Quinone – Annonaceous Acetogenins: Synthesis and Complex I Inhibition Studies of a New Class of Natural Product Hybrids**

Sabine Arndt,[a] Ulrich Emde,[a] Stefan Bäurle,[a] Thorsten Friedrich,[b] Lutz Grubert,[a] and Ulrich Koert*[a]

Abstract: The natural product hybrids quinone – mucocin and quinone- squamocin D were synthesized. In these hybrids, the butenolide unit of the annonaceous acetogenins mucocin and squamocin D is exchanged for the quinone moiety of the natural complex I substrate ubiquinone. For both syntheses, a modular, highly convergent approach was applied. Quinone – mucocin was constructed out of a tetrahydropyran (THP) component **1**, a tetrahydrofuran (THF) unit **2**, and a quinone precursor **3**. A stereoselective, organometallic coupling reaction was chosen for the addition of the THP unit to the rest of the molecule. In the final step, the oxidation to the free quinone was achieved by using cerium(IV) ammonium nitrate (CAN) as the oxidizing agent. Quinone – squamocin D was assembled in a similar manner, from the chiral side chain bromide **16**, the central bis-THF core **17**, and the quinone precursor **18**. Inhibition of complex I (isolated from bovine heart mitochondria) by the quinone acetogenins and several smaller building blocks was examined; quinone – mucocin and quinone – squamocin D act as strong inhibitors of complex I. These results and the data from the smaller substructures indicate that other substructures of the acetogenins besides the butenolide group, such as the polyether component and the lipophilic left-hand side chain, are necessary for the strong binding of the acetogenins to complex I.

Keywords: annonaceous acetogenins · complex I inhibitors · natural products · quinones · synthesis design

Introduction

The annonaceous acetogenins are a class of natural products isolated from various plant species of the Annonaceae (custard apple) family. They show cytotoxic, immunosuppressive, pesticidal, and antimicrobial activities.[1]

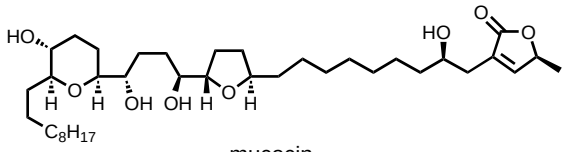
Structurally, the annonaceous acetogenins are a series of C-35/C-37 natural products. They are usually characterized by a long aliphatic chain bearing a terminal α,β-unsaturated γ-butyrolactone with one, two, or three tetrahydrofuran (THF) rings located along the hydrocarbon chain. To date, over 350 annonaceous acetogenins have been isolated from 37 species and several efficient synthetic approaches to this class of natural products have been developed.[1, 2]

[a] Prof. U. Koert, Dr. S. Arndt, Dr. U. Emde, Dr. S. Bäurle, Dr. L. Grubert
Institut für Chemie, Humboldt-Universität zu Berlin
Hessische Strasse 1 – 2, 10115 Berlin (Germany)
Fax: (+49) 30-20937266
E-mail: koert@chemie.hu-berlin.de

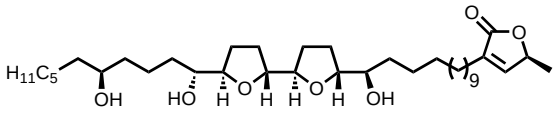
[b] Dr. T. Friedrich
Institut für Biochemie, Heinrich-Heine Universität
Universitätsstrasse 1, 40225 Düsseldorf (Germany)

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author.

Total syntheses of squamocin D[3] and mucocin[4] have recently been accomplished in our group.[5, 6] Squamocin D is a typical member of the bis-THF acetogenins, which are known to be among the most potent annonaceous acetogenins in cytotoxicity tests. Mucocin belongs to a small subgroup of acetogenins bearing a tetrahydropyran (THP) ring.



mucocin



squamocin D

The main mode of action of the annonaceous acetogenins is the blockage of mitochondrial complex I (NADH: ubiquinone oxidoreductase).[7] Complex I of the respiratory chain is by far the largest and most complicated of the proton-

translocating enzymes involved in oxidative phosphorylation. Mammalian complex I has an L-shaped structure with more than 40 subunits, possessing an NADH binding site in the soluble domain and an ubiquinone binding site in the membraneous domain (Figure 1). Many details of the electron

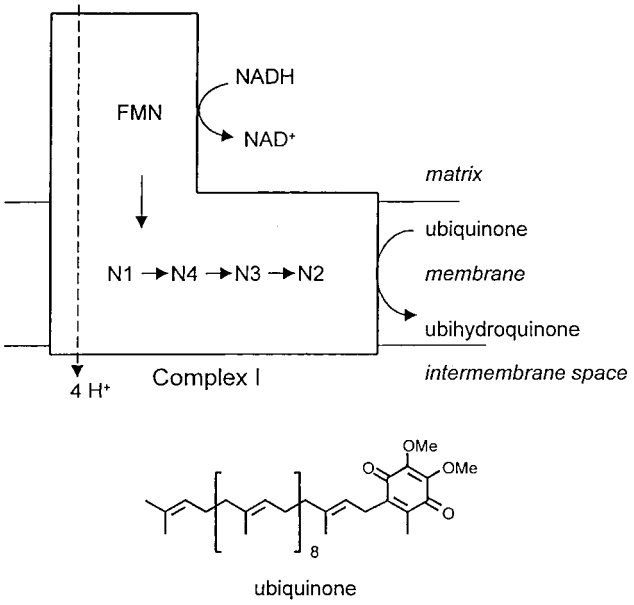


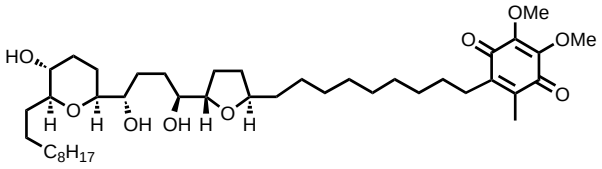
Figure 1.

pathway from NADH (matrix) to ubiquinone (membrane) and the links betwee this process and the translocation of protons are still not fully understood and are under active investigation.[7]

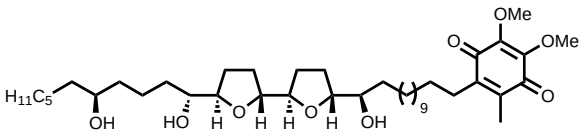
Abstract in German: *Berichtet wird über die Synthese der Naturstoffhybride Chinomucocin und Chinosquamocin D. In diesen Verbindungen ist die Butenolideinheit der Annonin-Acetogenine Mucocin und Squamocin D durch die Chinon-Gruppierung des natürlichen Komplex I-Substrats Ubichinon ersetzt worden. Für die Synthese beider Verbindungen wurde ein modularer, hoch-konvergenter Zugang angewandt. Chinomucocin wurde aus einem THP-Abschnitt **1**, einem THF-Teil **2** und dem Chinon-Vorläufer **3** hergestellt. Eine metallorganische Additionsreaktion diente zur stereoselektiven Anküpfung des THP-Teils an den Rest des Moleküls. Im letzten Syntheseschritt ließ sich die freie Chinongruppierung durch eine CAN-Oxidation generieren. Chinosquamocin D wurde auf einem ähnlichen Weg aus dem chiralen Seitenkettenbromid **16**, dem zentralen Bis-THF-Teil **17** und dem Chinon-Vorläufer **18** aufgebaut. Die Inhibierung von aus Rinderherz-Mitochondrien isoliertem Komplex I durch die Chino-Annonine und einige andere, kleinere Bausteine wurde untersucht. Chinomucocin und Chinoquamocin D erwiesen sich dabei als starke Komplex I Inhibitoren. Die Resultate weisen darauf hin, dass neben der Butenolid-Gruppierung andere Annonin-Substrukturen wie etwa der Polyether-Teil oder die lipophile linke Seitenkette für eine starke Bindung der Annonin-Acetogenine an Komplex I notwendig sind.*

The annonaceous acetogenins are among the most potent inhibitors of mammalian complex I.[8] They may possibly act at the terminal electron transfer step of complex I between the Fe–S cluster N2 and the ubiquinone reduction step.[7]

With the goals of further investigation of the mode of action of the annonaceous acetogenins and of providing molecular probes for complex I studies, we designed natural product hybrids in which the butenolide subunit of the annonaceous acetogenins is exchanged for the quinone portion of the natural complex I substrate ubiquinone. On the basis of our previous synthetic work we chose quinone–mucocin and quinone–squamocin D as synthetic targets. The butenolide



quinone–mucocin



quinone–squamocin D

unit has some structural similarities to the quinone group, and our goal was to investigate whether the two natural product hybrids quinone–mucocin and quinone–squamocin D were also potent complex I inhibitors.

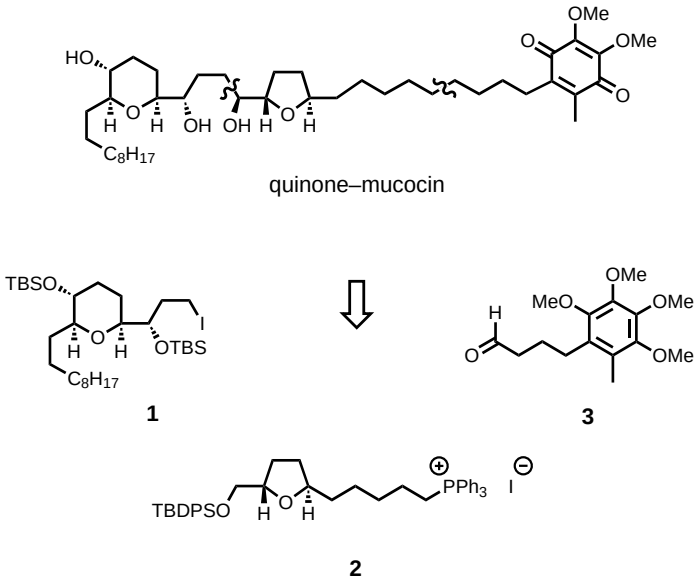
Results and Discussion

Syntheses of the quinone–acetogenins: The syntheses of the quinone natural product hybrids were based on the modular strategy developed for our total syntheses of mucocin[6a,b] and squamocin D.[5] A retrosynthetic analysis of quinone–mucocin implied the three building blocks **1**, **2**, and **3** (Scheme 1). The advantage of this modular approach was that we could make use of the known iodide **1** from the mucocin synthesis.

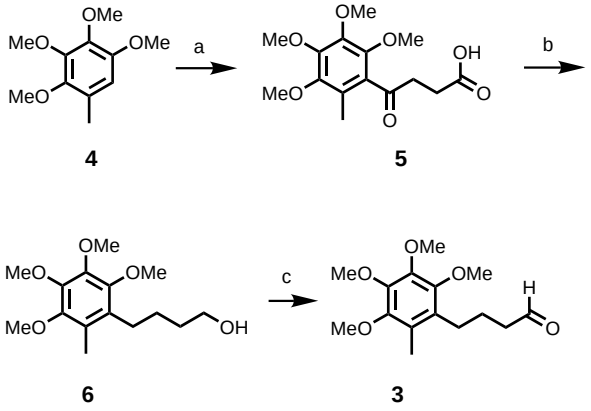
The starting point for the synthesis of the aromatic building block **3** was treatment of *ortho*-lithiated 2,3,4,5-tetramethoxytoluene **4**[9] with succinic anhydride to provide the keto carboxylic acid **5** (Scheme 2). Reduction of **5** to a diol with $LiAlH_4$, followed by deoxygenation of the benzylic alcohol function with $Et_3SiH/BF_3 \cdot OEt_2$ gave the primary alcohol **6**.[10] A Swern oxidation of **6** afforded the aldehyde **3**.

The THF-building block **2** could be prepared from the known THF aldehyde **7** (Scheme 3).[11] A Wittig reaction between **7** and a C-4 phosphonium salt gave the alkene **8** ($Z/E = 20:1$). The latter could be hydrogenated over Pt/C to **9**, which was converted into the primary alcohol **10** by cleavage of the benzyl ether with H_2 and Pd/C. One-step transformation of **8** into **10** using H_2 and Pd/C had severe drawbacks, because of side reactions at the THF moiety arising from

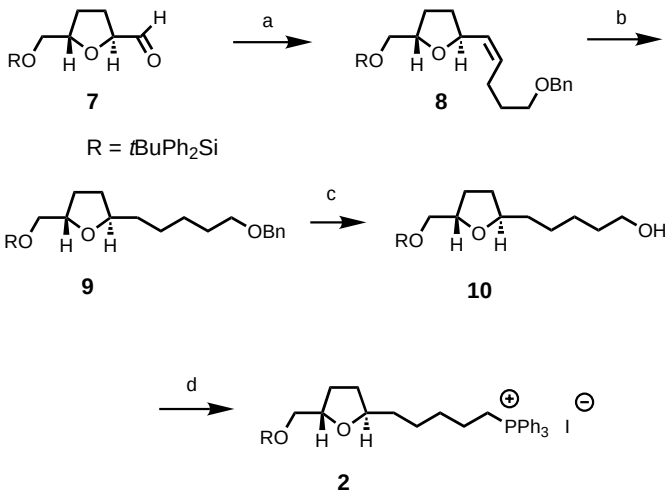
© WILEY-VCH Verlag GmbH, D-69451 Weinheim, 2001
0947-6539/01/0705-0994 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 5



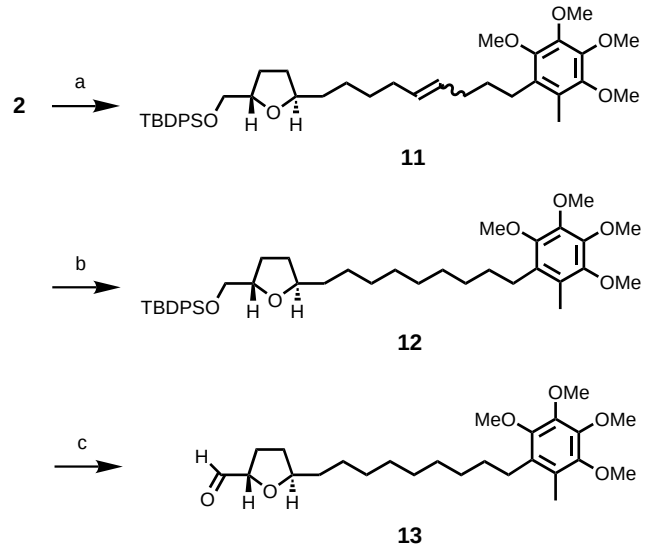
Scheme 1. Retrosynthetic analysis of quinone – mucocin. TBS = *tert*-butyldimethylsilyl.



Scheme 2. Synthesis of building block **3**. a) *n*BuLi (1.5 equiv), TMEDA, *n*-hexane, 0 °C, 30 min, succinic anhydride (1.1 equiv), THF, 2 h, 63 %; b) 1.) $LiAlH_4$ (5.0 equiv), THF, 3 h, 72 %; 2.) Et_3SiH (3 equiv), $BF_3 \cdot OEt_2$ (4.5 equiv), CH_2Cl_2, 12 h, 88 %; c) $(COCl)_2$ (2.0 equiv), DMSO (4.0 equiv), NEt_3 (5.0 equiv), CH_2Cl_2, −40 °C, 2.5 h, 78 %; TMEDA = tetramethylethylenediamine.



