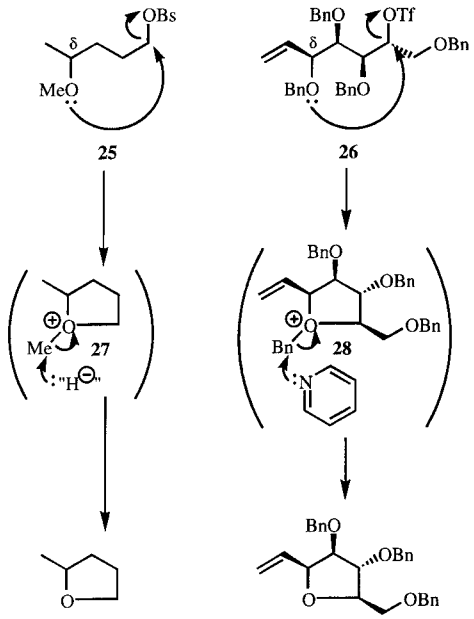
Scheme 8. a) Tf_2O (1.4 equiv.), excess pyridine, CH_2Cl_2, −20°C → −30°C, 1 h; CuI (1.1 equiv.), H_2C=CH-MgBr (10 equiv.), THF, −30°C → 0°C; 62%



bined in an S_N2 reaction to the target ether **1**. Indeed, Cu(I)-catalyzed S_N reactions of primary triflates bearing an alkoxy group on C^β – i. e. substitutions similar to our intended transformation of **22** to **1** – have been reported.[17] As it was, the presumed triflate intermediate **22** did react quantitatively under these conditions. However, what we isolated in 62% yield was a compound *which showed no olefinic proton in the* ^{1}H-NMR spectrum. Moreover, (a) according to the ^{1}H-NMR integral and (b) according to the peak-count in the 55.16−55.66 ppm range of the DEPT ^{13}C-NMR spectrum it contained only four and not five methoxy groups as we had expected. Other noteworthy features of this DEPT spectrum were the presence of five oxygenated methine-type carbon atoms (δ = 75.31, 75.51, 75.95, 77.97, and 81.46) and of one oxygenated methylene carbon atom (δ = 75.50). Taking these data together we concluded that the product of our "Grignard reaction" was the tetrahydrofuran **24**, a notion which was also supported by the elemental analysis.

How can one explain this unexpected reaction of triflate **22**? Obviously, the triflate experienced an intramolecular nucleophilic attack through the methoxy group at C^δ rather than an intermolecular nucleophilic attack through vinylmagnesium bromide. This methoxy group involvement must have led to the oxonium ion **23** which was probably demethylated by the excess pyridine which we used. In δ-alkoxylated brosylates (cf. compound **25**, Scheme 9),[18] mesylates,[19], and triflates likewise (cf. compound **26**, Scheme 9),[20] intramolecular S_N reactions with participation of the δ-alkoxy group are known. They lead via heterocyclic five-membered oxonium ions – compounds **27** and **28**, respectively – to tetrahydrofurans – e. g. to compounds **29** and **30**, respectively. The nucleophilic participation of the methoxy group in the course of the failed $LiAlH_4$ reduction of the δ-methoxybrosylate **25** (Scheme 9)[18] constitutes a particularly close analogy to the methoxy-group participation leading to our undesired tetrahydrofuran **24** of Scheme 8.

Scheme 9

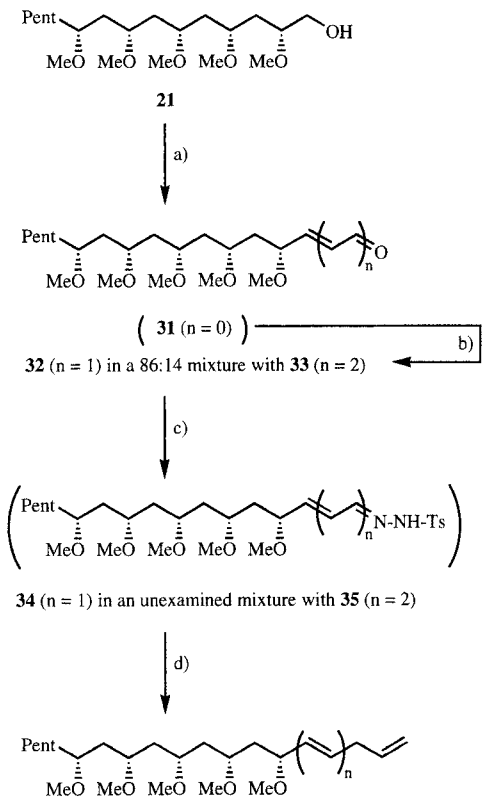


(35% of the recovered material)

Because of the difficulty to funnnel larger amounts of material through the bottle-neck of the present synthesis – i. e. through the preparative HPLC required for the purification of lactone **2** (Scheme 5) – very little pentamethoxy alcohol **21** remained for finding an alternative path to the *Tolypothrix* pentaether (**1**). Thus, we were satisfied to find that the reactions depicted in Scheme 10 provide such a path but refrained from optimizing the involved reaction conditions; after all, they were irrelevant to the central issue of the present study which was to develop a novel synthesis *strategy*. According to Scheme 10 we first oxidized the alcohol **21** to the aldehyde **31**. Then, we treated this aldehyde with Ph_3P=CH-CH=O in refluxing toluene. α-Oxygenated aldehydes like our substrate **31** *can* be condensed with Ph_3P=CH-CH=O to γ-oxygenated α,β-unsaturated aldehydes.[21] Yet, there is a possibility to loose some or all of this primary condensation product through a follow-up condensation with unreacted phosphorane. Thereby, one obtains ε-oxygenated α,β,γ,δ-unsaturated aldehydes.[22] Monitoring by TLC the reaction of aldehyde **21** with Ph_3P=CH-CH=O showed a slow conversion to *one* new spot until all of the starting aldehyde had disappeared. Nonetheless, the desired α,β-unsaturated aldehyde **32** and the overreacted α,β,γ,δ-unsaturated aldehyde **33** had already *both* formed. They were indistinguishable by TLC and unseparable by flash chromatography.[10] Thus, we

gained them only as an 86:14 mixture. This was evidenced by their low-field ^{1}H-NMR resonances: The α,β-unsaturated aldehyde **32** contained three low-field signals ($\delta_{olefinic}$ = 6.27 and 6.73, $\delta_{CH=O}$ = 9.61) and the α,β,γ,δ-unsaturated aldehyde **33** five ($\delta_{olefinic}$ = 6.14, 6.18, 6.49, and 7.14, $\delta_{CH=O}$ = 9.59)

Scheme 10. a) (i) Oxalyl chloride (1.1 equiv.), DMSO (2.2 equiv.), −78°C, 10 min; **21**; 30 min; Et_3N (3.0 equiv.), −78°C, 30 min; room temp., 30 min; 89% (used crude). – b) Ph_3P=CH−CH=O (2.0 equiv.), toluene, Δ, 6 h; 76%. – c) $TsNHNH_2$ (1.1 equiv.), EtOH, 50°C, 15 min; the crude tosylhydrazones **34/35** were used. – d) $NaBH_4$ (10 equiv.), HOAc (conc.), room temp., 1 h; 70°C, 2 h; 92% over the two steps



The 86:14 mixture of the α,β-unsaturated aldehyde **32** and the α,β,γ,δ-unsaturated aldehyde **33** was condensed with tosyl hydrazide to an unexamined mixture of the corresponding tosylhydrazones **34** (α,β-unsaturated) and **35** (α,β,γ,δ-unsaturated). These hydrazones were treated – after exchanging the solvent from ethanol to acetic acid – by $NaBH_4$.[22] Such a reduction of a conjugated tosylhydrazone is accompanied by a C=C bond migration because the involved diazene intermediate decomposes via a retro-ene reaction. Thus, the main constituent **34** of our tosylhydrazone mixture was reduced such that it delivered the target polyether **1** while the minor tosylhydrazone was reduced such that it delivered the CH=CH-richer pentaether **36**.

Compounds **1** and **36** formed a chromatographically unseparable 89:11 mixture and were isolated in 92% yield with respect to the aldehydes **32/33**. The ^{1}H- and ^{13}C-NMR spectra of this mixture showed the presence of **1** through concurrence with the published data.[3] The identity of 11 mol-% of the contaminant **36** was inferred from mechanistic requirements (*vide supra*) and independently from the following ^{1}H-NMR signals: ① the multiplets of a vinyl group ($\delta_{methylene\ protons}$ = 5.00−5.06, $\delta_{methine\ proton}$ superimposed by a signal from **1**); ② the resonances of a *trans*-configured C=C bond (δ_H = 5.32 and 5.68, J_{vic} = 15.5 Hz); ③ the dublet of dublet (with addititional allyl couplings) of a CH_2 group located between two sp^2-hybridized carbon atoms (δ_H = 2.82); and ④ the dublet of triplet of the methine proton adjacent to the allylic C–O bond (δ_H = 3.68).

In the present study, a new approach to 1,3,5,7,...-polyols has been established by the example of a successful total synthesis of the *Tolypothrix* pentaether **1**. It exhibits, apart from ist novelty, strengths as well as weaknesses. Among its strengths are the viability of the proposed γ-butyrolactone → 1,3-diol degradation strategy and its incorporation into a considerably convergent synthesis. The weaknesses were having used an enantiomerically not pure enough starting material **7** (which enforced the purification by preparative HPLC of lactone intermediate **2**) and the interference of a competing silyl group migration in the methylation reaction *syn*-**6** → **4** (which made two extra-steps necessary for obtaining the methylation product **4** *pure*). Luckily, these weaknesses are no inherent problems of our butyrolactone → 1,3-diol strategy as demonstrated in a second synthesis from our laboratory of the same *Tolypothrix* pentaether. It is described in the immediately following paper.