Scheme 3. Synthesis of THF-building block **2**. a) $BnO(CH_2)_4PPh_3I$ (2 equiv), THF, −30 °C, NaHMDS (1.3 equiv), 1 h, −78 °C, **7** (1 equiv), 0 °C, 1 h, 79 %; b) Pt/C, H_2, EtOAc, 6 h, 95 %, c) Pd/C, H_2, MeOH, 16 h, 92 %; d) 1. imidazole (3 equiv), PPh_3 (1.1 equiv), I_2 (1.2 equiv) 0 °C, 88 %; 2. PPh_3 (3 equiv), toluene, 89 %; NaHMDS = sodium hexamethyldisilazide.

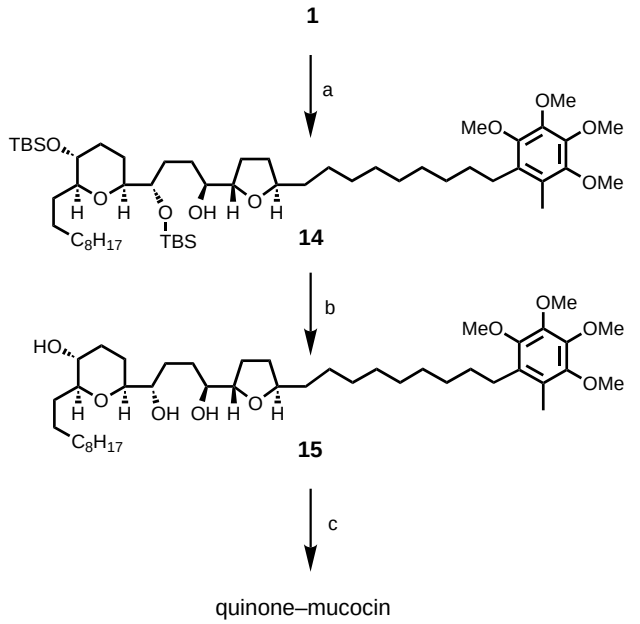


Scheme 4. Synthesis of aldehyde **13**. a) **2** (1.6 equiv), NaHMDS (1.1 equiv), THF, 0 °C, 20 min, then **3** (1.0 equiv), 0 °C, 1 h, 87 %; b) Pt/C (0.02 equiv), H_2, EtOAc, 6 h, 97 %; c) 1.) TBAF (4.3 equiv), THF, 2.5 h, 95 %; 2.) $(COCl)_2$ (2.0 equiv), DMSO (4.0 equiv), NEt_3 (5.0 equiv), CH_2Cl_2, −40 °C, 1.5 h, 89 %. TBAF = tetrabutylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl.

reductive cleavage of the allyl ether. After conversion of the alcohol **10** into the corresponding iodide, the phosphonium salt **2** was obtained by using PPh_3 in toluene.

The next sequence (Scheme 4) started with a Wittig reaction to connect the THF phosphonium salt **2** with the aromatic aldehyde **3.** The desired alkene **11** could be obtained in 87 % yield with a *Z*/*E* selectivity of 20:1. After hydrogenation of the double bond (**11** → **12**), a subsequent fluoride-mediated removal of the TBDPS group afforded the corresponding primary alcohol, which was transformed into the aldehyde **13** by a Swern oxidation.

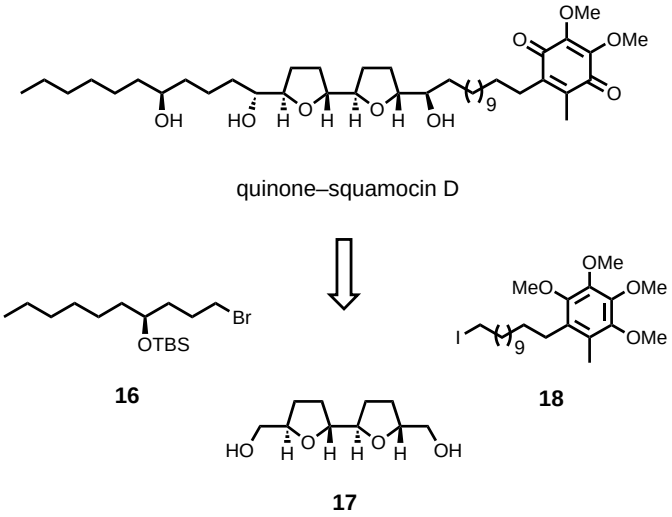
The final part of the synthesis required the stereoselective coupling of the iodide **1** with the aldehyde **13** (Scheme 5). To this end, a chelation-controlled addition of an organomagnesium compound prepared from the iodide **1**[6a,b] to the aldehyde **13** was examined. Because of the small scale of the coupling reaction, the organomagnesium compound was not produced by using magnesium turnings but by a homogeneous method via the corresponding organolithium compound, followed by transmetallation using $MgBr_2 \cdot OEt_2$. With use of this method, the desired alcohol **14** was obtained in 47 % yield, with 7:1 stereoselectivity. (The stereoselectivity for the related coupling step in the mucocin synthesis was 4:1.)[6a,b] The undesired minor epimer could be separated by chromatography. After deprotection to give the triol **15**, the final step of the synthesis required the oxidation of the hydroquinone dimethyl ether to the quinone. Cerium(IV) ammonium nitrate (CAN)[12] was the reagent of choice, producing the target molecule quinone – mucocin in 68 % yield.



Scheme 5. Synthesis of quinone–mucocin. a) **1** (1.3 equiv), *t*BuLi (2.4 equiv), Et_2O, $-105\,^{\circ}C$, 4 min, $MgBr_2 \cdot OEt_2$ (2.8 equiv), $-100 \rightarrow -40\,^{\circ}C$, 2 h, $-78\,^{\circ}C$, **13** (1.0 equiv) $\rightarrow -10\,^{\circ}C$, 2 h, 47%, diastereomer ratio 7:1, chromatographic separation of epimers; b) HF (3.8 equiv), CH_3CN/CH_2Cl_2, 1 h, 90%; c) pyridine-2,6-dicarboxylic acid (9.4 equiv), CAN (8 equiv), CH_3CN/H_2O, $0\,^{\circ}C$, 4 h, 68%. CAN = cerium(IV) ammonium nitrate, TBS = *t*-butyldimethylsilyl.

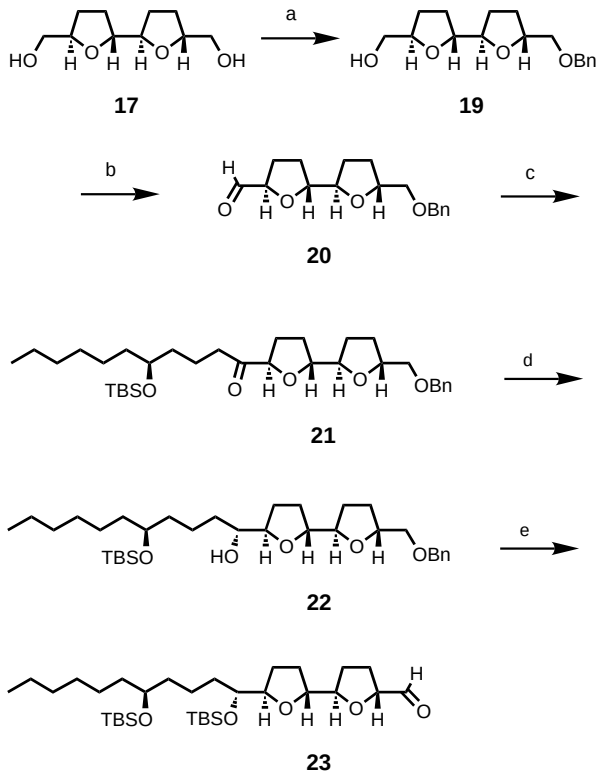
Our retrosynthetic analysis of quinone–squamocin D suggested a bis-THF core **17** and the two side chains **16** and **18** (Scheme 6).

The *trans-threo-trans* bis-THF diol **17** had been used previously as a key building block in the syntheses of squa-



Scheme 6. Retrosynthetic analysis of quinone–squamocin D. TBS = *tert*-butyldimethylsilyl.

mocin A and squamocin D.[5] Monobenzylation (Scheme 7) to the benzyl ether **19** (29% **19**, 32% dibenzylated compound, 17% recovered diol) and subsequent Swern oxidation provided the aldehyde **20**. For the attachment of the left-hand side chain, the bromide **16**[5, 13] was converted into the



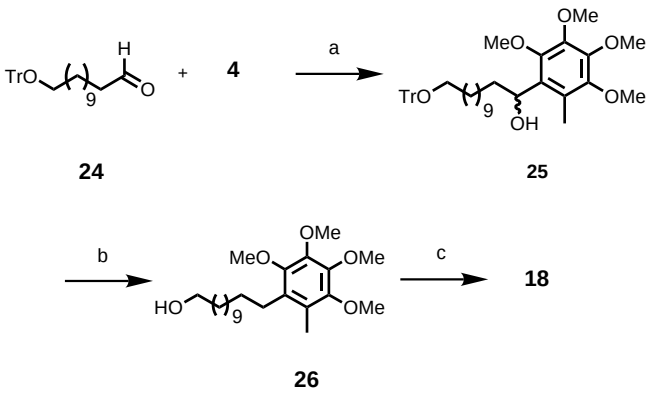
Scheme 7. Synthesis of aldehyde **23**. a) NaH (1.5 equiv), THF, $0\,^{\circ}C$, 29%; b) $(COCl)_2$ (2.5 equiv), DMSO (5.5 equiv), NEt_3 (7.8 equiv), CH_2Cl_2, $-45\,^{\circ}C$, 1.5 h, 89%; c) 1.) Mg, **16**, 1,2-dibromoethane, $35\,^{\circ}C$, 30 min, $CuBr \cdot Me_2S$, **20**, Et_2O, 12 h; 74% 2.) Pyridinium chlorochromate, $20\,^{\circ}C$, 1 h, 60%; d) L-selectride (5 equiv), THF, $-60\,^{\circ}C$, 1.5 h, 77%; e) 1.) TBDMSOTf (3.5 equiv) 2,6-lutidine (10 equiv), CH_2Cl_2, $0\,^{\circ}C$, 2 h, 99%; 2.) Pd/C, H_2, EtOAc, 4 h, 86%; 3.) $(COCl)_2$ (6.0 equiv), DMSO (30 equiv), NEt_3 (38 equiv), CH_2Cl_2, $-40\,^{\circ}C$, 1.5 h, 89%. TBS = *tert*-butyldimethylsilyl.

corresponding Grignard reagent. Addition of this Grignard reagent to the aldehyde **20** gave two epimeric alcohols in a 2:1 ratio ($R_f = 0.60$ and 0.63, PE/MTBE 1:1), which were oxidized by Pyridinium chlorochromate to the ketone **21**. A subsequent stereoselective L-selectride reduction[14] of **21** afforded the alcohol **22** in 77% yield. The stereoselectivity of the L-selectride reduction was >98:2, as determined by NMR spectroscopy. TBS-protection of the secondary hydroxy group in **22**, followed by the hydrogenolytic cleavage of the benzyl ether and a subsequent Swern oxidation, provided the aldehyde **23**.

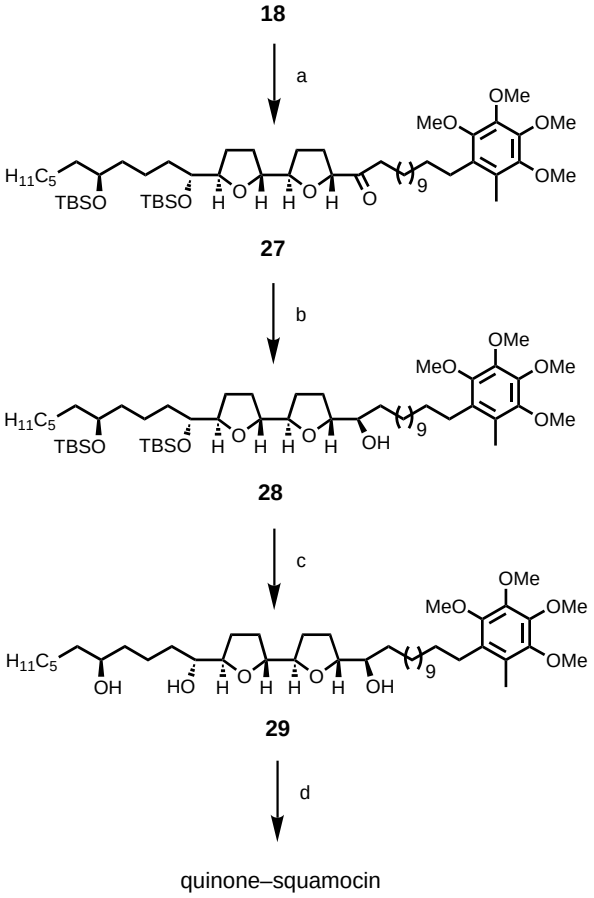
The C-12 aldehyde **24**[15] was a suitable precursor for the right-hand side chain building block **18** (Scheme 8). Treatment of **24** with the *ortho*-lithiated compound **4** provided **25**. Use of $Et_3SiH/BF_3 \cdot OEt_2$ permitted simultaneous deoxygenation and removal of the trityl group[16] to afford the alcohol **26** in 81% yield. Treatment of **26** with PPh_3/I_2 produced the iodide **18**.

The subsequent Grignard reaction was again carried out by means of a homogeneous method (Scheme 9). The iodide **18** was lithiated and then transmetallated by using $MgBr_2 \cdot OEt_2$. Addition to the aldehyde **23** (mixture of epimers at the new stereogenic center: 2:1) and a subsequent Swern oxidation gave the ketone **27**. L-selectride reduction of the ketone provided the corresponding alcohols in 99% yield. The

© WILEY-VCH Verlag GmbH, D-69451 Weinheim, 2001
0947-6539/01/0705-0996 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 5



Scheme 8. Synthesis of iodide **18**. a) *n*BuLi (2.2 equiv), TMEDA, *n*-hexane, 0 °C, 2.5 h, 54 %; b) Et_3SiH (5 equiv), $BF_3 \cdot OEt_2$ (7.5 equiv), CH_2Cl_2, 14 h, 81 %; c) imidazole (3 equiv), PPh_3 (1.1 equiv), I_2 (1.2 equiv) 0 °C, 4 h, 65 %.



Scheme 9. Synthesis of quinone – squamocin D. a) 1.) **18** (2.1 equiv), *t*BuLi (3.9 equiv), Et_2O, −105 °C, 4 min, $MgBr_2 \cdot OEt_2$ (4.9 equiv), −100 → −40 °C, 1.5 h, −78 °C, **23** (1.0 equiv) → 0 °C, 3.5 h, 52 %, diastereomer ratio 1:1, 2.) $(COCl)_2$ (75 equiv), DMSO (150 equiv), NEt_3 (250 equiv), CH_2Cl_2, −40 °C, 1,5 h, 96 %; b) L-selectride (15 equiv), THF, −70 °C, 1.5 h, 99 %, diastereomer ratio 88:12, chromatographic separation of epimers; c) HF, CH_3CN/CH_2Cl_2, 1.5 h, 77 %; d) pyridine-2,6-dicarboxylic acid (6 equiv), CAN (12 equiv), CH_3CN/H_2O, 0 °C, 4 h, 70 %. TBS = *tert*-butyldimethylsilyl.

stereoselectivity of the reduction, determined by NMR spectroscopy, was 88:12. The desired epimer **28** could be isolated by column chromatography, and cleavage of its silyl protecting groups gave the triol **29**. The last step of the synthesis was the oxidation of the hydroquinone dimethyl ether **29** with CAN to provide the target compound quinone – squamocin D in 70 % yield.

Complex I inhibition studies: Mucocin, quinone – mucocin, quinone – squamocin D, and the compounds **13** and **25** were tested as inhibitors of complex I (Table 1). In addition, the synthetic building blocks **30** – **37** were also tested (Table 2).

Table 1. Inhibition of the mitochondrial complex I by natural acetogenins and quinone – natural product hybrids.

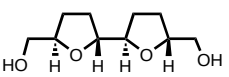
Compound	$K_i(50)$ [nM]	$IC_{(50)}$ [μmol mg^{-1} protein]	$IC_{(50)}$ [19] [μmol mg^{-1} protein]
mucocin	34	45	33.3
15	123	163	
quinone – mucocin	*3.6*	*4.9*	
squamocin A	1.0	1.3	
Squamocin D			8.7
29	4.7	6.2	
quinone – squamocin D	1.7	2.3	
rotenone	1.0	1.3	

Table 2. Inhibition of the mitochondrial complex I by annonaceous acetogenin fragments.

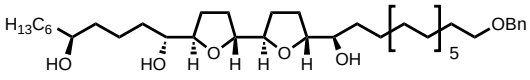
Compound	$K_i(50)$ [nM]
30	> 300000
31	94000
32	*173*
33	42000
34	32000
35	19500
36	16700
37	2500

For the complex I studies, bovine heart mitochondria were prepared as described previously.[17] The inhibition of oxygen uptake was measured. A Clark-type oxygen electrode (100 mM sodium phosphate pH = 7.4, 1 mM EDTA, 1 mM $MgCl_2$, 0.5 mg mL^{-1} protein) was used.[18] The known strong inhibitor rotenone served as reference sample.

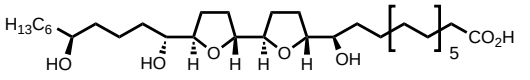
It was found that most of the smaller annonaceous acetogenin fragments were only weak inhibitors of complex I (Table 2). This suggests that all the different structural parts of these natural products—the ether core, the butenolide unit, and two aliphatic hydrocarbon chains— contribute to the activity. Smaller units such as **30**, **33**, and **34**, showed either no or only very weak activity. Compounds **35** and **36** also exhibited weak activity. If the butenolide unit and an ether component were located in the same molecule, however, more activity was found (**37**). It is remarkable that a carboxylic acid in place of the butenolide **32** resulted in a good inhibitor, while the corresponding benzyl ether **31** was nearly inactive. On the basis of structural data relating to the ubiquinone binding site of the bacterial reaction center,[21] one could postulate a participation of the carboxylic acid in the hydrogen bond network involved in the binding to ubiquinone.



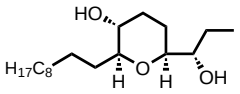
30[5]



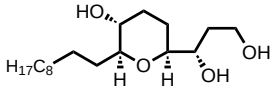
31[5]



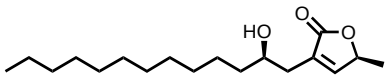
32[5]



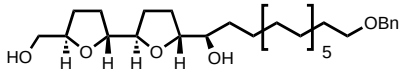
33[6a,b]



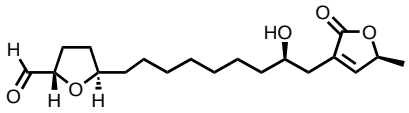
34[6a,b]



35[25]



36[5]



37[6a,b]

The quinone–acetogenins are very good inhibitors of complex I: quinone–mucocin is ten times more active than mucocin itself. In contrast, the hydroquinone–mucocin dimethyl ether **13** showed less activity than the natural product. Quinone–squamocin D and the hydroquinone–squamocin dimethyl ether **25** also displayed activities in the nanomolar range.

These results emphasize the importance of the butenolide unit for inhibitor activity.[20] However, it is possible to substitute this structural unit with a quinone group without loss of activity, and by a carboxylic acid with only a little loss of activity. Therefore, these structural features probably interact with complex I in a related fashion.

Despite these structural similarities, the reduction potentials of ubiquinone and a butenolide unit are very different. The reduction potential of an α-alkyl-α,β-unsaturated butyrolactone ($E_p = -2.69$ V (irreversible), CH_3CN versus SCE) is much more negative than the reduction potentials of the quinone group (E_p(cI) $= -0.75$ V, E_p(cII) $= -1.48$ V, CH_3CN versus SCE).[22]

Therefore, an electron transfer from the ubiquinone reduction side cannot be ruled out in the case of the quinone-natural product hybrids, while the butenolide unit of the annonaceous acetogenins should not be reduced under physiological conditions. It is therefore reasonable to assume that, apart from the electron transfer, there must be other important structural factors involved in the binding of the annonaceous acetogenins with complex I. The ether core and/or lipophilic interactions with the aliphatic side chains might also play an important role.[23]

It has been reported that the ubiquinone reduction site is quite large, so that the two acetogenin subunits, the butenolide, and the ether core could all probably bind there.[24] A systematic variation of both structural features—the butenolide and the ether components—would potentially be helpful for evaluation of the critical factors for the interaction of the annonaceous acetogenins with complex I.

Conclusion

The synthesis of these natural product hybrids was successfully accomplished by combining the ether component of the annonaceous acetogenins with the quinone component of ubiquinone. Our modular approach to these hybrid natural products allows efficient synthetic access to compounds with different moieties substituting for the butenolide moiety. The novel natural product hybrids are strong inhibitors of complex I of the respiratory chain. Natural product hybrids like quinone–mucocin and quinone–squamocin D offer the potential to be useful probes for complex I studies. It has been demonstrated that the butenolide moiety of the annonaceous acetogenins can be exchanged for the quinone of ubiquinone. Considering all the facts, it is becoming clearer that more than one structural entity is responsible for enzyme inhibition in the interaction of complex I with the annonaceous acetogenins.

Experimental Section

General: All boiling points and melting points are uncorrected values. IR: Biorad FTS 3000MX. NMR: Bruker AC-300, DPX-300, and AMX-600. For ^{1}HNMR, $CDCl_3$ as solvent $\delta_H = 7.24$; for ^{13}CNMR, $CDCl_3$ as solvent $\delta_c = 77.0$. Elemental analysis: CHN Rapid (Heraeus), CHNS-932 Analysator (Leco). HR-MS: Finnigan MAT 95. All reactions were performed under an inert atmosphere of argon in oven- or flame-dried glassware. HPLC: Rainin–Dynamax, SD-200 and SD-1, PDA1. Dry solvents: THF, Et_2O, benzene, and toluene were distilled from sodium benzophenone. Pyridine, Et_3N, and CH_2Cl_2 were distilled from CaH_2. All commercially available reagents were used without purification unless otherwise noted. All reactions were monitored by thin layer chromatography (TLC) carried out on Merck F-254 silica glass plates viewed under UV light and/or by heat-gun treatment with 5% phosphomolybdic acid in ethanol. Column chromatography and flash column chromatography were performed with Merck silica gel 60 (70–200 mesh and 230–400 mesh). PE: light petroleum ether, b.p. 40–60 °C; MTBE: methyl *tert*-butyl ether.

4-(2′,3′,4′,5′-Tetramethoxy-6′-methylphenyl)-4-oxo-butyric acid (5): Tetramethoxytoluene **4** (0.48 g, 2.26 mmol) was dissolved in *n*-hexane (5 mL). TMEDA (0.67 mL, 4.52 mmol) and *n*BuLi (1.34 mL, 3.30 mmol) were added slowly at 0 °C. After 30 min, the yellow suspension was diluted with THF (25 mL) and succinic anhydride (236 mg, 2.36 mmol) in THF (5 mL) was added. After 2 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl (5 mL). The aqueous layer was extracted with MTBE (2×15 mL). The combined organic layers were dried with $MgSO_4$ and the solvents were evaporated. The residue contained unconsumed tetramethoxytoluene **4** (321 mg, 1.51 mmol). The aqueous layer was acidified with $NaHSO_4$ solution (1 M) and extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with saturated

© WILEY-VCH Verlag GmbH, D-69451 Weinheim, 2001
0947-6539/01/0705-0998 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 5

aqueous NaCl (10 mL) and dried with $MgSO_4$. The solvents were removed in vacuo. The crude product was purified by column chromatography (20 g silica, CH_2Cl_2/acetone/HOAc 220:20:1) to provide **5** (147 mg, 0.47 mmol, 63 % yield based on conversion) as a colorless solid. $R_f = 0.39$ (CH_2Cl_2/acetone 11:1, 1 % HOAc); IR (film): $\tilde{\nu} = 3516$(s), 2939(s), 2874(m), 1710(s), 1585(w), 1467(s), 1360(s), 1275(m), 1091(m), 1040(m), 1000(m), 962(m), 846(w), 842(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 2.05$ (s, 3H; Me), 2.74 (t, $J = 6.5$ Hz, 2H; 3-H_2), 3.07 (t, $J = 6.5$ Hz, 2H; 2-H_2), 3.76 (s, 3H; OMe), 3.78 (s, 3H; OMe), 3.87 (s, 3H; OMe), 3.90 (s, 3H; OMe); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 11.9$ (6-Me), 27.7, 39.4 (C-2, C-3), 60.7, 61.1, 61.2, 61.9 (2′, 3′, 4′, 5′-OMe), 123.3, 131.1 (C-1′, C-6′), 144.5, 146.0, 148.0, 148.2 (C-2′, C-3′, C-4′, C-5′), 177.7 (C-1), 204.3(C-4); elemental analysis (%) for $C_{15}H_{20}O_7$ (312.32): calcd: C 57.69, H 6.46; found: C 57.42, H 6.94.

1-(4′-Hydroxybutyl)-2,3,4,5-tetramethoxy-6-methylbenzene (6): Compound **5** (256 mg, 0.82 mmol), dissolved in THF (1 mL), was added dropwise to a suspension of $LiAlH_4$ (156 mg, 4.10 mmol) in THF (7 mL) at 0 °C. After stirring for 3 h at 20 °C, the reaction was quenched by slow addition of H_2O (0.16 mL), 2 N NaOH (0.48 mL), and H_2O (0.16 mL). The suspension was refluxed for 10 min, filtered through a pad of Celite, and washed with THF. Solvent was removed in vacuo. Column chromatography (10 g silica, MTBE) of the residue afforded the diol (1.77 mg, 0.59 mmol, 72 %) as a colorless oil.

1-(1′,4′-Dihydroxybutyl)-2,3,4,5-tetramethoxy-6-methylbenzene: $R_f = 0.21$ (MTBE); IR (film): $\tilde{\nu} = 3395$(s), 2938(s), 2868(m), 1584(w), 1467(s), 1343(s), 1264(w), 1196(m), 1108(s), 1083(s), 1036(s), 962(m), 884(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 1.65 - 1.89$ (m, 4H; 2′, 3′-H_2), 2.14 (s, 3H; Me), 3.62 – 3.71 (m , 2H; 4′-H_2), 3.73 (s, 3H; OMe), 3.84 (s, 3H; OMe), 3.88 (s, 3H; OMe), 3.92 (s, 3H; OMe), 4.77 – 4.83 (m, 1H; 1′-H); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 11.5$ (6-Me), 30.3, 35.6 (C-2′, C-3′), 60.7, 60.9, 61.0, 61.4 (2,3,4,5-OMe), 62.8, 71.4 (C-1′, C-4′), 123.8, 130.0 (C-1, C-6), 144.6, 146.1, 147.7, 147.8 (C-2, C-3, C-4, C-5).

The diol (196 mg, 0.65 mmol) was dissolved in CH_2Cl_2 (4 mL) and cooled to − 78 °C. Et_3SiH (0.31 mL, 1.96 mmol) and $BF_3 \cdot OEt_2$ (0.37 mL, 2.94 mmol) were added and the reaction mixture was stirred for 12 h. Then a saturated aqueous sodium bicarbonate solution (4 mL) was added and the aqueous layer was extracted with MTBE (3 × 5 mL). The combined organic layers were washed with saturated aqueous NaCl (5 mL) and dried with $MgSO_4$, and the solvents were removed in vacuo. The residue was purified by flash column chromatography (10 g silica, MTBE) to yield alcohol **6** (163 mg, 0.57 mmol, 88 %) as a colorless oil. $R_f = 0.79$ (MTBE); IR (film): $\tilde{\nu} = 3432$(s), 2937(s), 2864(m), 1584(w), 1467(s), 1352(m), 1260(m), 1196(m), 1106(s), 1059(s), 1033(s), 976(m), 880(m) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 1.40 - 1.72$ (m, 4H; 2′,3′-H_2), 2.14 (s, 3H; Me), 2.58 – 2.65 (m, 2H; 1′-H_2), 3.68 – 3.72 (m, 2H; 4′-H_2), 3.76 (s, 3H; OMe), 3.80 (s, 3H; OMe), 3.87 (s, 3H; OMe), 3.88 (s, 3H; OMe); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 11.6$ (6-Me), 26.3, 26.4 (C-2′, C-3′), 32.7 (C-1′), 60.6, 61.0, 61.1, 61.1 (2,3,4,5-OMe), 62.8 (C-4′), 124.9, 129.7 (C-1, C-6), 144.6, 145.1, 147.6, 147.7 (C-2, C-3, C-4, C-5); elemental analysis calcd (%) for $C_{15}H_{24}O_5$ (284.35): C 63.36, H 8.51; found: C 63.60, H 8.64.