We are indebted to the *Deutsche Forschungsgemeinschaft* for financing this project. We are grateful to Prof. Dr. *W. König* (Universität Hamburg) for measuring the *ee* values of compounds **14** and **15**, and we deeply appreciate an academic loan of $RhCl_3$ by the *Johnson Matthy Technology Center* (Reading) and a donation of Ph_2tBuSiCl by *Wacker AG* (Burghausen).

Experimental Section

General remarks: See ref.[2]– IR (film): Perkin-Elmer FT-IR 1600.

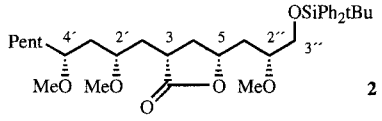
(4S,6S,8R,10R,12R)-4,6,8,10,12-Pentamethoxy-1-heptadecene (**1**) *in a 89:11* Mixture with (6R,8R,10R,12R,14R)-6,8,10,12,14-Pentamethoxy-1,4-nonadecadiene* (**36**): **32** (in a 86:14 mixture with **33**; 0.0205 g, 0.0509 mmol) was dissolved in EtOH (2 ml). Tosylhydrazide (0.0108 g, 0.0561 mmol, 1.1 equiv.) was added. The solution was warmed to 50°C for 15 min. After recooling to room temp. the solvent was evaporated and conc. HOAc (3 ml) was added to the crude **34/35** mixture. Then $NaBH_4$ (0.0193 g, 0.509 mmol, 10 equiv.) was added at 0°C. After 1 h at room temp. and 2 h at 70°C the reaction was quenched with H_2O (10 ml) and the mixture extracted extracted with Et_2O (3 x 20 ml) and dried with Na_2SO_4. Flash chromatography (petroleum ether:Et_2O, 10:1 to 3:1) yielded the title mixture (0.0182 g, 81% **1**, 11% **36**). – $[\alpha]_{23}^{D}$ = + 7.5 (*c* = 1.02, $CHCl_3$) {natural **1**:[3] $[\alpha]_{23}^{D}$ = + 7.39 (*c* = 0.77, $CHCl_3$); synthetic **1**:[3] $[\alpha]_{23}^{D}$ = + 7.57 (*c* = 0.78 in $CHCl_3$)}. – *Determined by comparison of the integrals over the alkene protons. – IR: $\tilde{\nu}$ = 2930 cm^{-1}, 2820, 1735, 1640, 1460, 1375, 1190, 1095, 915. – $C_{22}H_{44}O_5$ (388.6): calcd. C 68.00, H 11.41; found C 68.39, H 11.22.

1: ^{1}H NMR (500 MHz): δ = 0.90 (t, $J_{17,16}$ = 7.0, 17-H_3), 1.25−1.39 (m, 14-H_2, 15-H_2, 16-H_2) 1.48−1.62 and 1.77−1.85 (2 m, 5-H_2, 7-H_2, 9-H_2, 11-H_2, 13-H_2), AB signal (δ_A = 2.30, δ_B = 2.34, J_{AB} = 15.0, in addition split by $J_{A,2}$ = 8.5, $J_{A,4}$ = 6.2, J_{allyl} =

1.4, $J_{B,2}$ = 8.5, $J_{B,4}$ = 6.5, J_{allyl} = 1.2, 3-H_2), ca. 3.16 - ca. 3.46 (m, 4-H, 6-H, 8-H, 10-H, 12-H), superimposed by 3.309, 3.311, 3.313, 3.32, and 3.35 (5 s, 5 x OMe), 5.09 (ddt, J_{cis} = 10.1, J_{gem} = J_{allyl} = 1.1, 1-H^E), 5.11 (ddt, J_{trans} = 16.9, J_{gem} = 2.0, J_{allyl} = 1.7, 1-H^Z), 5.84 (dddd, J_{trans} = 17.3, J_{cis} = 10.2, $J_{2,3\text{-H(A)}}$ = $J_{2,3\text{-H(B)}}$ = 7.0, 2-H).

36: (500 MHz; as far as signals are identifiable besides **1**): δ = 2.82 (dddt, $J_{3,2}$ = $J_{3,4}$ = 6.6, $^4J_{3,5}$ = $^4J_{3,1}$ = 1.4, 3-H_2), 3.68 (dt, $J_{6,4}$ = $J_{6,5}$ = 7.4, 6-H), 3.24, 3.28 and 3.29 (3 s, 3 x OMe), 5.00−5.06 (m, 1-H_2), 5.32 (ddt, $J_{5,4}$ = 15.4, $J_{5,6}$ = 8.3, $^4J_{5,3}$ = 1.4, 5-H), 5.68 (dt, $J_{4,5}$ = 15.6, $J_{4,3}$ = 6.5, 4-H).

(3R,5R)-5-[(2R)-3-[(tert-Butyldiphenylsilyl)oxy]-2-methoxypropyl]-3-[(2S,4R)-2,4-dimethoxynonyl]-4,5-dihydro-2(3H)-furanone (**2**):



2

Diisopropylamine (2.2 ml, 1.6 g, 16 mmol, 2.5 equiv.) in THF (20 ml) was deprotonated with *n*BuLi (1.50 M in hexane, 10 ml, 15 mmol, 2.5 equiv.) at −78°C and stirred for 1 h. Lactone **4** (3.0473 g, 7.386 mmol, 1.15 equiv.) in THF (10 ml) was added slowly via syringe, and stirring was continued for another h at −78°C. Methyldiphenylchlorosilane (1.6 ml, 1.8 g, 7.5 mmol, 1.2 equiv.) in THF (10 ml) was added to the enolate. After 40 min one warmed to room temp. for 4 h. The mixture was cooled to −78°C, and freshly prepared aldehyde **3** (1.283 g, 6.342 mmol) in THF (10 ml) was added via syringe. After 40 min at −78°C the cooling bath was removed, and after another 2 h trimethylchlorsilane (1.4 ml, 1.2 g, 11 mmol, 1.7 equiv.) was added. One stirred for 1 h at 45 °C, then the reaction was quenched by addition of satd. aqueous NH_4Cl (50 ml). The aqueous layer was extracted with tBuOMe (4 × 50 ml), the combined organic layers were dried ($MgSO_4$), and the solvent was removed. Flash chromatography (Et_2O:petroleum ether 1:5 → 1:3) yielded a 70:30 *E*:*Z* mixture (ratio determined by the integrals over the olefinic protons in the ^{1}H-NMR spectrum which could not be interpreted in more detail) of the 4 diastereoisomers of **16** (2.6375 g, slightly impure, 70%). This mixture was directly submitted to hydrogenation: **16** (977.2 mg, 1.637 mmol; consequently only 37% of the aforementioned product of the condensation reaction were used) was hydrogenated (6 bar) in AcOEt (12 ml) in the presence of Rh (5% on carbon, 81.9 mg) for 20 h. Filtration through Celite and evaporation of the solvent yielded **2** in an 80:20 mixture (932.3 mg, 95%) with the *cis*-lactone **17** and the *trans*-isomers of **2** and of **17**. Preparative HPLC [250 mm × 25 mm, absorbent: LiChrosorb Si60 (7 μm, CAT.51435); eluent: AcOEt/petroleum ether, 1:4; R_T = 12 min, flow rate: 18 ml/min, UV detection (λ = 254 nm)] allowed the separation of pure **2** (556.6 mg, 0.9293 mmol, 56%; 35% overall yield from **4** and **3**).

2: $[\alpha]_{25}^{D}$ = -19 (*c* = 1.01 in CH_2Cl_2). – ^{1}H NMR (500 MHz): δ = 0.90 (t, $J_{9',8'}$ = 7.0, 9'-H_3), 1.06 [s, $C(CH_3)_3$], 1.25−1.36 (m, 6'-H_2, 7'-H_2, 8'-H_2), 1.43−1.58 (m, 3'-H^1, 5'-H_2), superimposes in part 1.55 (ddd, J_{gem} = $J_{4\text{-H(1)},3}$ = 12.4, $J_{4\text{-H(1)},5}$ = 10.7, 4-H^1), 1.62 (ddd, J_{gem} = 14.3, $J_{1'\text{-H(1)},3}$ = 10.5, J_c = 3.5, 1'-H^{1*}), 1.87 (dd, J_{gem} = 14.2, J_b = 5.6, coupling with 2''-H not detectable, 1''-H^{1*}), superimposes 1.89 (ddd, J_{gem} = 14.2, J_b = 5.0, J_c = 1.6, 3'-H^{2*}), 2.05 (ddd, J_{gem} = 14.0, $J_{1''\text{-H(2)},5}$ = $J_{1''\text{-H(2)},2''}$ = 7.0, 1''-H^2), 2.10 (ddd, J_{gem} = 14.5, $J_{1'\text{-H(2)},2'}$ = 8.6, $J_{1'\text{-H(2)},3}$ = 3.8, 1'-H^2), 2.49 (ddd, J_{gem} = 12.4, $J_{4\text{-H(2)},3}$ = 8.4, $J_{4\text{-H(2)},5}$ = 5.3, 4-H^2), 2.80 (dddd, $J_{3,4\text{-H(1)}}$ = 12.3, $J_{3,1'\text{-H(1)}}$ = 10.2, $J_{3,4\text{-H(2)}}$ = 8.4, $J_{3,1'\text{-H(2)}}$ = 3.8, 3-H), 3.25 (m_c, 4'-H), 3.307 and 3.314 (2 s à 3 and 6 H, 3 × OMe), 3.37−3.46 (m, 2'-H, 2''-H), AB signal (δ_A = 3.70, δ_B = 3.73, J_{AB} = 11.0, in addition split by $J_{A,2''}$ = 4.6, $J_{B,2''}$ = 4.8, 3''-H_2), 4.42 (dddd, $J_{5,4\text{-H(1)}}$ ≈ 11, $J_{5,4\text{-H(2)}}$ ≈ $J_{5,1''\text{-H(1)}}$ ≈ $J_{5,1''\text{-H(2)}}$ ≈ 6, 5-H), 7.31−7.46 and 7.66−7.69 (2 m à 6 and 4 Ar-H, respectively); * assignments interchangeable. – ^{13}C NMR (100 MHz): δ = "+" 13.98 (C-9'), "0" 19.17 [$C(CH_3)_3$], "-" 22.58 (C-8'[24]), "-" 24.60 (C-6'[24]), "+" 26.80 [$C(CH_3)_3$], "-" 31.98, "-" 33.39, "-" 34.24, "-" 36.18, "-" 37.02, and "-" 37.26 (C-4, C-1', C-3', C-5', C-7'[24], C-1''), "+" 37.60 (C-3), "+" 55.97, "+" 56.23, "+" 57.47 (3 × OCH_3), "-" 64.52 (C-3''), "+" 75.70, "+" 76.11, "+" 77.71, "+" 78.14 (C-5, C-2', C-4', C-2''), "+" 127.69 (4 × *meta*-C), "+" 129.74 (2 × *para*-C), "0" 133.19 and "0" 133.33 (2 × *ipso*-C), "+" 135.54 and "+" 135.60 (2 × 2 *ortho*-C), 179.09 (C-2). – $C_{35}H_{54}O_6Si$ (598.9): calcd. C 70.19, H 9.09; found C 70.51, H 9.16.