1-(4′-Oxo-butyl)-2,3,4,5-tetramethoxy-6-methylbenzene (3): DMSO (0.17 mL, 2.55 mmol) was added at − 78 °C to a solution of oxalyl chloride (0.11 mL, 1.28 mmol) in CH_2Cl_2 (10 mL). After 5 min stirring, a solution of the alcohol **6** (180 mg, 0.63 mmol) in CH_2Cl_2 (1 mL) was added dropwise. After stirring for 15 min, NEt_3 (0.44 mL, 3.19 mmol) was added dropwise. The mixture was stirred for 2.5 h (− 78 °C → − 40 °C). The reaction was quenched by addition of water (10 mL). The aqueous layer was extracted with MTBE (3 × 15 mL) and the combined organic layers were washed with saturated aqueous NaCl (15 mL) and dried with $MgSO_4$. The solvents were removed in vacuo and the residue was purified by column chromatography (10 g silica, PE/MTBE 2:1) to yield aldehyde **3** (138 mg, 0.49 mmol, 78 %) as a colorless oil. $R_f = 0.31$ (*n*-hexane/MTBE 2:1); ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 1.74 - 1.79$ (m, 2H; 2′-H_2), 2.14 (s, 3H; Me), 2.44 – 2.48 (m, 2H; 3′-H_2), 2.56 – 2.64 (m, 2H; 1′-H_2), 3.74 (s, 3H; OMe), 3.78 (s, 3H; OMe), 3.86 (s, 3H; OMe), 3.87 (s, 3H; OMe), 9.74 – 9.76 (m, 1H; 4′-H); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 11.6$ (6-Me), 22.3, 26.0 (C-1′, C-2′), 43.4 (C-3′), 60.6, 60.9, 61.0, 61.0 (2,3,4,5-OMe), 125.0, 128.6 (C-1, C-6), 144.5, 145.1, 147.7, 147.8 (C-2, C-3, C-4, C-5), 202.5 (C-4′).

(2*S*,5*R*,*Z*)-2-*tert*-Butyldiphenylsilyloxymethyl-5-(5′-benzyloxypent-1′-enyl)tetrahydrofuran (8): BnO-$(CH_2)_4$-PPH_3I (5.38 g, 9.74 mmol) was dissolved in THF (50 mL) and cooled to − 30 °C. NaHMDS (6.33 mL, 6.33 mmol, 1 M in THF) was added dropwise. After stirring for 1 h at 20 °C, the orange solution was cooled to − 78 °C and aldehyde **7** (1.80 g, 4.87 mmol), dissolved in THF (5 mL) and cooled to − 78 °C, was added. After 1 h at 0 °C, the reaction was quenched by the addition of saturated aqueous NH_4Cl (20 mL). The aqueous layer was extracted with MTBE (3 × 40 mL) and the combined organic layers were washed with saturated aqueous NaCl (30 mL) and dried with $MgSO_4$. The solvents were removed in vacuo. The residue was purified by column chromatography (100 g silica, PE/MTBE 20:1) to yield the alkene **8** (1.97 g, 3.83 mmol, 79 %) as a colorless oil. *Z*/*E* = 20:1 (^{1}HNMR); $R_f = 0.18$ (*n*-hexane/MTBE 20:1); $[\alpha]_D^{23}$ − 15.2 ($c = 0.52$, $CHCl_3$); IR (film): $\tilde{\nu} = 3446$(s), 2930(s), 2857(s), 1639(m), 1428(m), 1362(w), 1113(s), 1074(m), 739(m), 701(s), 613(m), 505(m) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 1.05$ (s, 9H; $SiC(CH_3)_3$), 1.48 – 1.74 (m, 3H; 4,4′-H_2), 1.79 – 1.95 (m, 1H; 3-H_2), 1.97 – 2.11 (m, 2H; 3,4-H_2), 2.11 – 2.21 (m, 2H; 3′-H_2), 3.43 (t, $J = 6.6$ Hz, 2H; 5′-H_2), 3.66 (d, $J = 5.8$ Hz, 2H; CH_2-OTBDPS), 4.09 – 4.24 (m, 1H; 2-H), 4.46 (s, 2H; CH_2-Ph), 4.66 – 4.79 (m, 1H; 5-H), 5.36 – 5.55 (m, 2H; 1′,2′-H), 7.29 – 7.39 (m, 11H; Ph,SiPh), 7.65 – 7.70 (m, 4H; SiPh); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 19.3$ ($SiC(CH_3)_3$), 24.3 (C-3′), 26.8 ($SiC(CH_3)_3$), 28.5 (C-3), 29.8 (C-4′), 33.3 (C-4), 66.6 (CH_2-OTBDPS), 69.7 (C-5′), 72.9 (CH_2-Ph), 75.0 (C-5), 79.1 (C-2), 127.6 (SiPh), 128.3 (Ph), 129.5 (SiPh), 131.4, 131.5 (C-1′, C-2′), 133.7 (SiPh), 135.6 (SiPh), 138.6 (Ph); HRMS: (EI): found: 513.2818 $[M - H]^+$; calcd: 513.2825.

(2*S*,5*R*)-2-*tert*-Butyldiphenylsilyloxymethyl-5-(5′-benzyloxypentyl)tetrahydrofuran (9): Pt/C (37 mg, 10 μmol, 5 % Pt on C) was suspended in AcOEt (25 mL). The mixture was degassed and stirred under hydrogen atmosphere. Alkene **8** (831 mg, 1.61 mmol), dissolved in AcOEt (1 mL), was added and the mixture was stirred vigorously for 6 h. Then the solution was filtered through a pad of silica gel, which was washed with AcOEt (40 mL), and the solvent was evaporated. The residue **9** (790 mg, 1.53 mmol, 95 %) was a colorless oil; it was spectroscopically pure and needed no further purification. $R_f = 0.38$ (n-hexane/MTBE 10:1); $[\alpha]_D^{23} = 1.6$ ($c = 0.52$, $CHCl_3$); IR (film): $\tilde{\nu} = 3446$(s), 2933(s), 2857(s), 1425(m), 1362(w), 1193(w), 1110(s), 1002(m), 822(m), 739(m), 702(s), 613(w), 506(m) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 1.04$ (s, 9H; $SiC(CH_3)_3$), 1.25 – 1.51 (m, 7H; 4,1′,2′,3′-H_2),1.53 – 1.67 (m, 2H; 4′-H_2), 1.74 – 1.88 (m, 1H; 3-H_2), 1.94 – 2.06 (m, 2H; 3,4-H_2), 3.45 (t, $J = 6.8$ Hz, 2H; 5′-H_2), 3.60 – 3.65 (m, 2H; CH_2-OTBDPS), 3.84 – 3.95 (m, 1H; 5-H), 4.09 – 4.15 (m, 1H; 2-H), 4.49 (s, 2H; CH_2-Ph), 7.26 – 7.39 (m, 11H; Ph, SiPh), 7.65 – 7.70 (m, 4H; SiPh); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 19.2$ ($SiC(CH_3)_3$), 26.2, 26.3 (C-2′, C-3′), 26.8 ($SiC(CH_3)_3$), 28.1 (C-3), 29.7 (C-4′), 32.0 (C-4), 35.8 (C-1′), 66.6 (CH_2-OTBDPS), 70.4 (C-5′), 72.8 (CH_2-Ph), 78.8 (C-2), 79.5 (C-5), 127.6 (SiPh), 128.3 (Ph), 129.5 (SiPh), 133.7 (SiPh), 135.6 (SiPh), 138.7 (Ph); elemental analysis calcd (%) for $C_{33}H_{44}O_3Si$ (516.80): C 76.70, H 8.58; found: C 76.59, H 8.61.

(2*S*,5*R*)-2-*tert*-Butyldiphenylsilyloxymethyl-5-(5′-hydroxypentyl)tetrahydrofuran (10): Pd on activated carbon (10 %, 61 mg, 57 μmol) was suspended in MeOH (2 mL) at 0 °C. The mixture was degassed and stirred under a hydrogen atmosphere for 5 min. A solution of the benzyl ether **9** (390 mg, 0.755 mmol) in AcOEt (1 mL) was added, and the mixture was vigorously stirred at room temperature for 16 h. The suspension was filtered through a pad of silica gel, which was washed with AcOEt (30 mL). The solvents were removed in vacuo and the residue was purified by column chromatography (15 g silica, PE/MTBE 2:1). The alcohol **10** (297 mg, 0.696 mmol, 92 %) was obtained as a colorless oil. $R_f = 0.25$ (*n*-hexane/MTBE 2:1); $[\alpha]_D^{23} = 3.4$ ($c = 0.96$, $CHCl_3$); IR (film): $\tilde{\nu} = 3401$(m), 2931(s), 2858(s), 1428(m), 1188(w), 1113(s), 1084(m), 1006(m), 824(m), 741(m), 702(s), 614(m), 505(m) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 1.04$ (s, 9H; $SiC(CH_3)_3$), 1.25 – 1.51 (m, 7H; 4,1′,2′,3′-H_2),1.52 – 1.62 (m, 2H; 4′-H_2), 1.74 – 1.87 (m, 1H; 3-H_2), 1.93 – 2.04 (m, 2H; 3,4-H_2), 3.57 – 3.66 (m, 4H; CH_2-OTBDPS, 5′-H_2), 3.85 – 3.95 (m, 1H; 5-H), 4.07 – 4.15 (m, 1H; 2-H), 7.29 – 7.44 (m, 6H; SiPh), 7.63 – 7.71 (m, 4H; SiPh); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 19.2$ ($SiC(CH_3)_3$), 25.8, 26.2 (C-2′, C-3′), 26.8 ($SiC(CH_3)_3$), 28.1 (C-3), 32.0 (C-4), 32.7 (C-4′), 35.8 (C-1′), 62.9 (C-5′), 66.6 (CH_2-OTBDPS), 78.8 (C-2), 79.5 (C-5), 127.6, 129.5, 133.7, 135.6 (SiPh); elemental analysis calcd (%) for $C_{26}H_{38}O_3Si$ (426.67): C 73.19, H 8.98; found: C 73.11, H 8.99.

Preparation of the phosphonium salt (2): Iodine (536 mg, 2.11 mmol) was added to a solution of imidazole (359 mg, 5.27 mmol) and PPh_3 (509 mg, 1.94 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The solution was stirred for 5 min, and the alcohol **10** (750 mg, 1.76 mmol), dissolved in CH_2Cl_2 (2 mL), was then added slowly. The reaction mixture was stirred for 4 h with exclusion

of light. It was then quenched by the addition of an aqueous $Na_2S_2O_3$ solution (10 mL). The aqueous layer was extracted with MTBE (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried with $MgSO_4$. The solvents were removed in vacuo. The crude product was purified by flash column chromatography (20 g silica, PE/MTBE 20:1) to yield the iodide (836 mg, 1.54 mmol, 88 %) as a colorless oil.

(2*S*,5*R*)-2-*tert*-Butyldiphenylsilyloxymethyl-5-(5′-iodopentyl)tetrahydrofuran: $R_f = 0.23$ (*n*-hexane/MTBE 20:1); $[\alpha]_D^{23} = 2.0$, ($c = 0.35$, $CHCl_3$); IR (film): $\tilde{\nu} = 3071$(w), 2958(m), 2931(s), 2858(s), 1472(w), 1428(m), 1188(w), 1113(s), 1084(m), 1006(m), 824(m), 741(m), 702(s), 613(m), 505(m) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 1.04$ (s, 9H; $SiC(CH_3)_3$), 1.25 – 1.60 (m, 7H; 4,1′,2′,3′-H_2), 1.78 – 1.89 (m, 3H; 3,4′-H_2), 1.92 – 2.05 (m, 2H; 3,4-H_2), 3.16 (t, $J = 7.1$ Hz, 2H; 5′-H_2), 3.60 – 3.66 (m, 2H; CH_2-OTBDPS), 3.85 – 3.90 (m, 1H; 5-H), 4.06 – 4.15 (m, 1H; 2-H), 7.29 – 7.44 (m, 6H; SiPh), 7.63 – 7.71 (m, 4H; SiPh); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 7.1$ (C-5′), 19.3 ($SiC(CH_3)_3$), 25.4 (C-2′), 26.8 ($SiC(CH_3)_3$), 28.1 (C-3), 30.6 (C-3′), 32.0 (C-4), 33.5 (C-4′), 35.6 (C-1′), 66.6 (CH_2-OTBDPS), 78.9 (C-2), 79.4 (C-5), 127.6, 129.5, 133.7, 135.6 (SiPh); HR-MS (EI): found: 479.0910 [$M - C_4H_9$]$^+$; calcd: 479.0903.

The iodide (836 mg, 1.56 mmol) and PPh_3 (1.23 g, 4.67 mmol) were dissolved in toluene (15 mL). The mixture was stirred for 4 d at 80 °C, then cooled to room temperature, and the solvent was removed in vacuo. The residue was washed with Et_2O until the rinsing liquid was free of PPh_3 (TLC). The phosphonium salt **2** (1.10 g, 1.38 mmol, 89 %) was dried in vacuo and used in the Wittig reaction without further purification; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 0.99$ (s, 9H; $SiC(CH_3)_3$), 1.25 – 1.47 (m, 5H; 4, 1′, 2′-H_2), 1.55 – 1.84 (m, 5H; 3, 3′, 4′-H_2), 1.88 – 2.00 (m, 2H; 3, 4-H_2), 3.50 – 3.73 (m, 4H; CH_2-OTBDPS, 5′-H_2), 3.76 – 3.86 (m, 1H; 5-H), 4.00 – 4.09 (m, 1H; 2-H), 7.29 – 7.41 (m, 6H; SiPh), 7.60 – 7.81 (m, 4H; SiPh); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 19.2$ ($SiC(CH_3)_3$), 22.7 (C-5′), 23.4 (C-4′), 25.9 (C-2′), 26.8 ($SiC(CH_3)_3$), 28.1 (C-3), 30.4 (C-3′), 31.9 (C-4), 35.2 (C-1′), 66.5 (CH_2-OTBDPS), 78.8 (C-2), 79.3 (C-5), 117.5, 118.7, 130.4, 130.6, 133.6, 135.0, 135.1 (PPh_3), 127.6, 129.5, 133.7, 135.0 (SiPh).

(2*S*,5*R*)-2-*tert*-Butyldiphenylsilyloxymethyl-5-(9′-(2″,3″,4″,5″-tetramethoxy-6″-methylphenyl)non-5′-enyl)tetrahydrofuran (11): The phosphonium salt **2** (951 mg, 1.19 mmol) was suspended in THF (10 mL) and cooled to − 40 °C. After addition of NaHMDS (0.82 mL, 0.82 mmol, 1M in THF), the orange solution was stirred for 20 min at 0 °C, and then cooled to − 78 °C. Aldehyde **3** (210 mg, 0.74 mmol), dissolved in THF (1 mL), was added. Stirring was maintained for 20 min at − 30 °C and 20 min at 0 °C. The reaction was quenched by addition of semisaturated aqueous NH_4Cl (5 mL). After addition of H_2O (10 mL) and Et_2O (10 mL), the phases were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (2 × 10 mL) and dried with $MgSO_4$. The solvents were removed in vacuo. The crude product was purified by column chromatography (20 g silica, PE/MTBE 10:1) to afford alkene **11** (439 mg, 0.65 mmol, 87 %) as a colorless oil. *Z*/*E* = 20:1 (^{1}HNMR). $R_f = 0.19$ (*n*-hexane/MTBE 10:1); $[\alpha]_D^{23} = 0.7$ ($c = 1.10$, $CHCl_3$); IR (film): $\tilde{\nu} = 2933$(s), 2859(s), 1586(w), 1466(s), 1411(m), 1352(m), 1110(s), 882(w), 823(w), 740(w), 704(m), 613(w), 505(m) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 1.03$ (s, 9H; $SiC(CH_3)_3$), 1.25 – 1.59 (m, 9H; 4, 1′,2′,3′,8′-H_2), 1.73 – 1.89 (m, 1H; 3-H_2), 1.95 – 2.12 (m, 6H; 3,4,4′,7′-H_2), 2.13 (s, 3H; 6″-Me), 2.51 – 2.57 (m, 2H; 9′-H_2), 3.61 – 3.66 (m, 2H; CH_2-OTBDPS), 3.76 – 3.88 (m, 13H; 5-H, 2″,3″,4″,5″-OMe), 4.10 – 4.15 (m, 1H; 2-H), 5.37 – 5.41 (m, 2H; 5′, 6′-H), 7.29 – 7.44 (m, 6H; SiPh), 7.63 – 7.71 (m, 4H; SiPh); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 11.6$ (6″-Me), 19.2 ($SiC(CH_3)_3$), 26.1, 26.7 (C-2′, C-9′), 26.8 ($SiC(CH_3)_3$), 27.3, 27.6 (C-3′, C-8′), 28.1 (C-3), 29.9, 30.3 (C-4′, C-7′), 32.0 (C-4), 32.7 (C-4′), 35.8 (C-1′), 60.6, 61.0, 61.1, 61.1 (2″,3″,4″,5″-OMe), 66.6 (CH_2-OTBDPS), 78.8 (C-2), 79.5 (C-5), 124.9, 129.5 (C-1″, C-6″), 129.4, 130.2 (C-5′, C-6′), 127.6 129.5, 133.7, 135.6 (SiPh), 144.6, 144.6, 147.8, 147.8 (C-2″, C-3″, C-4″, C-5″); calcd (%) for $C_{41}H_{58}O_6Si$ (674.99): C 72.96, H 8.66; found: C 72.68, H 8.68.

(2*S*,5*R*)-2-*tert*-Butyldiphenylsilyloxymethyl-5-(9′-(2″,3″,4″,5″-tetramethoxy-6″-methylphenyl)nonyl)tetrahydrofuran (12): Pt/C (26 mg, 7.0 μmol, 5 % Pt on C) was suspended in AcOEt (6 mL) at 0 °C. The mixture was degassed and stirred under hydrogen atmosphere (1 atm) for 10 min. Alkene **11** (246 mg, 0.364 mmol), dissolved in AcOEt, (4 mL) was added and the mixture was stirred vigorously for 6 h. Then the solution was filtered through a pad of silica, which was washed with AcOEt (40 mL), and the solvent was evaporated. The residue **12** (240 mg, 0.354 mmol, 97 %) was a colorless oil, which was spectroscopically pure and needed no further purification. $R_f = 0.19$ (*n*-hexane/MTBE 10:1); $[\alpha]_D^{23} = 0.4$ ($c = 1.01$, $CHCl_3$); IR (film): $\tilde{\nu} = 2930$(s), 2857(s), 1586(w), 1466(s), 1411(m), 1352(m), 1110(s), 880(w), 821(w), 740(w), 704(m), 614(w), 502(m) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 1.03$ (s, 9H; $SiC(CH_3)_3$), 1.24 – 1.59 (m, 17H; 4, 1′,2′,3′,4′,5′,6′,7′,8′-H_2), 1.73 – 1.88 (m, 1H; 3-H_2), 1.92 – 2.02 (m, 2H; 3, 4-H_2), 2.14 (s, 3H; 6″-Me), 2.51 – 2.57 (m, 2H; 9′-H_2), 3.61 – 3.65 (m, 2H; CH_2-OTBDPS), 3.76 – 3.88 (m, 13H; 5-H, 2″,3″,4″,5″-OMe), 4.11 – 4.19 (m, 1H; 2-H), 7.29 – 7.44 (m, 6H; SiPh), 7.63 – 7.71 (m, 4H; SiPh); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 11.6$ (6″-Me), 19.2 ($SiC(CH_3)_3$), 26.4 (C-2′), 26.8 ($SiC(CH_3)_3$), 27.0, 28.1, 29.5, 29.6, 29.7, 29.8, 30.1, 30.4 (C-3, 3′,4′,5′,6′,7′,8′,9′), 32.0 (C-4), 35.9 (C-1′), 60.6, 61.0, 61.0, 61.1 (2″,3″,4″,5″-OMe), 66.6 (CH_2-OTBDPS), 78.8 (C-2), 79.6 (C-5), 124.9, 130.4 (C-1″, C-6″), 127.6, 129.5, 133.8, 135.6 (SiPh), 144.3, 144.4, 147.7, 147.7 (C-2″, C-3″, C-4″, C-5″); calcd (%) for $C_{41}H_{60}O_6Si$ (677.01): C 72.74, H 8.93; found: C 72.59, H 8.85.

(2*S*,5*R*)-2-Formyl-5-(9′-(2″,3″,4″,5″-tetramethoxy-6″-methylphenyl)-nonyl)-tetrahydrofuran (13): Silyl ether **12** (224 mg, 0.33 mmol) and TBAF (460 mg, 1.45 mmol) were dissolved in THF (30 mL). After 2.5 h, the reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL). AcOEt (10 mL) was added, the phases were separated, and the aqueous layer was extracted with AcOEt (4 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (2 × 20 mL), dried with $MgSO_4$, and the solvents were removed in vacuo. The residue was purified by column chromatography (20 g silica, PE/MTBE 1:1) to yield the alcohol (136 mg, 0.31 mmol, 95 %) as a colorless oil.

(2*S*,5*R*)-2-Hydroxymethyl-5-(9′-(2″,3″,4″,5″-tetramethoxy-6″methylphenyl)-nonyl)-tetrahydrofuran: $R_f = 0.24$ (*n*-hexane/MTBE 1:1); $[\alpha]_D^{23} = 4.2$ ($c = 0.81$, $CHCl_3$); IR (film): $\tilde{\nu} = 3445$(m), 2929(s), 2857(s), 1586(w), 1466(s), 1411(m), 1351(m), 1195(w), 1108(s), 1060(s), 1039(s), 974(m), 880(w), 724(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 1.23 – 1.70$ (m, 17H; 4,1′,2′,3′,4′,5′,6′,7′,8′-H_2), 1.90 – 2.09 (m, 3H; 3, 4-H_2), 2.13 (s, 3H; 6′-Me), 2.49 – 2.55 (m, 2H; 9′-H_2), 3.44 – 3.50 (m, 1H; CH_2-OH), 3.57 – 3.64 (m, 1H; CH_2-OH), 3.76 – 3.88 (m, 13H; 5-H, 2″,3″,4″,5″-OMe), 4.07 – 4.12 (m, 1H; 2-H); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 11.6$ (6″-Me), 26.2, 27.0, 27.5, 29.4, 29.5, 29.6, 29.7, 30.1, 30.3 (C-3, 2′, 3′, 4′, 5′, 6′, 7′, 8′, 9′), 32.0 (C-4), 35.7 (C-1′), 60.6, 61.0, 61.1, 61.1 (2″,3″,4″,5″-OMe), 65.1 (CH_2-OH), 78.8 (C-2), 79.5 (C-5), 124.8, 130.3 (C-1″, C-6″), 144.6, 144.7, 147.6, 147.7 (C-2″, C-3″, C-4″, C-5″); calcd (%) for $C_{25}H_{42}O_6$ (438.61): C 68.46, H 9.65; found: C 68.44, H 9.68.

Oxalyl dichloride (0.052 mL, 0.59 mmol) was dissolved in CH_2Cl_2 (7 mL) and the solution was cooled to − 78 °C. DMSO (0.084 mL, 0.59 mmol) was added. After 5 min stirring, a solution of the alcohol (130 mg, 0.296 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The reaction mixture was stirred for 15 min and NEt_3 (0.21 mL, 1.48 mmol) was added dropwise. The mixture was stirred for 1.5 h (− 78 °C → − 35 °C). The reaction was quenched by addition of phosphate buffer solution (10 mL, pH = 7). The aqueous layer was extracted with MTBE (3 × 15 mL) and the combined organic layers were washed with saturated aqueous NaCl (20 mL) and dried with $MgSO_4$. The solvents were removed in vacuo and the residue was purified by column chromatography (10 g silica, PE/MTBE 2:1) to yield aldehyde **13** (115 mg, 0.263 mmol, 89 %) as a colorless oil. $R_f = 0.32$ (*n*-hexane/MTBE 2:1); ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 1.26 – 1.69$ (m, 17H; 4,1′,2′,3′,4′,5′,6′,7′,8′-H_2), 1.85 – 2.09 (m, 3H; 3, 4-H_2), 2.12 (s, 3H; 6″-Me), 2.49 – 2.54 (m, 2H; 9′-H_2), 3.74 – 3.88 (m, 13H; 5-H, 2″,3″,4″,5″-OMe), 3.90 – 4.01 (m, 2H; $CH_2C{=}O$), 4.25 – 4.31 (m, 1H; 2-H), 9.63 (s, 1H; $HC{=}O$); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 11.5$ (6″-Me), 26.1, 27.0, 27.2, 29.4, 29.5, 29.6, 29.7, 30.0, 30.3, 31.1 (C-3, 4, 2′, 3′, 4′, 5′, 6′, 7′, 8′, 9′), 35.3 (C-1′), 60.5, 60.9, 61.0, 61.1, 61.1 (2″,3″,4″,5″-OMe, $CH_2C{=}O$), 81.2 (C-5), 82.3 (C-2), 124.8, 130.3 (C-1″, C-6″), 144.5, 144.6, 147.6, 147.7 (C-2″, C-3″, C-4″, C-5″), 203.2 ($C{=}O$); HRMS (EI): found: 436.2827 [M]$^+$; calcd: 436.2825;.

19-*O*,23-*O*-Di-(*tert*-Butyldimethylsilyl)hydroquinone – mucocin dimethyl ether (14): Iodide **1** (206 mg, 0.314 mmol) was dissolved in diethyl ether (5 mL) and the solution was cooled to − 105 °C. *t*BuLi (0.38 mL, 0.57 mmol, 1.5M in pentane) was added, followed after 4 min by magnesium bromide etherate (0.36 mL, 0.66 mmol, 1.83M in Et_2O), and the solution was allowed to warm to − 40 °C over 2 h. Then the mixture was cooled to − 78 °C and a solution of aldehyde **13** (105 mg, 0.241 mmol) in Et_2O (1 mL) was added. The mixture was stirred for 2 h (− 78 °C → − 10 °C). The reaction was quenched by addition of phosphate buffer solution (1M, pH = 7, 2 mL). The mixture was diluted with water (5 mL) and MTBE (10 mL). The aqueous layer was extracted with MTBE (5 × 7 mL) and the combined organic

© WILEY-VCH Verlag GmbH, D-69451 Weinheim, 2001
0947-6539/01/0705-1000 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 5

layers were washed with saturated aqueous NaCl (2 × 5 mL) and dried with $MgSO_4$. The solvents were removed in vacuo and the residue was purified by flash column chromatography (20 g silica, PE/MTBE 5:1 → 3:1 → MTBE) to yield the coupling product **14** (109 mg, 0.113 mmol, 47 %) as a colorless oil. The 7:1 mixture of the C-16 epimers was separated by flash column chromatography. Major isomer **14**: $R_f = 0.40$ (*n*-hexane/MTBE 5:1); $[\alpha]_D^{23} = -25.3$ ($c = 0.40$, $CHCl_3$); IR (film): $\tilde{\nu} = 2927$(s), 2855(s), 1467(m), 1407(m), 1353(m), 1252(m), 1106(s), 836(m), 775(m) 669(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 0.02$ (s, 12H; $SiCH_3$), 0.85 (s, 21H; $SiC(CH_3)_3$, 34-H_3), 1.23 – 1.70 (m, 40H; alkyl), 1.82 – 2.04 (m, 6H; 13,14,18,22-H_2), 2.13 (s, 3H; 35-Me), 2.44 (d, $J = 2.7$ Hz, 1H; 16-OH), 2.48 – 2.54 (m, 2H; 3-H_2), 2.98 (m, 1H; 24-H), 3.14 – 3.27 (m, 2H; 20-H, 23-H), 3.27 – 3.38 (m, 1H; 16-H), 3.60 – 3.64 (m, 1H; 19-H), 3.74 – 3.88 (m, 14H; 12,15-H, 1,36,37,38-OMe); ^{13}CNMR (75 MHz, $CDCl_3$): $\Delta = -4.6$, -4.0 ($SiCH_3$), 11.6 (35-Me), 14.1 (C-34), 18.0 ($SiC(CH_3)_3$), 25.8, 25.9 ($SiC(CH_3)_3$), 22.7, 25.1, 25.6, 26.2, 28.4, 28.7, 28.8, 29.3, 29.6, 29.7, 29.8, 30.1 31.9, 32.7, 33.5, 35.7 (C-3, 4 – 11, 13, 14, 17, 18, 21, 22, 25 – 33), 60.4, 61.0, 61.1, 61.1 (1,36,37,38-OMe), 71.0 (C-23), 74.2 (C-19), 74.6 (C-16), 79.3 (C-12), 79.9 (C-20), 82.0 (C-15), 82.3 (C-24), 124.7, 130.3 (C-2, C-35), 144.6, 144.7, 147.6, 147.7 (C-1, 36, 37, 38); HRMS (EI): found: 964.7214 $[M]^+$; calcd: 964.7219. Minor isomer: $R_f = 0.34$ (*n*-hexane/MTBE 5:1); ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 0.00 - 0.04$ (s, 12H; $SiCH_3$), 0.82 – 0.90 (m, 21H; $SiC(CH_3)_3$, 34-H_3), 1.18 – 2.09 (m, 44H; alkyl), 2.13 (s, 3H; 35-Me), 2.37 (d, $J = 2.5$ Hz, 1H; 16-OH), 2.48 – 2.54 (m, 2H; 3-H_2), 2.94 – 3.04 (m, 1H; 24-H), 3.16 – 3.26 (m, 2H; 20, 23-H), 3.57 – 3.74 (m, 2H; 16, 19-H), 3.74 – 3.88 (m, 14H; 12,15-H, 1,36,37,38-OMe); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = -4.8$, -3.9 ($SiCH_3$), 11.6 (35-Me), 14.1 (C-34), 18.2 ($SiC(CH_3)_3$), 25.8, 25.9 ($SiC(CH_3)_3$), 22.7, 25.1, 25.1, 25.3, 25.5, 26.1, 29.0, 29.1, 29.4, 29.5, 29.6, 29.6, 29.7, 29.8, 31.9, 32.3, 32.7, 33.5, 36.1, 37.0 (C-3, 4 – 11, 13, 14, 17, 18, 21, 22, 25 – 33), 60.6, 61.0, 61.1, 61.1 (1,36,37,38-OMe), 71.0 (C-23), 72.6 (C-16), 74.2 (C-19), 79.3 (C-12), 79.9 (C-20), 81.6 (C-15), 82.4 (C-24), 124.9, 130.3 (C-2, C-35), 144.6, 144.7, 147.6, 147.7 (C-1, 36, 37, 38).