(2R,4R)-2,4-Dimethoxynonanal (**3**): Oxalyl chloride (0.68 ml, 1.0 g, 7.9 mmol, 1.1 equiv.) in THF (10.0 ml) was treated with DMSO (1.1 ml, 1.2 g, 16 mmol, 2.2 equiv.) in THF (7.0 ml) for 15 min at −78°C. Alcohol **14** (1.4728 g, 7.209 mmol) in THF (10 ml) was added followed 20 min later by Et_3N (3.0 ml, 2.2 g, 22 mmol, 3 equiv.). After 10 min at −78°C the mixture was warmed to room temp., stirred for 40 min, and quenched with ice cold 1 M HCl (30 ml). Extraction with *t*BuOMe (2 × 50 ml), washing of the combined organic layers with satd. aqueous $NaHCO_3$ (25 ml) and satd. aqueous NaCl (25 ml), drying with Na_2SO_4, and removal of the solvent furnished the crude title aldehyde (1.283 g, 88%) which was used immediately. – ^{1}H NMR (250 MHz): δ = 0.89 (t, $J_{9,8}$ ≈ 6.5, 9-H_3), 1.22- ca. 1.67 (m, 5-H_2, 6-H_2, 7-H_2, 8-H_2), 1.89−1.99 (m, 3-H_2), 3.24 and 3.45 (2 s, 2 × OMe), 3.29−3.39 (m, 4-H), 3.70 (t with fine splitting, $J_{2,3}$ ≈ 5.4, 2-H), 9.60 (d, $J_{1,2}$ = 1.0, 1-H).

(5R)-5-[(2R)-3-[(tert-Butyldiphenylsilyl)oxy]-2-methoxypropyl]-4,5-dihydro-2(3H)-furanone (**4**) *and (5R)-5-[(2R)-2-[(tert-Butyldiphenylsilyl)oxy]-3-methoxypropyl]-4,5-dihydro-2(3H)-furanone* (*iso*-**4**). - *Method A (Methylation of the Hydroxy Lactone syn*-**6**): Lactone *syn*-**6** (2.7106 g, 6.801 mmol) in a mixture of THF (10 ml) and Me_2SO_4 (3.0 ml, 4.0 g, 32 mmol, 5 equiv.) was treated with KH (491.6 mg, 12.26 mmol, 1.8 equiv.) in small portions. One stirred for 1 d. The reaction was quenched with satd. aqueous NH_4Cl/conc. NH_3 (4:1, 10 ml), *t*BuOMe (75 ml) was added and the organic layer was washed with satd. aqueous NH_4Cl:conc. NH_3, 4:1 (15 ml) and satd. aqueous NH_4Cl (10 ml). After drying with $MgSO_4$ evaporation of the solvent and flash chromatography [*t*BuOMe/petroleum ether, 1:4 to 1:1) a 92:8 mixture of **4**:*syn*-**4** (1.7486 g, 61%) and recovered starting material (*syn*-**6**, 462.6 mg, 17%) were obtained.

Method B (Silylation of the Hydroxy Lactone **15**): A 92:8 mixture of the regioisomeric lactones **15**/*iso*-**15** (2.2270 g, 12.78 mmol) was treated with *tert*-butyldiphenylchlorosilane (3.0 ml, 3.2 g, 12 mmol, 0.9 equiv.) and imidazole (1.39 g, 20.5 mmol, 1.6 equiv.) for 2 h in THF (20 ml). About 50% of the solvent was removed under reduced pressure and the crude mixture purified by flash chromatography (*t*BuOMe/petroleum ether, 1:2 to 2:1) to yield a 98:2 mixture of **4** and *iso*-**4** (4.544 g, 86%). – $[\alpha]_{22}^{D}$ = -1.6 (*c* = 2.57 in CH_2Cl_2). – ^{1}H NMR (400 MHz): δ = 1.06 [s, $(CH_3)_3C$], 1.83−1.94 (m, 1'-H^A, 4-H^1), B part of AB signal centered at 2.03 (J_{AB} = 14.1, in addition split by $J_{B,5}$ = $J_{B,2'}$ = 7.0, 1'-H^B), 2.30 (dddd, J_{gem} = 12.5, $J_{4\text{-H(2)},3\text{-H(A)}}$ = 7.9, $J_{4\text{-H(2)},5}$ = 6.5, $J_{4\text{-H(2)},3\text{-H}}$B = 5.6, 4-$H^2$), AB signal ($\delta_A$ = 2.50, δ_B = 2.53, J_{AB} = 17.5, in addition split by $J_{A,4\text{-H(1)}}$ = 9.6, $J_{A,4\text{-H(2)}}$ = 8.1, $J_{B,4\text{-H(1)}}$ = 9.5, $J_{B,4\text{-H(2)}}$ = 5.6, 3-H_2), 3.31 (s, OMe), 3.38 (m_c, presumably interpretable as dddd, $J_{2',1'\text{-H(B)}}$ ≈ 7, all other *J* ≈ 4.7, 2'-H), AB signal (δ_A = 3.69, δ_B = 3.73, J_{AB} = 11.0, in addition split by $J_{A,2'}$ = 4.6, $J_{B,2'}$ = 4.7, 3'-H_2), 4.57 (dddd, J_a = 8.2, $J_{5,4\text{-H(2)}}$ = $J_{5,1'\text{-H(B)}}$ = J_d = 6.7, 5-H), 7.36−7.47 and 7.65−7.70

(2 m à 6 and 4 Ar-H, respectively). – A COSY NMR spectrum showed cross peaks for all indicated couplings. – ^{13}C NMR (63 MHz): δ = "0" 19.18 [*C*(CH_3)], "+" 26.80 [C(*C*H_3)], "-" 28.20 (C-4*), "-" 28.77 (C-3*), "-" 37.08 (C-1'*), "+" 57.51 (OMe), "-" 64.46 (C-3'), "+" 78.12 (C-5* and C-2'*), "+" 127.71 (*meta*-C), "+" 129.75 (*para*-C), "0" 133.18 and "0" 133.31 (2 × *ipso*-C), "+" 135.54 and "+" 135.60 (2 × 2 *ortho*-C), "0" 177.04 (C-2); *assignment based on a C,H correlation. – $C_{24}H_{32}O_4Si$ (412.6): calcd. C 69.86, H 7.82; found C 69.85, H 7.76.

(2R,4R)-1-[(tert-Butyldiphenylsilyl)oxy]-2,4-nonanediol (*syn*-**5**): Et_3B (1.0 M in THF, 18 ml, 18 mmol, 1.1 equiv.) was added to a 4:1 mixture of THF/MeOH (100 ml). The mixture was stirred for 1 h., cooled to −78°C, and hydroxy ketone **11** (6.91 g, 16.8 mmol) in THF (20 ml) added dropwise. After 1 h solid $NaBH_4$ (697 mg, 18.4 mmol, 1.1 equiv.) was added, and the mixture was left for 3 h at −78°C. The reaction was quenched at −78°C by addition of AcOEt (40 ml) and satd. aqueous NH_4Cl (40 ml). After extraction with AcOEt (3 × 50 ml) and drying with Na_2SO_4 the solvent was evaporated, and methanol was added in portions and evaporated again at about 40°C until no borinic ester was detectable via TLC. Flash chromatography (*t*BuOMe/petroleum ether, 1:5 to 1:3) furnished *syn*-**5** (6.37 g, 92%). – $[\alpha]_{23}^{D}$ = -0.3 (*c* = 2.03 in CH_2Cl_2). – ^1H NMR (250 MHz): δ = 0.88 (t, $J_{9,8}$ = 6.5, 9-H_3), 1.07 [s, $(CH_3)_3C$], 1.22−1.60 (m, 3-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2), 3.15 (d, *J* = 2.7, 1 OH*), 3.45 (d, *J* = 1.8, 1 OH*), AB signal (δ_A = 3.53, δ_B = 3.60, J_{AB} = 10.1, in addition split by $J_{A,2}$ = 7.1, $J_{B,2}$ = 4.2, 1-H_2), 3.84 (m_c, 4-H**), 3.97 (m_c, 2-H**), 7.33−7.49 and 7.60−7.71 (2 m à 6 and 4 Ar-H, respectively); *exchangeable with D_2O; **assignments based on a COSY spectrum. – ^{13}C NMR (63 MHz): δ = 14.33 (C-9), 19.51 [*C*(CH_3)$_3$], 22.91 (C-8), 25.36 (C-6[24]), 27.12 [C(*C*H_3)$_3$], 32.14 (C-7[24],*), 38.06, 39.18, (C-3, C-5), 68.23 (C-1*), 72.34 (C-4*), 73.32 (C-2*), 128.08 (4 × *ortho*-C), 130.14 (2 × *para*-C), 133.29 and 133.32 (2 × *ipso*-C), 135.80 (4 × *meta*-C); *assignment based on a C,H-correlation spectrum. – $C_{25}H_{38}O_3Si$ (414.7): calcd. C 72.41, H 9.24; found C 72.38, H 9.11.

2-Bromo-1-heptene (**8**): Preparation as described in ref.[5] (78% yield; ref.:[5] 80%).

(R)-1-[(tert-Butyldiphenylsilyl)oxy]-4-methylene-2-nonanol (**10**): Vigourously stirred magnesium turnings (2.391 g, 98.39 mmol, 2.0 equiv.) in THF (25.0 ml) were treated at 35−40°C first with a few drops of conc. bromoolefin **8** and – later after the reaction started – with diluted **8** (total amount: 12.79 g, 72.23 mmol, 1.5 equiv.) in THF (75.0 ml). The mixture was stirred for 4 h at room temp. The resulting brownblack solution was cannulated over a period of 10 min into a cooled (−40°C) suspension of CuI (983.7 mg, 5.2 mmol, 0.1 equiv.) in THF (30 ml). After 15 min a solution of epoxide **9** (15.05 g, 48.18 mmol) in THF (50 ml) was added. After another 12 min the temp. was raised to 0°C, and one stirred for another 2.5 h. The reaction was quenched by addition of satd. aqueous NH_4Cl (100 ml). After extractions with *t*BuOMe (3 × 200 ml), drying of the combined organic layers with Na_2SO_4, evaporation of the solvent, and flash chromatography (petroleum ether to petroleum ether/*t*BuOMe, 25:1) pure **10** (18.79 g, 95%) was obtained. – $[\alpha]_{21}^{D}$ = + 3.0 (*c* = 12.2 in CH_2Cl_2). – ^1H NMR (250 MHz): δ = 0.88 (t, $J_{9,8}$ = 6.7, 9-H_3), 1.07 [s, $(CH_3)_3C$], 1.20−1.48 (m, 6-H_2, 7-H_2, 8-H_2), 1.99 (t, $J_{5,6}$ = 7.5, 5-H_2), 2.09−2.28 (m, 3-H_2), 2.42 (d, $J_{OH,2}$ = 3.1, OH), AB signal (δ_A = 3.57, δ_B = 3.65, J_{AB} = 10.1, in addition split by $J_{A,2}$ = 6.8, $J_{B,2}$ = 4.0, 1-H_2), 3.86 (m_c, 2-H), 4.76 and 4.79 (2 br. s, 1'-H_2), 7.30−7.48 and 7.61−7.75 (2 m à 6 and 4 Ar-H, respectively). – $C_{26}H_{38}O_2Si$ (216.4): calcd. C 76.04, H 9.33; found C 76.35, H 9.52.

(R)-1-[(tert-Butyldiphenylsilyl)oxy]-2-hydroxy-4-nonanone (**11**): Ozone was bubbled into a solution of olefin **10** (7.87 g, 19.1 mmol) in CH_2Cl_2 (25 ml) at −78°C until the blue color persisted. Triphenylphosphane (7.87 g, 30 mmol, 1.5 equiv.) was added. The solvent was exchanged for petroleum ether, the resulting solution cooled (4°C) for one hour and filtered. The solvent was removed under reduced pressure and the crude material was purified by flash chromatography (*t*BuOMe/petroleum ether, 1:20 to 1:2) to yield **11** (7.0589 g, 90%). – $[\alpha]_{22}^{D}$ = +10.1 (*c* = 2.4 in CH_2Cl_2). – ^1H NMR (250 MHz): δ = 0.89 (t, $J_{9,8}$ = 6.8, 9-H_3), 1.06 [s, $(CH_3)_3C$], 1.21−1.37 (m, 7-H_2, 8-H_2), 1.56 (tt, $J_{6,7}$ = $J_{6,5}$ = 7.3, 6-H_2*), 2.42 (t, $J_{5,6}$ = 7.4, 5-H_2*), 2.53−2.68 (m, 3-H_2*), 2.96 (d, $J_{OH,2}$ = 4.1, OH), 3.56−3.68 (m, 1-H_2), 4.18 (br. ddddd, all *J* including $J_{2,OH} \approx$ 5.5, 2-H), 7.32−7.49 and 7.58−7.70 (2 2 m à 6 and 4 Ar-H, respectively, respectively); *assignments based on a COSY spectrum. – $C_{25}H_{36}O_3Si$ (412.6): calcd. C 72.77, H 8.79; found C 72.77, H 8.80.

(2R,4R)-1-[(tert-Butyldiphenylsilyl)oxy]-2,4-dimethoxynonane (**12**) *and (2R,4R)-2-[(tert-Butyldiphenylsilyl)oxy]-1,4-dimethoxynonane* (**13**): A solution of *syn*-**5** (4.7579 g, 11.59 mmol) in dimethylsulfate (10 ml, 13 g, 11 mmol, 9 equiv.) and THF (25 ml) was treated portionwise with KH (1.931 g, 4.815 mmol, 4 equiv.) at 0°C. Gentle gas evolution and precipitation of a white salt were observed. After 1 d more dimethyl sulfate (5.0 ml, 6.5 g, 5.5 mmol, 4.5 equiv.) was added, and the cooling bath was removed. The mixture was stirred for another day, and then the reaction was quenched by addition of satd. aqueous NH_4Cl (30 ml). After extraction with *t*BuOMe (4 × 50 ml), drying ($MgSO_4$), removal of the solvent and extensive flash chromatography (*t*BuOMe/petroleum ether, 1:70 to 1:20) pure **12** (3.9238 g, 76%) could be obtained. In a similar experiment small amounts of the regioisomer **13** (<6%, impure) together with **12** (70%) were formed.

12: $[\alpha]_D^{23}$ = 8.9 (*c* = 3.62 in CH_2Cl_2). – ^1H NMR (250 MHz): δ = 0.89 (t, $J_{9,8}$ = 7.1, 9-H_3), 1.062 [s, $(CH_3)_3C$], 1.24−1.56 (m, 5-H_2, 6-H_2, 7-H_2, 8-H_2), 1.70 (m_c, 3-H_2), 3.19−3.38 (m, 2-H, 4-H), superimposed by 3.25 and 3.34 (2 s, 2 × OMe), AB signal (δ_A = 3.65, δ_B = 3.68, J_{AB} = 10.7, in addition split by $J_{A,2}$ = 4.4, $J_{B,2}$ = 5.2, 1-H_2), 7.32−7.48 and 7.63−7.73 (2 m à 6 and 4 Ar-H, respectively). $C_{27}H_{42}O_3Si$ (442.7): calcd. C 73.25, H 9.56; found C 72.99, H 9.88.

13 (250 MHz, impure): δ = 0.80 (t, $J_{9,8} \approx$ 7, 9-H_3), 1.05 [s, $(CH_3)_3C$], 1.09−1.32 (m, 6-H_2, 7-H_2, 8-H_2), AB signal (presumably interpretable as: δ_A = 1.59, δ_B = 1.75, J_{AB} = 14.1, in addition split by J_{Aa} = 6.9, J_{Ab} = 5.3, $J_{B,2}$ = $J_{B,4}$ = 6.2, 3-H_2), A part of an AB signal centered at 3.13 (dd, J_{AB} = 10.3, $J_{A,2}$ = 5.9, 1-H^A), B part 3.21−3.28 [(d)d, low-field moieties superimposed by the following methoxy signals, $J_{B,2}$ = 4.6, 1-H^B], partly superimposed by 3.26 and 3.29 (2 s, 2 × OMe), 3.46 (dddd, $J_a \approx J_b \approx J_c \approx$ 6, $J_d \approx$ 3, 4-H), 3.79 (m_c, 2-H), 7.32−7.47 and 7.64−7.74 (2 m à 6 and 4 Ar-H, respectively).

(2R,4R)-2,4-Dimethoxy-1-nonanol (**14**) *and (2R,4R)-1,4-Dimethoxy-2-nonanol* (*iso*-**14**): **12** (contaminated with a little **13**; 8.7967 g, 19.87 mmol) was treated for 3 h with Bu_4NF (1.0 M in THF, 22 ml, 24 mmol, 1.2 equiv.). Then satd. aqueous NaCl (50 ml) was added, and the aqueous layer was extracted with *t*BuOMe (4 × 50 ml). After drying with Na_2SO_4, removal of the solvent, and flash chromatography (*t*BuOMe/petroleum ether, 1:5 to 1:1) pure **14** (3.921 g, 97%) and its regioisomer **iso-14** (121.3 mg, 2%) were obtained. The enantiomeric purity of **14** was measured by GLC (50 m, 2,6-dimethyl-3-pentyl-ß-cyclodextrin, 125°C) as *ee* = 92%.