Hydroquinone – mucocin dimethyl ether (15): Disilylether **14** (28 mg, 29 μmol) was dissolved in CH_2Cl_2 (1 mL) and treated with HF (0.35 mL, 5 % in CH_3CN) at 0 °C. After stirring for 1 h at room temperature, the reaction was quenched by addition of phosphate buffer solution (1 mL, pH = 7). The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL) and ethyl acetate (2 × 5 mL). Washing of the combined organic layers with saturated aqueous NaCl (5 mL), drying with $MgSO_4$, evaporation of the solvents and purification by column chromatography (1 g silica, *n*-hexane/EtOAc 1:2) provided **15** (19 mg, 26 μmol, 90 %) as a colorless solid. M.p. 71 °C; $R_f = 0.31$ (*n*-hexane/EtOAc 1:2); $[\alpha]_D^{23} = -22.8$ ($c = 0.32$, $CHCl_3$); IR (film): $\tilde{\nu} =$ 3445(m), 2925(s), 2854(s), 1467(m), 1407(m), 1353(m), 1263(w), 1104(m), 1063(s), 1039(s), 880(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J =$ 6.8 Hz, 3H; 34-H_3), 1.13 – 1.88 (m, 42H; alkyl), 1.89 – 2.05 (m, 2H; 13,14-H_2), 2.05 – 2.14 (m, 4H; 22-H_2, 35-Me), 2.50 – 2.55 (m, 2H; 3-H_2), 2.70 (brs, 1H; OH), 2.83 (brs, 1H; OH), 3.02 (dt, $J = 8.8$, 2.2 Hz, 1H; 24-H), 3.08 – 3.18 (m, 1H; 20-H), 3.18 – 3.32 (m, 1H; 23-H), 3.34 – 3.52 (m, 2H; 16, 19-H), 3.74 – 3.94 (m, 14H; 12, 15-H, 1,36,37,38-OMe); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 11.6$ (35-Me), 14.1 (C-34), 22.7, 25.5, 26.2, 26.9, 27.0, 28.3, 28.3, 28.7, 28.7, 29.3, 29.5, 29.6, 29.6, 29.7, 30.1, 30.3, 31.9, 32.3, 32.6, 35.6 (C-3, 4 – 11, 13, 14, 17, 18, 21, 22, 25 – 33), 60.6, 61.0, 61.1, 61.1 (1,36,37,38-OMe), 70.6 (C-23), 73.5 (C-19), 73.8 (C-16), 79.4 (C-12), 80.1 (C-20), 81.9 (C-15), 82.0 (C-24), 124.9, 130.3 (C-2, C-35), 144.6, 144.7, 147.6, 147.7 (C-1, 36, 37, 38); HRMS (EI): found: 736.5488 $[M]^+$; calcd: 736.5489.

Quinone – mucocin: Pyridine-2,6-dicarboxylic acid (7.0 mg, 38.5 μmol) and **15** (3.0 mg, 4.1 μmol) were dissolved in CH_3CN (0.55 mL) and water (0.2 mL) at 0 °C. CAN (18.0 mg, 33.0 μmol) in water/CH_3CN (0.5 mL, 1:1) was added dropwise. After the mixture had been stirred for 4 h, $CHCl_3$/*i*PrOH (1 mL, 1:1) and water (1 mL) were added and the phases were separated. The aqueous layer was extracted with $CHCl_3$/*i*PrOH (5 × 2 mL, 1:1) and the combined organic layers were dried with $MgSO_4$. The solvents were removed in vacuo and the residue was purified by flash column chromatography (0.5 g silica, *n*-hexane/*i*PrOH 9:1) to yield quinone – mucocin (2.0 mg, 2.8 μmol, 68 %) as a yellow solid; $R_f = 0.48$ (*n*-hexane/*i*PrOH 9:1); $[\alpha]_D^{22} = -21$ ($c = 0.044$, $CHCl_3$); IR (film): $\tilde{\nu} = 3475$(m), 2923(s), 2854(s), 1649(m), 1611(m), 1458(m), 1266(m), 1205(w), 1066(s), 947(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 0.85$ (t, $J = 6.4$ Hz, 3H; 34-H_3), 1.13 – 1.88 (m, 42H; alkyl), 1.89 – 2.14 (m, 3H; 13,14,22-H_2), 1.99 (s, 3H; 35-Me), 2.42 (t, $J = 6.8$ Hz, 2H; 3-H_2), 2.69 (brs, 1H; OH), 2.82 (brs, 1H; OH), 3.02 (dt, $J = 8.8$, 2.2 Hz, 1H; 24-H), 3.08 – 3.18 (m, 1H; 20-H), 3.18 – 3.32 (m, 1H; 23-H), 3.34 – 3.52 (m, 2H; 16,19-H), 3.71 – 3.90 (m, 2H; 12,15-H), 3.96 (s, 6H; 37,38-OMe); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 11.9$ (35-Me), 14.1 (C-34), 22.7, 25.5, 26.2, 26.4, 26.9, 28.3, 28.3, 28.7, 28.7, 29.3, 29.4, 29.4, 29.5, 29.6, 29.7, 29.7, 29.8, 31.9, 32.0, 32.4, 32.6, 35.6 (C-3, 4 – 11, 13, 14, 17, 18, 21, 22, 25 – 33), 61.1 (37, 38-OMe), 70.6 (C-23), 73.5 (C-19), 73.8 (C-16), 79.3 (C-12), 80.1 (C-20), 81.9 (C-15), 82.0 (C-24), 138.6, 143.1, 144.3 (C-2, C-35, C-37, C-38), 184.2, 184.7 (C-1, C-36); HRMS (EI): found: 708.5166 $[M + 2H]^+$; calcd: 708.5176.

(all-*R*)-[5′-(5″-Benzyloxymethyltetrahydrofuran-2″-yl)-tetrahydrofuran-2′-yl]-methanol (19): NaH (95 %, 85 mg, 3.4 mmol) and BnBr (270 μL, 2.27 mmol), dissolved in 10 mL THF, were added to a solution of bis-THF diol **17** (457 mg, 2.26 mmol) in THF (20 mL) at 0 °C. The mixture was stirred overnight at room temperature. The reaction was quenched with a mixture of saturated aqueous NH_4Cl (10 mL) and MTBE (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (40 mL) and dried with $MgSO_4$. Removal of the solvents and purification by column chromatography (60 g silica, PE/MTBE 1:2, MTBE and MTBE/MeOH 20:1) afforded the bisbenzyl ether (273 mg, 714 μmol, 32 %, yield based on conversion: 38 %) and alcohol **19** (190 mg, 650 μmol, 29 %, yield based on conversion: 35 %) as colorless liquids. The combined aqueous layers were extracted three times with $CHCl_3$/2-propanol 2:1 (25 mL) and the resulting combined organic layers were dried with $MgSO_4$. Removal of the solvents and purification of the residue by column chromatography (20 g silica, $CHCl_3$/MeOH 10:1) was performed to isolate unconverted bi-THF diol **17** (78 mg, 386 μmol). Compound **19**: $R_f = 0.35$ (silica, MTBE); $[\alpha]_D^{21} = +3.0$ ($c = 0.34$, $CHCl_3$); ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 1.55 - 1.79$ (m, 4H; 3′-H′, 3″-H′, 4′-H′, 4″-H′), 1.87 – 2.07 (m, 4H; 3′-H″, 3″-H″, 4′-H″, 4″-H″), 2.58 (brs, 1H; OH), 3.42 – 3.55 (m, 3H; 1-H′, 1‴-H_2), 3.61 – 3.71 (m, 1H; 1-H″), 3.84 – 3.96 (m, 2H; 5′-H, 2″-H), 4.05 – 4.24 (m, 2H; 2′-H, 5″-H), 4.53 (PhCH_2O), 7.23 – 7.35 (m, 5H; Ph); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 27.3$, 28.2, 28.5, 28.6 (C-3′, C-3″, C-4′, C-4″), 64.4 (C-1), 72.6 (C-1‴), 73.1 (Ph*C*H_2O), 78.2, 79.8, 81.9 (C-2′, C-2″, C-5′, C-5″), 127.3, 127.5, 128.1, 138.2 (Ph); elemental analysis calcd (%) for $C_{16}H_{32}O_4Si$ (292.37): C 69.84, H 8.27; found: C 69.77, H 8.16.

(all-*R*)-5′-(5″-Benzyloxymethyl-tetrahydrofuran-2″-yl)-tetrahydrofuran-2′-carbaldehyde (20): Oxalyl dichloride (140 μL, 1.61 mmol) was dissolved in CH_2Cl_2 (10 mL). The solution was cooled to − 60 °C and DMSO (250 μL, 3.54 mmol) in CH_2Cl_2 (5 mL) was added. At − 50 °C a solution of alcohol **19** (188 mg, 643 μmol) in CH_2Cl_2 (3 mL) was added. After 45 min at − 45 °C, the mixture was treated with Et_3N (700 μL, 5.02 mmol). After 5 min, the temperature was allowed to rise to 0 °C and H_2O (10 mL) was added to stop the reaction. The aqueous layer was extracted twice with CH_2Cl_2 (15 mL). The combined organic layers were washed with saturated aqueous NaCl (15 mL) and dried with $MgSO_4$. Removal of the solvents and purification by column chromatography (35 g silica, MTBE) yielded aldehyde **20** (166 mg, 572 μmol, 89 %) as a liquid. $R_f = 0.35$ (silica, MTBE); $[\alpha]_D^{21} =$ +30.9 ($c = 0.33$, $CHCl_3$); IR (film): $\tilde{\nu} = 3030$(w), 2970(m), 2872(s), 2719(w), 1733(s), 1496(w), 1454(w), 1365(w), 1314(w), 1273(w), 1202(w), 1070(s), 938(w), 883(w), 819(w), 739(m), 699(m), 609(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 1.65 - 1.81$ (m, 3H; 4′-H′, 3″-H′, 4″-H′), 1.87 – 2.09 (m, 4H; 3′-H′, 4′-H″, 3″-H″, 4″-H″), 2.14 – 2.25 (m, 1H; 3″-H″), 3.44 – 3.54 (m, 2H; 1‴-H_2), 3.92 – 4.05 (m, 2H; 5′-H, 2″-H), 4.15 – 4.23 (m, 1H; 5″-H), 4.29 – 4.35 (m, 1H; 2′-H), 4.54 (PhCH_2O), 7.23 – 7.32 (m, 5H; Ph), 9.66 (d, $J = 1.9$ Hz, 1H; CHO); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 27.4$, 27.9, 28.4, 28.7 (C-3′, C-3″, C-4′, C-4″), 72.7 (C-1‴), 73.3 (Ph*C*H_2O), 78.6 (C-5″), 81.5, 83.2, 83.3 (C-2′, C-5′, C-2″), 127.5, 127.6, 128.3, 138.4 (Ph), 202.9 (CHO); HRMS (EI): found: 290.1523 $[M]^+$; calcd: 290.1518.

(5*S*,2′*R*,5′*R*,2″*R*,5″*R*)-1-[5′-(5″-Benzyloxymethyl-tetrahydrofuran-2″-yl)-tetrahydrofuran-2′-yl]-5-(*tert*-butyldimethylsilyloxy)undecan-1-one (21): A three-necked flask (100 mL) equipped with a dropping funnel, a reflux condenser, and a magnetic stirrer bar was flame-dried in vacuo and, after cooling to room temperature, flushed with argon. The flask was charged with Mg (541 mg, 22.3 mmol) and the same drying procedure was repeated. Et_2O (3 mL) was added and the mixture was stirred vigorously. The dropping funnel was charged with a solution of bromide **16** (1.00 g, 2.85 mmol) in Et_2O (10 mL) and 1,2-dibromoethane (350 μL, 4.06 mmol). A quantity of this solution (7 mL) was added quickly to the vigorously stirred mixture. After the mixture had been warmed slightly with a heat gun, the Grignard reaction started. The remaining bromide solution was added over 20 min and the mixture was stirred for 15 min at 35 °C and for

30 min at room temperature. The Grignard solution was transferred by cannula into a Schlenk flask and cooled to $-60\,^{\circ}C$. $CuBr \cdot Me_2S$ (33mg, 161 μmol) was added and the mixture was stirred at $-60\,^{\circ}C$ for another 15 min. A solution of aldehyde **20** (159 mg, 548 μmol) in Et_2O (10 mL) was added dropwise. The reaction mixture was stirred overnight, during which period the temperature was allowed to rise to room temperature. Addition of saturated aqueous NH_4Cl (25 mL) and Et_2O (25 mL) terminated the reaction. The aqueous layer was extracted twice with Et_2O (25 mL). The combined organic layers were washed with saturated aqueous NaCl (50 mL) and dried with $MgSO_4$. Removal of the solvents and purification by column chromatography (40 g Silica, PE/MTBE 4:1, 1:1) afforded a mixture (2:1 by ^{13}CNMR) of the epimeric alcohols [228 mg, 405 μmol, 74%, $R_f = 0.60$ and 0.63 (silica, PE/MTBE 1:1)] as a colorless liquid. The epimeric alcohols (189 mg, 336 μmol) were dissolved in CH_2Cl_2 (10 mL). Molecular sieves (4 Å, 227 mg) and PCC (275 mg, 1.28 mmol) were added. The mixture was stirred for 1 h at room temperature, then diluted with MTBE (50 mL) and filtered through a pad of Celite. The solvents were removed in vacuo. Purification by column chromatography (40 g silica, PE/MTBE 4:1, 2:1) gave the desired ketone **21** (112 mg, 200 μmol, 60%) as a colorless liquid. $R_f = 0.22$ (silica, PE/MTBE 4:1); $[\alpha]_D^{23} = +21.4$ ($c = 1.87$, $CHCl_3$); IR (film): $\tilde{\nu} = 3031$(w), 2955(s) (CH), 2929(s) (CH), 2857(s) (CH), 1716(m) (C=O), 1462(w), 1406(w), 1256(m), 1199(w), 1074(s), 939(w), 836(m), 802(w), 774(m), 735(w), 698(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 0.01$ (s, 6H; $SiCH_3$), 0.82–0.88 (m, 12H; 11-H_3 and $SiC(CH_3)_3$), 1.18–2.04 and 2.16–2.25 (m, 22H; 3-H_2, 4-H_2, 6-H_2 to 10-H_2, 3′-H_2, 4′-H_2, 3″-H_2, 4″-H_2), 2.42–2.64 (m, 2H; 2-H_2), 3.42–3.53 (m, 2H; 1‴-H_2), 3.60 (quin., $J = 5.7$ Hz, 1H; 5-H), 3.89–4.06 (m, 2H; 5′-H, 2″-H), 4.16–4.23 (m, 1H; 5″-H), 4.37 (t, $J = 7.4$ Hz, 1H; 2′-H), 4.53 (s, 2H; PhCH_2O), 7.21–7.31 (m, 5H; Ph); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = -4.5$ ($SiCH_3$), 14.0 (C-11), 18.0 (SiC(CH_3)$_3$), 22.5 (C-10), 25.8 (SiC(CH$_3$)$_3$), 25.3, 26.9, 27.9, 28.2, 28.6, 29.2, 29.4, 31.8 (C-3, C-7 to C-9, C-3′, C-4, C-3″, C-4″), 36.5, 36.9 (C-4, C-6), 38.1 (C-2), 72.0 (C-5), 72.7 (C-1‴), 73.2 (PhCH$_2$O), 78.5 (C-5″), 81.4, 82.9 (C-5′, C-2″), 83.9 (C-2′), 127.4, 127.5, 128.2, 138.3 (Ph), 212.5 (C=O); HRMS (EI): found: 560.3901 $[M]^+$; calcd: 560.3897.