14: $[\alpha]_{24}^{D}$ = – 27.6 (*c* = 3.21 in CH_2Cl_2). – ^1H NMR (250 MHz): δ = 0.90 (t, $J_{9,8} \approx$ 6.7, 9-H_3), 1.21−1.60 (m, 5-H_2, 6-H_2, 7-H_2, 8-H_2), AB signal (δ_A = 1.66, δ_B = 1.80, J_{AB} = 14.7, in addition split by J_{Aa} = 7.0, J_{Ab} = 3.8, J_{Ba} = 7.9, J_{Bb} = 4.5, 3-H_2), 2.48 (t,

$J_{OH,1}$ = 6.4, OH), 3.32 and 3.38 (2 s, 2 × OMe) superimposed by 3.23–3.52 (m, 2-H, 4-H), AB signal (δ_A = 3.55, δ_B = 3.68, J_{AB} = 11.5, in addition split by $J_{A,OH} \approx J_{A,2} \approx 6$, $J_{B,OH}$ = 6.3, $J_{B,2}$ = 4.6, 1-H_2). – ^{13}C NMR (63 MHz): δ = 14.24 (C-9), 22.83 (C-8[24]), 24.85 (C-6[24]), 32.22, 33.39, 34.62 (C-3, C-5, C-7[24]), 56.37, 57.06 (2 × OMe), 63.80 (C-1), 77.79, 79.00 (C-2, C-4). – $C_{11}H_{24}O_3$ (204.3): calcd. C 64.67, H 11.84; found C 64.82, H 12.05.

iso-14: ^{1}H NMR (250 MHz): δ = 0.89 (t, $J_{9,8} \approx$ 6.7, 9-H_3), 1.22–1.69 (m, 3-H_2, 5-H_2, 6-H_2, 7-H_2, 8-H_2), 3.32–3.47 (m, 1-H_2, 4-H), superimposed by 3.35 and 3.39 (2s, 2 × OMe), 3.49 (d, $J_{OH,2}$ = 1.7, OH), 3.94 (m_c, 2-H).

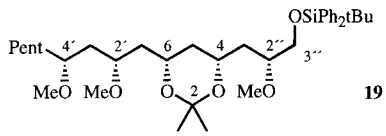
(5R)-5-[(2R)-3-Hydroxy-2-methoxypropyl]-4,5-dihydro-2(3H)-furanone (**15**) *and (5R)-5-[(2R)-2-Hydroxy-3-methoxypropyl]-4,5-dihydro-2(3H)-furanone* (*iso*-**15**): A 92:8 mixture of **4**/*syn*-**4** (2.0006 g, 4.778 mmol) was treated with Bu_4NF (1.1 M in THF, 5.2 ml, 5.7 mmol, 1.2 equiv.) and purified by flash chromatography without prior workup (*t*BuOMe to EtOH/*t*BuOMe, 1:5) to give a 92:8 mixture of regioisomers **15** and *iso*-**15** (771.7 mg, 93%). – By GLC (8 m; 2,6-dimethyl-3-pentyl-ß-cyclodextrin, 115°C) *ee* = 89% was determined for **15** and a content of about 9% of *iso*-**15** was detected as well. – $C_8H_{14}O_4$ (174.2): calcd. C 55.16, H 8.10; found C 55.43, H 8.45.

15: ^{1}H NMR (400 MHz): δ = 1.85–2.15 [m_c, 4 H, presumably interpretable as: AB signal (δ_A = 1.89, δ_B = 2.02, J_{AB} = 14.4, in addition split by $J_{A,2'}$ = 7.0, $J_{A,5}$ = 4.7, $J_{B,5}$ = 8.4, $J_{B,2'}$ = 5.5, 1'-H_2), very speculative 1.93 (dtd, $J_{gem} \approx$ 12.7, $J_{4\text{-}H(1),3} \approx$ 9.9, $J_{4\text{-}H(1),5} \approx$ 8.6, 4-H^1), B part of preceding AB signal superimposes 2.02 (br. t, $J_{OH,1} \approx$ 6, OH), OH, 1'- H_2, 4-H^1], 2.38 (dtd, J_{gem} = 12.9, $J_{4\text{-}H(2),3} \approx J_{4\text{-}H(2),5} \approx$ 6.5, 4-H^2), 2.56 (m_c, 3-H_2), 3.40 (s, OMe), 3.48 (dddd, $J_{2',1'\text{-}H(A)}$ = 6.8, $J_{2',1'\text{-}H(B)} = J_{2',3'\text{-}H(A)}$ = 5.1, $J_{2',3'\text{-}H(B)}$ = 3.6, 2'-H), AB signal (δ_A = 3.60, δ_B = 3.80, J_{AB} = 14.0, in addition split by $J_{A,OH}$ = 6.6, $J_{A,2'}$ = 5.0, $J_{B,OH}$ = 5.2, $J_{B,2'}$ = 3.7, 3'-H_2), 4.62 (dddd, $J_{5,1'\text{-}H(B)} = J_{5,4\text{-}H(1)}$ = 8.3, $J_{5,4\text{-}H(2)}$ = 6.5, $J_{5,1'\text{-}H(A)}$ = 4.6, 5-H).

iso-**15**: ^{1}H NMR (400 MHz, most resonances superimposed by **15**): δ = A part centered at 1.81 (J_{AB} = 14.3, J_b = 5.9, J_c = 4.3, 1'-H^A), 3.97 (ddddd, $J_a \approx J_b \approx J_c \approx$ 7.4, $J_d \approx J_e \approx$ 3.7, 2'-H), 4.73 (m_c, 5-H).

(2R,4R,6S,8S,10R)-1-[(tert-Butyldiphenylsilyl)oxy]-2,8,10-trimethoxy-4,6-pentadecanediol (**18**): Lactone **2** (705.2 mg, 1.177 mmol) in THF (12 ml) was treated with MeLi (1.6 M in Et_2O, 2.2 ml, 3.5 mmol, 3 equiv.) at −78°C. After 35 min the reaction was quenched with precooled (−78°C) THF/MeOH, 2:1 (8.0 ml). Then satd. aqueous $NaHCO_3$ (8.0 ml) was added, the organic layer was dried ($MgSO_4$), and evaporation of the sovent under reduced pressure furnished the crude lactols (792.3 mg). They were stirred at 0°C with 83% H_2O_2 (8.0 ml) and 13 drops of glacial HOAc in THF for 5.5 h. The mixture was poured into icecold satd. aqueous $NaHCO_3$ (20 ml). Extraction with petroleum ether (7 × 30 ml), drying (Na_2SO_4) and removal of the solvent under reduced pressure furnished the crude hydroperoxides (740.3 mg). They were dissolved in CH_2Cl_2 (20 ml) and successively treated with DMAP (about 10 mg), triethylamine (0.52 ml, 0.38 g, 3.8 mmol, 3.2 equiv.), and Ac_2O (0.33 ml, 0.36 g, 3.5 mmol, 3.0 equiv.) at 0°C. The mixture was slowly warmed to room temp. and stirred for 9 h. The reaction was quenched by addition of satd. aqueous $NaHCO_3$ (20 ml). After extraction with *t*BuOMe (6 × 25 ml), drying of the combined organic layers with Na_2SO_4, and removal of the solvent under reduced pressure the crude material was dissolved in water-saturated toluene (16 ml). Solid $NaHCO_3$ (0.304 g, 3.62 mmol, 3 equiv.) was added, and then the mixture was heated to 80°C for 5 h. Then H_2O (5.0 ml) was added, and the aqueous phase was extracted with *t*BuOMe (6 × 25 ml). After drying (Na_2SO_4) and removal of the solvent a mixture of the crude acetates was obtained (742.1 mg). It was dissolved in THF (16 ml) and treated with DIBAL (1.0 M in hexane, 4.7 ml, 4.7 mmol, 4 equiv. ; after 1 h and 2 h more DIBAL (1.5 ml + 1.0 ml => totally: 7.2 ml, 7.2 mmol, 6 equiv.) was added at −78°C. The reaction was quenched after 2.5 h by addition of EtOH (5.0 ml) and the mixture was poured into satd. aqueous sodium tartrate (30 ml). After extraction with *t*BuOMe (6 × 50 ml, then extraction of the aqueous layer for 2 d with 50 ml tBuOMe, and again for 1 d with 50 ml *t*BuOMe), the combined organic layers were dried (Na_2SO_4) and purified by flash chromatography (Et_2O:-petroleum ether, 1:5 to 3:1) to yield **18** (494.9 mg, 72%). – $[\alpha]_{25}^{D}$ = -2.7 (*c* = 0.61 in CH_2Cl_2). – ^{1}H NMR (500 MHz): δ = 0.90 (t, $J_{15,14}$ = 7.0, 15-H_3), 1.06 [s, C(CH_3)$_3$], 1.24–1.37 (m, 12-H_2, 13-H_2, 14-H_2), 1.46–1.73 and 1.83 (m à 9 H and ddd with J_{gem} = 14.3, J_b = 7.9, J_c = 4.9, 3-H_2, 5-H_2, 7-H_2, 9-H_2, 11-H_2), 3.25, 3.50, and 3.56 (3 m_c, 2-H, 8-H, 10-H), 3.31, 3.34, 3.37 (3 s, 3 × OMe), AB signal (δ_A = 3.66, δ_B = 3.70, J_{AB} = 11.0, in addition split by $J_{A,2}$ = 4.5, $J_{B,2}$ = 4.9, 1-H_2), 3.98–4.06 (m, 4-H, 6-H), 4.15 and 4.23 (2 br. s, 2 × OH*), 7.36–7.46 and 7.65–7.71 (2 m à 6 and 4 Ar-H, respectively); *exchangeable with D_2O. – ^{13}C NMR (100 MHz): δ = "+" 14.05 (C-15), "0" 19.23 [*C*(CH_3)$_3$], "-" 22.65 (C-14[24]), "-" 24.66 (C-12[24]), "+" 26.85 [C(*C*H_3)$_3$], "-" 32.05, "-" 33.49, "-" 37.63, "-" 39.04, "-" 41.47, and "-" 44.14 (C-3, C-5, C-7, C-9, C-11, C-13*), "+" 56.00, "+" 56.21, "+" 57.60 (3 × OCH_3), "-" 65.32 (C-1), "+" 70.81, "+" 70.86 (C-4, C-6), "+" 77.77, "+" 78.29, "+" 81.46 (C-2, C-8, C-10), "+" 127.71 (4 × *meta*-C), "+" 129.75 (2 × *para*-C), "0" 133.36 and "0" 133.48 (2 × *ipso*-C), "+" 135.62 and "+" 135.66 (2 × 2 *ortho*-C). – $C_{34}H_{56}O_6Si$ (588.9): calcd. C 69.35, H 9.59; found C 68.99, H 9.82.