(1*R*,5*S*,2′*R*,5′*R*,2″*R*,5″*R*)-1-[5′-(5″-Benzyloxymethyltetrahydrofuran-2″-yl)tetrahydrofuran-2′-yl]-5-(*tert*-butyldimethylsilyloxy)undecan-1-ol (22): L-Selectride (1M in THF, 900 μL, 900 μmol), which had been precooled at $-110\,^{\circ}C$, was added to a solution of the ketone **21** (104 mg, 185 μmol) in THF (5 mL) at $-110\,^{\circ}C$. The mixture was stirred for 1 h 30 min, during which period the temperature was allowed to rise to $-60\,^{\circ}C$. At $0\,^{\circ}C$, 2M NaOH (7 mL) and 30% H_2O_2 (10 mL) were added carefully. The mixture was stirred for 1 h and then treated with H_2O (25 mL) and MTBE (25 mL). The aqueous layer was extracted with MTBE (30 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous NaCl (20 mL), and dried with $MgSO_4$. Removal of the solvents and purification by column chromatography (35 g silica, PE/MTBE 2:1) afforded alcohol **22** (80 mg, 142 μmol, 77%) as a colorless oil. The stereoselectivity was determined by ^{13}CNMR analysis to be better than 98:2. $R_f = 0.28$ (silica, PE/MTBE 2:1); $[\alpha]_D^{20} = +8.1$ ($c = 1.60$, $CHCl_3$); IR (film): $\tilde{\nu} = 3470$(br m) (OH), 3031(w), 2954(s)/ 2929(s)/ 2857(s) (C-H), 1496(w), 1463(m), 1407(w), 1305(w), 1255(m), 1198(w), 1071(s), 939(w), 836(m), 808(w), 774(m), 735(w), 698(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 0.01$ (s, 6H; $SiCH_3$), 0.82–0.88 (m, 12H; 11-H_3 and $SiC(CH_3)_3$), 1.18–1.49 (m, 16H; 2-H_2 to 4-H_2, 6-H_2 to 10-H_2), 1.56–1.75 (m, 4H; 3′-H′, 4′-H′, 3″-H′, 4″-H′), 1.88–2.06 (m, 4H; 3′-H″, 4′-H″, 3″-H″, 4″-H″), 2.50 (br s, 1H; OH), 3.31–3.39 (m, 1H; 1-H), 3.41–3.52 (m, 2H; 1‴-H_2), 3.59 (t, $J = 5.0$ Hz, 1H; 5-H), 3.77–3.95 (m, 3H; 2′-H, 5′-H, 2″-H), 4.14–4.23 (m, 1H; 5″-H), 4.53 (s, 2H; PhCH_2O), 7.21–7.31 (m, 5H; Ph); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = -4.50$, -4.46 ($SiCH_3$), 14.0 (C-11), 18.1 (SiC(CH_3)$_3$), 21.5 (C-3), 22.5 (C-10), 25.9 (SiC(CH$_3$)$_3$), 25.2, 28.27, 28.34, 28.7, 28.8, 29.4, 31.8 (C-7 to C-9, C-3′, C-4′, C-3″, C-4″), 33.6 (C-2), 37.0, 37.2 (C-4, C-6), 72.3 (C-5), 72.7 (C-1‴), 73.2 (PhCH$_2$O), 73.9 (C-1), 78.4 (C-5″), 81.79, 81.82 (C-5′, C-2″), 82.9 (C-2′), 127.4, 127.5, 128.2, 138.3 (Ph); HRMS: (EI): found 563.4119 $[M]^+$; calcd 563.4131.

(2′*R*,5′*R*,2″*R*,5″*R*,1‴*R*,5‴*S*)-1-[5′-(5″-(1‴,5‴-Di-(*tert*-butyldimethylsilyloxy)undecan-1‴yl)tetrahydrofuran-2″-yl)-tetrahydrofuran-2′-yl]-carbaldehyde (23): 2,6-Lutidine (150 μL, 1.29 mmol) and TBDMSOTf (100 μL, 435 μmol) were added at $-20\,^{\circ}C$ to a solution of alcohol **22** (69 mg, 123 μmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 2 h, during which period the temperature was allowed to rise to $0\,^{\circ}C$. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and the aqueous layer was extracted twice with CH_2Cl_2 (10 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried with $MgSO_4$. Removal of the solvents in vacuo and purification by column chromatography (25 g silica, PE/MTBE 4:1) afforded bis-TBDMS-protected triol (83 mg, 123 mmol, 99%) as a colorless liquid.

(1*R*,5*S*,2′R,5′*R*,2″*R*,5″*R*)-1-[5′-(5″-Benzyloxymethyl-tetrahydrofuran-2″-yl)tetrahydrofuran-2′-yl]-1,5-di-(*tert*-butyldimethylsilyloxy)undecane: $R_f = 0.57$ (silica, PE/MTBE 4:1); $[\alpha]_D^{21} = +12.1$ ($c = 0.43$, $CHCl_3$); IR (film): $\tilde{\nu} = 2955$(s)/ 2929(s)/ 2857(s) (CH), 1462(m), 1361(w), 1254(m), 1092(m), 1074(m), 1005(w), 939(w), 890(w), 835(m), 774(m), 733(w), 697(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = -0.01$, 0.01, 0.02, 0.04 (4 × s, 12H; $SiCH_3$), 0.84–0.89 (m, 21H; 11-H_3 and $SiC(CH_3)_3$), 1.19–1.47 (m, 16H; 2-H_2 to 4-H_2, 6-H_2 to 10-H_2), 1.59–1.75 (m, 4H; 3′-H′, 4′-H′, 3″-H′, 4″-H′), 1.83–2.05 (m, 4H; 3′-H″, 4′-H″, 3″-H″, 4″-H″), 3.42–3.54 (m, 2H; 1‴-H_2), 3.55–3.68 (m, 2H; 1-H, 5-H), 3.82–3.99 (m, 3H; 2′-H, 5′-H, 2″-H), 4.14–4.23 (m, 1H; 5″-H), 4.55 (s, 2H; PhCH_2O), 7.23–7.35 (m, 5H; Ph); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = -4.6$, -4.5, -4.4, -4.3 ($SiCH_3$), 14.1 (C-11), 18.1, 18.2 (SiC(CH_3)$_3$), 21.9 (C-3), 22.6 (C-10), 25.7, 26.0 (SiC(CH$_3$)$_3$), 25.2, 26.9, 28.2, 28.4, 28.75, 28.79, 29.5, 31.9 (C-3, C-7 to C-9, C-3′, C-4′, C-3″, C-4″), 32.5 (C-2), 37.0, 37.6 (C-4, C-6), 72.4 (C-5), 72.8 (C-1‴), 73.3 (PhCH$_2$O), 74.7 (C-1), 78.4 (C-5″), 81.77, 81.79 (C-5′, C-2″), 82.2 (C-2′), 127.5, 127.6, 128.3, 138.5 (Ph); HRMS (EI): found: 676.4922 $[M]^+$; calcd: 676.4918.

The bis-TBDMS-protected triol (81 mg, 121 μmol) was dissolved in AcOEt (2 mL) and *i*PrOH (2 mL). After addition of Pd (10% on activated carbon, 11.3 mg), the mixture was evacuated and filled with H_2 (1 bar). The mixture was stirred for 4 h at room temperature and filtered through a pad of Celite, washing the pad with CH_2Cl_2 (25 mL). Removal of the solvents and purification by column chromatography (20 g silica, PE/MTBE 2:1) afforded the primary alcohol (61 mg, 104 μmol, 86%) as a colorless, viscous oil. **(2′*R*,5′*R*,2″*R*,5″*R*,1‴*R*,5‴*S*)-1-[5′-(5″-(1‴,5‴-Di-(*tert*-butyldimethylsilyloxy)undecan-1‴yl)tetrahydrofuran-2″-yl)tetrahydrofuran-2′-yl]-methanol**: $R_f = 0.35$ (silica, PE/MTBE 2:1); $[\alpha]_D^{22} = +7.6$ ($c = 0.46$, $CHCl_3$); IR (film): $\tilde{\nu} = 3450$(br m) (OH), 2955(s)/ 2929(s)/ 2857(s) (CH), 1463(m), 1361(w), 1255(m), 1067(m), 1005(w), 836(m), 809(w), 774(m), 725(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 0.01$, 0.02, 0.04 (3 × s, 12H; $SiCH_3$), 0.82–0.88 (m, 21H; 11‴-H_3 and $SiC(CH_3)_3$), 1.19–1.46 (m, 16H; 2‴-H_2 to 4‴-H_2, 6‴-H_2 to 10‴-H_2), 1.56–1.75 (m, 4H; 3′-H′, 4′-H′, 3″-H′, 4″-H′), 1.84–1.98 (m, 4H; 3′-H″, 4′-H″, 3″-H″, 4″-H″), 3.45 (dd, $J = 11.7/5.3$ Hz, 1H; 1-H′), 3.55–3.71 (m, 3H; 1-H″, 1‴-H, 5‴-H), 3.80–3.99 (m, 3H; 5′-H, 2″-H, 5″-H), 4.05–4.14 (m, 1H; 2′-H); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = -4.6$, -4.5, -4.4, -4.3 ($SiCH_3$), 14.1 (C-11‴), 18.1, 18.2 (SiC(CH_3)$_3$), 21.9 (C-3‴), 22.6 (C-10‴), 25.9 (SiC(CH$_3$)$_3$), 25.2, 26.8, 27.4, 28.6, 28.7, 29.5, 31.9 (C-3′, C-4′, C-3″, C-4″, C-7‴ to C-9‴), 32.4 (C-2‴), 37.0, 37.5 (C-4‴, C-6‴), 64.6 (C-1), 72.4 (C-5‴), 74.6 (C-1‴), 79.8 (C-2′), 82.0, 82.1, 82.2 (C-5′, C-2″, C-5″); HRMS (EI): found: 571.4218 $[M - CH_3]^+$; calcd: 571.4214.

Oxalyl dichloride (50 μL, 573 μmol) was dissolved in CH_2Cl_2 (1 mL). The solution was cooled to $-60\,^{\circ}C$ and DMSO (200 μL, 2.82 mmol), dissolved in dichloromethane (3 mL), was added. At $-50\,^{\circ}C$ the alcohol (56 mg, 95 μmol), dissolved in CH_2Cl_2 (0.5 mL), was added. After 45 min at $-45\,^{\circ}C$ the mixture was treated with Et_3N (500 μL, 3.59 mmol). After 5 min, the reaction mixture was allowed to warm up to $0\,^{\circ}C$ and H_2O (3 mL) was added to stop the reaction. The aqueous layer was extracted twice with CH_2Cl_2 (10 mL). The combined organic layers were washed with saturated aqueous NaCl (5 mL) and dried with $MgSO_4$. Removal of the solvents and purification by column chromatography (10 g silica, PE/MTBE 4:1, 2:1) yielded aldehyde **23** (50 mg, 85 μmol, 89%) as a liquid. $R_f = 0.49$ (silica, PE/MTBE 2:1); $[\alpha]_D^{22} = +15.2$ ($c = 1.00$, $CHCl_3$); IR (film): $\tilde{\nu} = 2955$(s)/ 2930(s)/ 2857(s) (CH), 1736(m) (C=O), 1463(m), 1361(w), 1255(m), 1067(m), 872(w), 836(m), 774(m), 725(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 0.00$, 0.02, 0.03 (3 × s, 12H; $SiCH_3$), 0.84–0.86 (m, 21H; 11‴-H_3 and $SiC(CH_3)_3$), 1.19–1.47 (m, 16H; 2‴-H_2 to 4‴-H_2, 6‴-H_2 to 10‴-H_2), 1.65–1.95 (2 × m, 7H; 3′-H′, 4′-H_2, 3″-H_2, 4″-H_2), 2.17–2.21 (m, 1H; 3′-H″), 3.57–3.62 (m, 2H; 1‴-H, 5‴-H), 3.87–4.02 (m, 3H; 5′-H, 2″-H, 5″-H), 4.29–4.34 (m, 1H; 2′-H), 9.65 (d, $J = 1.9$ Hz, 1H; CHO); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = -4.6$, -4.5, -4.4, -4.3 ($SiCH_3$), 14.1 (C-11‴), 18.10, 18.13 (SiC(CH_3)$_3$), 21.7 (C-3‴), 22.6 (C-10‴), 25.9 (SiC(CH$_3$)$_3$), 25.2, 27.0, 27.4, 27.9, 28.6, 29.5, 31.9 (C-3′, C-4′, C-3″, C-4″, C-7‴ to C-9‴), 32.6 (C-2‴), 37.0, 37.5 (C-4‴, C-6‴), 72.3 (C-5‴), 74.6 (C-1‴), 81.4, 82.3, 83.2 (C-5′, C-2″, C-5″), 83.3 (C-2′), 203.0 (CHO); HRMS (EI): found: 569.4055 $[M - CH_3]^+$; calcd: 569.4058.

© WILEY-VCH Verlag GmbH, D-69451 Weinheim, 2001
0947-6539/01/0705-1002 $ 17.50+.50/0 *Chem. Eur. J.* **2001**, *7*, No. 5

1′-Hydroxy-12′-trityloxydodecyl-2,3,4,5-tetramethoxy-6-methylbenzene (25): 1,2,3,4-Tetramethoxy-5-methylbenzene **4** (149 mg, 0.70 mmol) was dissolved in *n*-hexane (10 mL) and cooled to 0 °C. TMEDA (0.27 mL, 1.82 mmol) and *n*BuLi (0.72 mL, 1.52 mmol) were added dropwise. After 30 min, aldehyde **24** (570 mg, 1.29 mmol) dissolved in *n*-hexane (5 mL) was added to the yellow suspension. The reaction was quenched after 2 h by addition of saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with MTBE (3 × 15 mL) and the combined organic layers were washed with saturated aqueous NaCl (10 mL) and dried with $MgSO_4$. The solvents were removed in vacuo and the residue was purified by column chromatography (20 g silica, PE/MTBE 5:1) to yield the alcohol **25** (246 mg, 0.38 mmol, 54 %) as a colorless oil. $R_f = 0.18$ (*n*-hexane/MTBE 5:1); IR (film): $\tilde{\nu} = 3445$(m), 2929(s), 2855(s), 1592(w), 1466(s), 1411(m), 1343(m), 1261(w), 1104(s), 1075(s), 1039(s), 897(w), 753(m), 704(s), 639(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 1.19 - 1.83$ (m, 20H; alkyl), 2.15 (s, 3H; Me), 3.02 (t, 2H; $J = 6.6$ Hz, 12′-H_2), 3.74 (s, 3H; OMe), 3.86 (s, 3H; OMe), 3.89 (s, 3H; OMe), 3.93 (s, 3H; OMe), 4.73 – 4.81 (m, 1H; 1′-H), 7.20 – 7.44 (m, 15H; Ph); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 11.6$ (6-Me), 26.3, 26.5, 27.0, 29.5, 29.6, 30.0, 38.7 (alkyl), 60.7, 60.9, 61.0, 61.3 (2,3,4,5-OMe), 63.7 (C-12′), 71.4 (C-1′), 86.2 (CPh_3), 123.7, 130.9 (C-1, C-6), 126.7, 127.6, 128.7, 144.6 (Ph), 144.5, 146.0, 147.7, 147.9 (C-2, C-3, C-4, C-5); HRMS (EI): found: 654.3925 $[M]^+$; calcd: 654.3920.