(4S,6R)-4-[(2R)-3-[(tert-Butyldiphenylsilyl)oxy]-2-methoxypropyl]-6-[(2R,4R)-2,4-dimethoxynonyl]-2,2-dimethyl-1,3-dioxane (**19**):



19

Diol **18** (41.9 mg, 0.0711 mmol) was treated with camphor sulfonic acid (cat.) for 45 min in 1:1 acetone/2,2-dimethoxypropane (2.0 ml). After neutralization with solid $NaHCO_3$ (ca. 50 mg) and stirring for 15 min the mixture was purified by flash chromatography without prior workup (Et_2O/petroleum ether, 1:1) to obtain **19** (34.7 mg, 78%). – $[\alpha]_{23}^{D}$ = +6.7 (*c* = 1.32 in in CH_2Cl_2). – ^{1}H NMR (500 MHz): δ = 0.90 (t, $J_{9',8'}$ = 7.1, 9'-H_3), 1.06 [s, C(CH_3)$_3$], ca. 1.24–1.37 (m, 6'-H_2, 7'-H_2, 8'-H_2), superimposes 1.31 and 1.32 [2 s, 2-(CH_3)$_2$], 1.46–1.56 (m, 5 H, although 6 H expected*) and 1.68 (ddd with J_a = 14.0, $J_b = J_c$ = 5.8, 1 H) and 1.72–1.83 (m, 3 H; together 5-H_2, 1'-H_2, 3'-H_2, 5'-H_2, 1''-H_2), 3.30, 3.31, and 3.35 (3 s, 3 × OMe), superimposes 3.28 and 3.37–3.46 (m_c à 1 H and m à 2 H, respectively, 2'-H, 2''-H, 4'-H), AB signal [δ_A = 3.66, δ_B = 3.70, J_{AB} = 10.9, in addition split by $J_{A,2''}$ = 5.2, $J_{B,2''}$ = 4.1, 3''-H_2), 3.92 and 3.96 [2 m_c, probably interpretable as 2 dddd, $J_a \approx$ 11.2, J_b = 7.3, J_c = 5.5, $J_d \approx$ 2.3 and J_a = 11.2, J_b = 7.5, J_c = 5.5, J_d = 2.1, respectively, 4-H, 6-H], 7.31–7.47 and 7.67–7.70 (2 m à 6 and 4 Ar-H, respectively); *1 H might be located at 1.10–1.19. – ^{13}C NMR (126 MHz, together with APT): δ = "+" 14.05 (C-9'), "-" 19.23 [*C*(CH_3)$_3$], "+" 19.73 (ax. 2-CH_3*), "-" 22.65 (C-8'[24]), "-" 24.52 (C-6'[24]), "+" 26.84 [C(*C*H_3)$_3$], "+" 30.23 (eq. 2-CH_3*), "-" 32.08, "-" 33.41, "-" 37.22, "-" 37.61, "-" 38.01, and "-" 40.09 (C-5, C-1', C-3', C-5', C-7'[24], C-1''), "+" 56.10, "+" 56.33, and "+" 57.52 (3 × OCH_3), "-" 65.13 (C-3''), "+" 65.87 and "+"

66.05 (C-4, C-6**), "+" 74.80, "+" 77.92, and "+" 78.23 (C-2', C-4', C-2''**), "-" 98.31 (C-2), "+" 127.66 (4 × *meta*-C), "+" 129.64 and "+" 129.65 (2 × *para*-C), "-" 133.55 and "-" 133.61 (2 × *ipso*-C), "+" 135.62 (4 × *ortho*-C); * assignments based on ref.[16]; ** assignment of C-4/C-6 vs. C-2'/C-4'/C-2'' based on the ^{13}C-NMR signals of the pentamethyl ethers **20** and **21** (where all CR_2OMe signals are located between 75.03–78.88 ppm) and model dioxolanes (where C-4/C-6 are located between 66.37–68.57 ppm).[25]. – $C_{37}H_{60}O_6Si$ (629.0): calcd. C 70.66, H 9.62; found C 70.91, H 9.89.

(2R,4R,6R,8R,10R)-1-[(tert-Butyldiphenylsilyl)oxy]-2,4,6,8,10-pentamethoxypentadecane (**20**): The diol **18** (485.7 mg, 0.8248 mmol) in THF (4.0 ml) was added to a suspension of KH (119.4 mg, 2.978 mmol, 3.6 equiv.) in THF (5.0 ml) at 0°C followed by addition of MeI (0.50 ml, 1.13 g, 8.0 mmol, 10 equiv.). After 8 min the cooling bath was removed while stirring was continued for 16 h. The reaction was quenched at 0°C by the addition of satd. aqueous NH_4Cl (8.0 ml). After extraction with *t*BuOMe (6 × 30 ml), drying with Na_2SO_4, removal of the solvent, and flash chromatography (Et_2O:petroleum ether, 1:10 to 1:3) **20** (413.0 mg, 81%) was obtained. – $[\alpha]_{26}^{D}$ = +11 (*c* = 1.24 in CH_2Cl_2). – ^{1}H NMR (400 MHz): δ = 0.90 (t, $J_{15,14}$ = 6.9, 15-H_3), 1.06 [s, $C(CH_3)_3$], 1.25–1.39 (m, 12-H_2, 13-H_2, 14-H_2), 1.46–1.65 and 1.68–1.85 (2 m à 5 H, 3-H_2, 5-H_2, 7-H_2, 9-H_2, 11-H_2), max. 3.25–3.46 (m, 2-H, 4-H, 6-H, 8-H, 10-H), 3.27, 3.28, 3.30, 3.31, 3.35 (5 s, 5 × OMe), AB signal (δ_A = 3.65, δ_B = 3.69, J_{AB} = 10.8, in addition split by $J_{A,2}$ = 4.5, $J_{B,2}$ = 5.2, 1-H_2), 7.35–7.45 and 7.67–7.71 (2 m à 6 and 4 Ar-H, respectively). – ^{13}C NMR (100 MHz): δ = "+" 14.05 (C-15), "0" 19.23 [*C*$(CH_3)_3$], "-" 22.66 (C-14[24]), "-" 24.62 (C-12[24]), "+" 26.86 [C(*C*$H_3)_3$], "-" 32.08, "-" 33.47, "-" 35.58, "-" 37.99, "-" 38.25, and "-" 38.30 (C-3, C-5, C-7, C-9, C-11, C-13[24]), "+" 56.13, "+" 56.18, "+" 56.21, "+" 56.27, and "+" 57.72 (5 × OCH_3), "-" 65.66 (C-1), "+" 75.36, "+" 75.44, "+" 75.54, "+" 78.00, and "+" 78.88 (C-2, C-4, C-6, C-8, C-10), "+" 127.67 (4 × *meta*-C), "+" 129.66 (2 × *para*-C), "0" 133.55 and "0" 133.63 (2 × *ipso*-C), "+" 135.63 and 135.66 (2 × 2 *ortho*-C). – $C_{36}H_{60}O_6Si$ (617.0): calcd. C 70.09, H 9.80; found C 70.10, H 10.02.

(2R,4R,6R,8R,10R)-2,4,6,8,10-pentamethoxy-1-pentadecanol (**21**). - *Method A (Desilylation of the Permethyl Ether* **20**): Compound **20** (373.4 mg, 0.6052 mmol) was treated with Bu_4NF (1.0 M in THF, 1.5 ml, 1.5 mmol, 2.5 equiv.) for 1 h at room temp. After addition of satd. aqueous NH_4Cl (10 ml), extraction with *t*BuOMe (4 × 20 ml), drying with Na_2SO_4, and flash chromatography (Et_2O:petroleum ether, 1:3 to Et_2O) **21** (190.1 mg, 83%) was obtained. – $[\alpha]_{26}^{D}$ = -37 (*c* = 1.49 in CH_2Cl_2).

Method B (Preparation from Trimethyl Ether **18** *without Purification of the Intermediate):* KH (0.019 g, 0.46 mmol, 3.6 Äquiv.) was added at 0°C to diol **18** (0.0758 g, 0.129 mmol) and MeI (0.080 ml, 0.18 g, 1.3 mmol, 10 equiv.) in THF (5 ml). The resulting solution was allowed to warm to room temp. after 10 min and quenched after 2 h with a satd. aqueous solution of NH_4Cl (4 ml) and aqueous NH_3 solution (25%, 1 ml). After extraction with Et_2O (3 x 15 ml) and drying with Na_2SO_4 a crude product (0.102 g, >100%) was obtained which was dissolved in THF (5 ml) and treated with Bu_4NF (1.0 M in THF, 0.15 ml, 0.15 mmol, 1.2 equiv.). After 12 h at room temp. the reaction was quenched with a satd. aqueous NH_4Cl solution (5 ml) and a satd. aqueous NH_4Cl solution (5 ml). Extraction with Et_2O (3 x 15 ml) and flash chromatography (petroleum ether:Et_2O, 1:1 to 1:3) yielded the title compound (0.0384 g, 79%). – $[\alpha]_{23}^{D}$ = -38.5 (*c* = 1.15, CH_2Cl_2). – ^{1}H NMR (400 MHz): δ = 0.90 (t, $J_{15,14}$ ≈ 7, 15-H_3), 1.24–1.38 (m, 12-H_2, 13-H_2, 14-H_2), 1.46–1.65 and 1.72–1.88 (2 m à 5 H, 3-H_2, 5-H_2, 7-H_2, 9-H_2, 11-H_2), 2.46 (t, $J_{OH,1}$ = 6.4, OH), max. 3.21–3.51 (m, 2-H, 4-H, 6-H, 8-H, 10-H), 3.308, 3.313 (double intensity), 3.33 and 3.39 (4 s, 5 × OMe), AB signal (δ_A = 3.56, δ_B = 3.70, J_{AB} ≈ 11, in addition split by $J_{A,2}$ ≈ $J_{A,OH}$ = 5.9, $J_{B,2}$ ≈ $J_{B,OH}$ ≈ 5.5, 1-H_2). – ^{13}C NMR (100 MHz): δ = "+" 14.03 (C-15), "-" 22.65 (C-14[24]), "-" 24.62 (C-12[24]), "-" 32.05 [C-13, assignment based on a C,H-correlation (125 MHz) and in accord with[24]], "-" 33.44, "-" 34.61, "-" 37.75, "-" 37.87, and "-" 38.13 (C-3, C-5, C-7, C-9, C-11), "+" 56.18 (double intensity), "+" 56.23, "+" 56.30, and "+" 56.86 (5 × OCH_3), "-" 63.64 (C-1), "+" 75.03, "+" 75.32, "+" 75.41, "+" 77.89, and "+" 78.62 (C-2, C-4, C-6, C-8, C-10). – $C_{20}H_{42}O_6$ (378.6): calcd. C 63.46, H 11.18; found C 63.78, H 11.43.

(2R,4R)-4-Methoxy-[(2R,4R,6R)-2,4,6-trimethoxyundecanyl]-tetrahydrofuran (**24**): Trifluoromethanesulfonic anhydride (33 µl, 55 mg, 0.20 mmol, 1.4 equiv.) was added at −32°C to alcohol **21** (52.8 mg, 0.139 mmol) in a mixture of CH_2Cl_2 (2.0 ml) and pyridine (0.10 ml). The solution was stirred for 1 h at −20°C to −30°C. The reaction was quenched with icecold 0.4 M HCl (25 ml). The mixture was extracted with *t*BuOMe (3 × 30 ml). The combined organic layers were washed with HCl (0.4 M, 10 ml), satd. aqueous $NaHCO_3$ (10 ml), and satd. aqueous NaCl (10 ml) and dried (Na_2SO_4). The crude material was dissolved in THF (1.0 ml) and cannulated into a cooled (−30°C) suspension of CuI (27.3 mg, 0.143 mmol, 1.1 equiv.) and H_2C=CH-MgBr (1.0 M in THF, 1.4 ml, 1.4 mmol, 10 equiv.) in THF (1.5 ml). After 5 min it was warmed to 0°C, stirred for 2 h and quenched by addition of conc. NH_3/satd. aqueous NH_4Cl, 1:3 (15 ml). Extraction with *t*BuOMe (5 × 20 ml), drying with Na_2SO_4, and flash chromatography (*t*BuOMe/petroleum ether, 1:1 to 3:1) yielded **24** (29.7 mg, 62%). – $[\alpha]_{24}^{D}$ = -12.7 (*c* = 0.90 in CH_2Cl_2). – ^{1}H NMR (400 MHz): δ = 0.89 (t, $J_{11',10'}$ = 6.9, 11'-H_3), 1.23–1.38 (m, 8'-H_2, 9'-H_2, 10'-H_2), 1.45–1.70 [m, 3-H^1 (a characteristic crosspeak to 3-H^2 at 2.13 ppm is visible in a COSY spectrum; in addition there is a weak crosspeak to C-3 in the C,H-correlation spectrum), 1'-H^{A}**, 3'-H^{A}**, 5'-H^{A}**, 7'-H_2], 1.75–1.93 (m, 1'-H^B, 3'-H^B, 5'-H^B), 2.13 (br. dd, J_{gem} = 13.0, $J_{3\text{-}H(2),2}$ = 5.4, 3-H^2; the COSY spectrum shows a crosspeak to 2-H but not to 4-H), 3.30 and 3.31 (2 s à 3 and 9 H, 4 × OMe), superimposes ca. 3.23–3.33 (m, 6'-H*), 3.35–3.49 (m, 2'-H*, 4'-H*), 3.69–3.75 (m, 5-H^1), 3.98–4.05 [m, 4-H, 5-H^2], 4.10 (m_c, probably ddt, J_a = 9.9, J_b = 6.8, $J_{2,3\text{-}H(2)}$ = 5.7, 2-H); *assignments interchangeable; **assignments based on a C,H-correlation spectrum. – ^{13}C NMR (100 MHz): δ = "+" 14.06 (C-11'), "-" 22.68 (C-10'[24]), "-" 24.63 (C-8'[24]), "-" 32.08 (C-9'[24]), "-" 33.49 (C-7'), "-" 37.92 (double intensity) and "-" 39.04 (C-1', C-3', C-5'), "-" 38.65 (C-3), "+" 56.16, "+" 56.26, "+" 56.31, and "+" 56.66 (4 × OCH_3), "-" 72.50 (C-5), "+" 75.13 (C-2), "+" 75.51, "+" 75.95, and "+" 77.97 (C-2', C-4', C-6'), "+" 81.46 (C-4). – $C_{19}H_{38}O_5$ (346.5): calcd. C 65.86, H 11.05; found C 65.75, H 10.83.

trans-(4R,6R,8R,10R,12R)-4,6,8,10,12-Pentamethoxy-2-heptadecenal (**32**) *in a 86:14 Mixture* with trans,trans-(6R,8R,10R,12R,14R)-6,8,10,12,14-Pentamethoxy-2,4-nonadecadienal* (**33**): DMSO (0.012 ml, 0.013 g, 0.17 mmol, 2.2 equiv.) was added at −78°C to oxalyl chloride (0.0071 ml, 0.011 g, 0.083 mmol, 1.1 equiv.) in THF (2 ml). After 10 min alcohol **21** (0.0284 g, 0.0754 mmol) in THF (2 ml) was added via cannula. After 30 min Et_3N (0.032 ml, 0.023 g, 0.23 mmol, 3.0 equiv.) was added. After another 30 min the reaction mixture was allowed to room temp. and quenched after another 30 min with H_2O (5 ml) and aqueous HCl (2 M, 3 ml). Extraction with Et_2O (3 x 15 ml) and drying with Na_2SO_4 yielded the crude aldehyde **31** (0.0252 g, ≤89%). It was dissolved in toluene (7 ml) and treated with (formylmethylene)triphenylphosphorane (0.0621 g, 0.204 mmol, ≥2.0 equiv.). The resulting mixture was refluxed for 6 h. After evaporation of the solvent the residue was purified by flash chromatography (petroleum

ether:Et_2O, 3:1 to 1:2) to yield the title mixture (0.0205 g, 72% **32**, 13% **33**). – *Determined by comparison of the integrals over the alkene protons. – IR: $\tilde{\nu}$ = 2930 cm^{-1}, 2825, 1735, 1695, 1640, 1460, 1380, 1190, 1095, 795. – $C_{22}H_{42}O_6$ (402.6): calcd. C 65.64, H 10.52; found C 65.74, H 10.56.

32: ^1H NMR (300 MHz; contaminated through small m at δ = 3.82–3.87): δ = 0.90 (t, $J_{17,16}$ = 6.6, 17-H_3), 1.18–1.41 and 1.45–1.99 (2 m, 5-H_2, 7-H_2, 9-H_2, 11-H_2, 13-H_2, 14-H_2, 15-H_2, 16-H_2), 3.21–3.50 (m, 6-H, 8-H, 10-H, 12-H), superimposed by 3.28, 3.29, 3.306, 3.312, and 3.33 (5 s, 5 x OMe), 4.06 (dt with incompletely resolved allylic coupling, $J_{4,3}$ = $J_{4,5}$ = 6.5, 4-H), 6.27 (ddd, J_{trans} = 15.8, $J_{2,1}$ = 7.9, $^4J_{2,4}$ = 1.3, 2-H), 6.73 (dd, J_{trans} = 15.6, $J_{3,4}$ = 6.2, 3-H), 9.61 (d, $J_{1,2}$ = 7.9, 1-H). – ^{13}C NMR (125 MHz, $CDCl_3$, impurity at δ = "+" 74.57): δ = "+" 14.01 (C-17), "-" 22.62, "-" 24.59, "-" 32.02, "-" 33.39, "-" 37.61, "-" 37.81, "-" 38.04, and "-" 38.75 (C-5, C-7, C-9, C-11, C-13, C-14, C-15, C-16), "+" 56.11, "+" 56.15, "+" 56.16, "+" 56.20, and "+" 57.16 (5 x OMe), "+" 74.65, "+" 75.11, "+" 75.35, "+" 77.69, and "+" 77.86 (C-4, C-6, C-8, C-10, C-12), "+" 132.21 (C-2) "+" 156.86 (C-3), "+" 193.32 (C-1).

33 (300 MHz; as far as signals are identifiable besides **32**): δ = 3.90 (dt, $J_{6,5}$ = $J_{6,7}$ = 6.4, 6-H),), 6.14 (dd, $J_{5,4}$ = 15.3, $J_{5,6}$ = 7.4, 5-H*), 6.18 (dd, $J_{2,3}$ = 15.3, $J_{2,1}$ = 8.2, 2-H*), 6.49 (dd, $J_{4,5}$ = 15.3, $J_{4,3}$ = 10.8, 4-H), 7.14 (dd, $J_{3,2}$ = 15.3, $J_{3,4}$ = 10.6, 3-H), 9.59 (d whose low-field branch is only visible as a shoulder under the high-field branch of the d of 1-H_{32}, $J_{1,2} \approx 7$, 1-H); *assignments interchangeable. – ^{13}C NMR (125 MHz; as far as signals are identifiable besides **32**): δ = "-" 24.71, "-" 29.66, "-" 37.75, "-" 38.13, "-" 38.21, "-" 38.98, and "-" 39.28 (7 signals for 8 centers: C-7, C-9, C-11, C-13, C-15, C-16, C-17, C-18), "+" 56.37, "+" 56.52, and "+" 56.76 (double intensity) (5 x OMe), "+" 74.84, "+" 75.17, "+" 75.39, "+" 75.41, and "+" 78.53 (C-6, C-8, C-10, C-12, C-14), "+" 129.41, "+" 131.90, "+" 145.16, and "+" 150.89 (C-2, C-3, C-4, C-5), "+" 193.59 (C-1).

☆ Dedicated to Professor *Waldemar Adam* (Universität Würzburg) on the occasion of his 60th birthday.

[1] [1a] First presented at the *15th* Regiosymposium of the Universities Basel, Freiburg, and Mulhouse in Falkau, September 27–29, 1995. – [1b] H. Priepke, *Dissertation*, Universität Würzburg, **1993**.

[2] H. Priepke, S. Weigand, R. Brückner, *Liebigs Ann.* **1997**, 1635–1644.

[3] Previous synthesis and structure determination: Y. Mori, Y. Kohchi, M. Suzuki, *J. Org. Chem.* **1991**, *56*, 631–637.

[4] [4a] Purchased from ALDRICH®. – [4b] Compound **7** must possess ca. 90% *ee* as revealed by GLC analysis of the compounds **14** (92% *ee*) and **15** (89% *ee*). – [4c] From the same batch of glycidol **7** from which the mentioned compounds **14** (92% *ee*) and **15** (89% *ee*) were derived we had obtained lactone *syn*-**6** as described in ref.[2]; accordingly, the *ee* values of this compound and its methyl ether **4** must be ca. 90%, too.

[5] J. Cousseau, *Synthesis* **1980**, 805–806.

[6] Method: C. Huynh, F. Derguini-Bouchemal, G. Linstrumelle, *Tetrahedron Lett.* **1979**, *20*, 1503–1506.

[7] K. Narasaka, F.-C. Pai, *Chem. Lett.* **1980**, 1415–1418. – K. Narasaka, F.-C. Pai, *Tetrahedron* **1984**, *40*, 2233–2238. – (b) K.-M. Chen, G. E. Hardtmann, K. Prasad, O. Repic, M. J. Shapiro, *Tetrahedron Lett.* **1987**, *26*, 2951–2954. – K.-M. Chen, K. G. Gunderson, G. E. Hardtmann, K. Prasad, O. Repic, M. J. Shapiro, *Chem. Lett.* **1987**, 1923–1926.

[8] Recent applications of this reduction include: D. Enders, F. Burkamp, J. Runsink, *J. Chem. Soc. Chem. Commun.* **1996**, 609–610. – L. Banfi, G. Guanti, M. T. Zannetti, *Tetrahedron Lett.* **1996**, *37*, 521–524. – I. Paterson, M. V. Perkins, *Tetrahedron* **1996**, *52*, 1811–1834. – K. C. Nicolaou, K. Ajito, A. P. Patron, H. Khatuya, P. K. Richter, P. Bertinato, *J. Am. Chem. Soc.* **1996**, *118*, 3059–3060.

[9] E. g.: J. Mulzer, B. Schöllhorn, *Angew. Chem.* **1990**, *102*, 433–435; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 431.

[10] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem* **1978**, *43*, 2923–2925.

[11] G. L. Larson, L. M. Fuentes, *J. Am. Chem. Soc.* **1981**, *103*, 2418–2419. – G. L. Larson, R. M. Betancourt de Perez, *J. Org. Chem.* **1985**, *50*, 5257–5260.

[12] D. J. Ager, *Synthesis* **1984**, 384–398. – D. J. Ager, Org. React. **1990**, *38*, 1–223. – A. G. M. Barrett, J. M. Hill, E. M. Wallace, J. A. Flygare, *Synlett* **1991**, 765–770.

[13] E. g.: D. J. Kempf, *J. Org. Chem.* **1986**, *51*, 3921–3926. – S. Hanessian, N. G. Cooke, B. DeHoff, Y. Sakito, *J. Am. Chem. Soc.* **1990**, *112*, 5276–5290. – T. Saito, L. Thijs, G.-J. Ettema, B. Zwanenburg, *Tetrahedron Lett.* **1993**, *34*, 3589–3592.

[14] E. g.: S. A. M. Tayyeb Hussain, W. D. Ollis, C. Smith, J. F. Stoddart, *J. Chem. Soc. Perkin Trans. 1*, **1975**, 1480–1492. – K. Tomioka, H. Mizuguchi, K. Koga, *Tetrahedron Lett.* **1978**, 4687–4690.

[15] Methodological work: F. E. Ziegler, A. Kneisley, J. K. Thottathil, R. T. Wester, *J. Am. Chem. Soc.* **1988**, *110*, 5434–5442. – Synthesis applications: C_1-C_7 Erythronolide synthon: F. E. Ziegler, A. Kneisley, *Heterocycles* **1987**, *25*, 105–108. – Prelog-Djerassi lactonic ester, *ent*-invictolide, and C_{19}-C_{27} fragment of rifamycin S: F. E. Ziegler, W. T. Cain, A. Kneisley, E. P. Stirchak, R. T. Wester, *J. Am. Chem. Soc.* **1988**, *110*, 5442–5452. – (-)-Denticulatins A and B: F. E. Ziegler, M. R. Becker, *J. Org. Chem.* **1990**, *55*, 2800–2805. – Vs. elaiophyllin: F. E. Ziegler, J. S. Tung, *J. Org. Chem.* **1991**, *56*, 6530–6537.

[16] S. D. Rychnovsky, D. J. Skalitzky, *Tetrahedron Lett.* **1990**, *31*, 945–948. – S. D. Rychnovsky, B. Rogers, G. Yang, *J. Org. Chem.* **1993**, *58*, 3511–3515. – D. A. Evans, D. L. Rieger, J. R. Gage, *Tetrahedron Lett.* **1990**, *31*, 7099–7100.

[17] H. Kotsuki, I. Kadota, M. Ochi, *Tetrahedron Lett.* **1989**, *30*, 1281–1284, 3999–4000.

[18] E. L. Allred, S. Winstein, *J. Am. Chem. Soc.* **1967**, *89*, 4008–4011.

[19] H. Dehmlow, J. Mulzer, C. Seitz, A. R. Strecker, A. Kohlmann, *Tetrahedron Lett.* **1992**, *33*, 3607–3610.

[20] O. R. Martin, F. Yang, F. Xie, *Tetrahedron Lett.* **1995**, *36*, 47–50.

[21] Recent examples include: M. Ihara, Y. Tokunaga, K. Fukumoto, *J. Org. Chem.* **1990**, *55*, 4497–4498; W. R. Roush, M. Kageyama, R. Riva, B. B. Brown, J. S. Warmus, K. J. Moriarty, *J. Org. Chem.* **1991**, *56*, 1192–1210; P. Herzegh, I. Kovács, F. J. Sztaricskai, *Tetrahedron* **1991**, *47*, 1541–1546; P. Alleri, M. Anastasia, P. Ciuffreda, A. M. Sanrito, *Tetrahedron Asymmetry* **1994**, *5*, 927–934.

[22] J. Rokach, R. N. Young, M. Kukushima, C.-K. Lau, R. Seguin, R. Frenette, Y. Guindon, *Tetrahedron Lett.* **1981**, *22*, 979–982; J. Rokach, R. Zamboni C.-K. Lau, Y. Guindon, *Tetrahedron Lett.* **1981**, *22*, 2759–2762; R. Zamboni, J. Rokach, *Tetrahedron Lett.* **1982**, *23*, 4751–4754.

[23] Experimental details: R. O. Hutchins, M. Kacher, L. Rua, *J. Org. Chem.* **1975**, *40*, 923–926. – R. O. Hutchins, N. R. Natale, *J. Org. Chem.* **1978**, *43*, 2299–2301.

[24] These assignments were made taking into account the ^{13}C-NMR shifts of 1-hexanol (J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, H. J. Reich, *J. Am. Chem. Soc.* **1970**, *92*, 1338–1347) and *tert*-butyl hexyl ether (C. Konno, H. Hikino, *Tetrahedron* **1976**, *32*, 325–331).

[25] Ref.[1b], pp. 331–332.

[97074]