1-(12′-Hydroxydodecyl)-2,3,4,5-tetramethoxy-6-methylbenzene (26): Alcohol **25** (240 mg, 0.37 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to −78 °C. Et_3SiH (0.30 mL, 1.85 mmol) and $BF_3 \cdot OEt_2$ (0.35 mL, 2.78 mmol) were added under stirring. After 14 h (−78 °C → RT), saturated aqueous $NaHCO_3$ (4 mL) was added and the phases were separated. The aqueous layer was extracted with MTBE (3 × 10 mL) and the combined organic layers were washed with saturated aqueous NaCl (5 mL) and dried with $MgSO_4$. The solvents were evaporated and the residue was purified by column chromatography (10 g silica, PE/MTBE 2:1) to provide the alcohol **26** (117 mg, 0.30 mmol, 81 %) as a colorless oil. $R_f = 0.23$ (*n*-hexane/MTBE 2:1); IR (film): $\tilde{\nu} = 3440$(m), 2928(s), 2855(s), 1466(s), 1412(m), 1351(m), 1261(w), 1110(s), 1060(s), 1039(s), 975(m), 897(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 1.19 - 1.62$ (m, 20H; alkyl), 2.14 (s, 3H; Me), 2.50 – 2.55 (m, 2H; 1′-H_2), 3.59 – 3.63 (m, 2H; 12′-H_2), 3.76 (s, 3H; OMe), 3.79 (s, 3H; OMe), 3.87 (s, 3H; OMe), 3.88 (s, 3H; OMe); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 11.6$ (6-Me), 25.7, 27.0, 29.4, 29.5, 29.6, 29.6, 30.1, 30.3, 32.8 (alkyl), 60.6, 61.0, 61.1, 61.1 (2,3,4,5-OMe), 63.1 (C-12′), 124.9, 130.3 (C-1, C-6), 144.6, 144.7, 147.6, 147.7 (C-2, C-3, C-4, C-5); HRMS (EI): found: 396.2876 $[M]^+$; calcd: 396.2876.

1-(12′-Iodododecyl)-2,3,4,5-tetramethoxy-6-methylbenzene: Iodine (84 mg, 0.332 mmol) was added to a solution of imidazole (57 mg, 0.831 mmol) and PPh_3 (80 mg, 0.305 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After the mixture had been stirred for 5 min, the alcohol **26** (110 mg, 0.277 mmol), dissolved in CH_2Cl_2 (1 mL), was added slowly. The reaction mixture was stirred for 4 h with light excluded. An aqueous $Na_2S_2O_3$ solution (10 mL) was then added. The aqueous layer was extracted with MTBE (3 × 10 mL). The combined organic layers were washed with saturated aqueous NaCl (10 mL), dried with $MgSO_4$, and the solvents were evaporated. The residue was purified by column chromatography (8 g silica, PE/MTBE 20:1) to yield **18** (91 mg, 0.180 mmol, 65 %) as a colorless oil. $R_f = 0.25$ (*n*-hexane/MTBE 2:1); IR (film): $\tilde{\nu} = 2926$(s), 2853(s), 1465(s), 1407(s), 1351(m), 1261(w), 1196(m), 1106(s), 1064(s), 1038(s), 978(m), 881(w), 721(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 1.20 - 1.49$ (m, 18H; alkyl), 1.77 – 1.82 (m, 2H; 11′-H_2), 2.14 (s, 3H; Me), 2.50 – 2.55 (m, 2H; 1′-H_2), 3.17 (t, $J = 7.1$ Hz, 2H; 12′-H_2), 3.76 (s, 3H; OMe), 3.80 (s, 3H; OMe), 3.87 (s, 3H; OMe), 3.88 (s, 3H; OMe); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta = 7.4$ (C-12′), 11.6 (6-Me), 27.0, 28.5, 29.4, 29.5, 29.5, 29.6, 30.1, 30.3, 30.5, 33.5 (alkyl), 60.6, 61.0, 61.1, 61.1 (2,3,4,5-OMe), 124.9, 130.3 (C-1, C-6), 144.6, 144.7, 147.6, 147.7 (C-2, C-3, C-4, C-5); HRMS (EI): found: 506.1897 $[M]^+$; calcd: 506.1893.

(1*R*,2′*R*,5′*R*,2″*R*,5″*R*,1‴*R*,5‴*S*)-1-[5′-(5″-(1‴,5‴-Di-(*tert*-butyldimethylsilyloxy)undecan-1‴-yl)tetrahydrofuran-2″-yl)-tetrahydrofuran-2′-yl]-13-(2⁗,3⁗,4⁗,5⁗-tetramethoxy-6⁗-methylphenyl)tridecan-1-one (27): Iodide **18** (86 mg, 170 μmol) was dissolved in Et_2O (3 mL) under an argon atmosphere in a flame-dried Schlenk flask (25 mL). The solution was cooled to −110 °C and *t*BuLi (1.48 mmol mL^{-1} in *n*-pentane, 210 μL, 306 μmol) was added. After 4 min, $MgBr_2 \cdot Et_2O$ (3.88 mmol mL^{-1} in Et_2O, 100 μL, 388 μmol) was added. The mixture was stirred for 1 h, 30 min, during which period the temperature was allowed to rise to −40 °C. The mixture was then cooled to −78 °C and a solution of aldehyde **23** (46 mg, 79 μmol) in Et_2O (1 mL) was added dropwise. The mixture was stirred for 3 h, 30 min, during which period the temperature was allowed to rise to 0 °C. Addition of aqueous phosphate buffer (pH 7, 2 mL) stopped the reaction. The mixture was diluted with MTBE (10 mL) and water (5 mL). The aqueous layer was extracted five times with MTBE (5 mL). The combined organic layers were washed with saturated aqueous NaCl (5 mL) and dried with $MgSO_4$. Removal of the solvents and purification by column chromatography (9 g silica, PE/MTBE 20:1, 2:1, MTBE) afforded a mixture (1:1 by ^{13}CNMR) of the epimeric alcohols [39 mg, 40 μmol, 52 %, $R_f = 0.38$ and 0.46 (silica, PE/MTBE 2:1)] as a colorless liquid. Oxalyl dichloride (150 μL, 1.72 mmol) was dissolved in CH_2Cl_2 (1 mL). The solution was cooled to −60 °C and DMSO (250 > L, 3.52 mmol) dissolved in CH_2Cl_2 (3 mL) was added. The epimeric alcohols (22 mg, 23 μmol) dissolved in CH_2Cl_2 (2 mL) were added at −50 °C. After 1 h at −40 °C, the mixture was treated with Et_3N (800 μL, 5.74 mmol). After 5 min, the reaction mixture was allowed to warm up to 0 °C and H_2O (2 mL) was added to stop the reaction. The aqueous layer was extracted three times with CH_2Cl_2 (5 mL). The combined organic layers were washed with saturated aqueous NaCl (5 mL) and dried with $MgSO_4$. Removal of the solvents and purification by column chromatography (10 g silica, PE/MTBE 10:1, 4:1) yielded ketone **27** (21 mg, 22 μmol, 96 %) as a colorless liquid. $R_f = 0.50$ (silica, PE/MTBE 4:1); $[\alpha]_D^{23} = +14.8$ ($c = 0.42$, $CHCl_3$); IR (film): $\tilde{\nu} = 2929$(s)/ 2856(s) (CH), 1717(m) (C=O), 1464(s), 1408(m), 1352(w), 1255(m), 1107(m), 1066(w), 1039(w), 1007(w), 979(w), 874(w), 836(m), 775(m), 724(w), 665(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta =$ 0.01, 0.03, 0.05 (3 × s, 18H; $SiCH_3$), 0.82 – 0.88 (m, 21H; 11‴-H_3, $SiC(CH_3)_3$), 1.19 – 1.62 (m, 36H; 3-H_2 to 12-H_2, 2‴-H_2 to 4‴-H_2, 6‴-H_2 to 10‴-H_2), 1.65 – 1.96 (m, 8H; 3′-H_2, 4′-H_2, 3″-H_2, 4″-H_2), 2.14 (s, 3H; CH_3-Ph), 2.40 – 2.64 (m, 4H; 13-H_2, 2-H_2), 3.55 – 3.64 (m, 2H; 1‴-H, 5‴-H), 3.76 (s, 3H; OCH_3), 3.79 (s, 3H; OCH_3), 3.83 – 4.05 (m, 9H; 5′-H, 2″-H, 5″-H, 2 × OCH_3), 4.38 (t, $J = 7.2$ Hz, 1H; 2′-H); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta =$ −4.6, −4.5, −4.4, −4.2 ($SiCH_3$), 11.6 (CH_3Ph), 14.1 (C-11‴), 18.1, 18.2 (Si*C*$(CH_3)_3$), 25.94, 25.96 (SiC(*C*$H_3)_3$), 21.7 (C-3‴), 22.6 (C-10‴), 23.2, 25.2, 27.0, 27.3, 28.0, 28.6, 29.2, 29.3, 29.47, 29.50, 29.53, 29.6, 29.7, 30.1, 30.3, 31.9 (C-3 to C-13, C-3′, C-4′, C-3″, C-4″, C-7‴ to C-9‴), 32.9 (C-2‴), 37.0, 37.6 (C-4‴, C-6‴), 38.2 (C-2), 60.6, 61.0, 61.08, 61.09 (4 × OCH_3), 72.3 (C-5‴), 74.9 (C-1‴), 81.3, 82.5, 82.8, 83.9 (C-2′, C-5′, C-2″, C-5″), 124.9, 130.4 (C-2⁗, C-6⁗), 144.6, 144.7, 147.65, 147.73 (C-2⁗, C-3⁗, C-4⁗, C-5⁗), 212.9 (C=O); HRMS (EI): found: 962.7023 $[M]^+$; calcd: 962.7062.

(1*R*,2′*R*,5′*R*,2″*R*,5″*R*,1‴*R*,5‴*S*)-1-[5′-(5″-(1‴,5‴-Di-(*tert*-butyldimethylsilyloxy)undecan-1‴yl)tetrahydrofuran-2″-yl)tetrahydrofuran-2′-yl]-13-(2⁗,3⁗,4⁗,5⁗-tetramethoxy-6⁗-methylphenyl)tridecan-1-ol (28): L-Selectride (1 mmol mL^{-1} in THF, 300 μL, 300 μmol), that had been precooled at −110 °C, was added to a solution of the ketone **27** (19.2 mg, 19.9 μmol) in THF (3 mL) at −110 °C,. The mixture was stirred for 1 h, 30 min, during which period the temperature was allowed to rise to −60 °C. At 0 °C, first water (5 mL) and then aqueous NaOH (2M, 7 mL) and 30 % H_2O_2 (7 mL) were added carefully. The aqueous layer was extracted three times with MTBE (15 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL) and saturated aqueous NaCl (10 mL), and dried with $MgSO_4$. Removal of the solvents and purification by column chromatography (6 g silica, PE/MTBE 4:1) afforded alcohol **28** (16.7 mg, 17.3 μmol, 87 %) as a colorless oil. The epimeric alcohol (2.3 mg, 2.4 μmol) was also isolated. The stereoselectivity was determined to be 88:12 by the products isolated. Major isomer **28**: $R_f = 0.22$ (silica, PE/MTBE 4:1); $[\alpha]_D^{24} = +6.1$ ($c = 0.33$, $CHCl_3$); IR (film): $\tilde{\nu} = 3398$(br m) (OH), 2928(s)/ 2856(s) (CH), 1466(m), 1408(m), 1352(w), 1255(m), 1196(w), 1106(w), 1065(m), 880(w), 836(m), 774(m), 723(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): $\delta = 0.01$, 0.03, 0.06 (3 × s, 18H; $SiCH_3$), 0.83 – 0.88 (m, 21H; 11‴-CH_3, $SiC(CH_3)_3$), 1.20 – 1.74 (m, 42H; 2-H_2 to 12-H_2, 3′-H′, 4′-H′, 3″-H′, 4″-H′, 2‴-H_2 to 4‴-H_2, 6‴-H_2 to 10‴-H_2), 1.82 – 1.98 (m, 4H; 3′-H″, 4′-H″, 3″-H″, 4″-H″), 2.14 (s, 3H; CH_3-Ph), 2.44 – 2.56 (m, 3H; 13-H_2 and OH), 3.31 – 3.39 (m, 1H; 1-H), 3.55 – 3.64 (m, 2H; 1‴-H, 5‴-H), 3.74 – 3.94 (m, 16H; 2′-H, 5′-H, 2″-H, 5″-H, 4 × OCH_3); ^{13}CNMR (75 MHz, $CDCl_3$): $\delta =$ −4.7, −4.5, −4.4, −4.2 ($SiCH_3$), 11.6 (CH_3Ph), 14.1 (C-11‴), 18.1, 18.2 (Si*C*$(CH_3)_3$), 25.9, 26.0 (SiC(*C*$H_3)_3$), 21.7 (C-3‴), 22.6 (C-10‴), 25.2, 25.7, 27.0, 27.4, 28.4, 28.7, 28.8, 29.50, 29.53, 29.65, 29.68, 29.8, 30.1, 30.3, 31.9 (C-3 to C-13, C-3′, C-4′, C-3″, C-4″, C-7‴ to C-9‴), 32.9 (C-2‴), 33.4 (C-2), 37.0, 37.5 (C-4‴, C-6‴), 60.6, 61.0, 61.08, 61.09 (4 × OCH_3), 72.4 (C-5‴), 74.1 (C-1), 75.0 (C-1‴), 81.65, 81.72, 82.4, 82.9 (C-2′, C-5′, C-2″, C-5″), 124.9, 130.4

(C-1‴, C-6‴), 144.6, 144.7, 147.65, 147.73 (C-2‴, C-3‴, C-4‴, C-5‴); HRMS (EI): found: 964.7226 $[M]^+$; calcd: 964.7219. Minor isomer: R_f = 0.10 (silica, PE/MTBE 4:1); ^{1}HNMR (300 MHz, $CDCl_3$): δ = 0.01, 0.03, 0.04 (3 × s, 18H; $SiCH_3$), 0.83 – 0.88 (m, 21H; 11‴-H_3, $SiC(CH_3)_3$), 1.18 – 1.96 (m, 46H; 2-H_2 to 12-H_2, 3′-H_2, 4′-H_2, 3″-H_2, 4″-H_2, 2‴-H_2 to 4‴-H_2, 6‴-H_2 to 10‴-H_2), 2.14 (s, 3H; CH_3-Ph), 2.48 – 2.56 (m, 3H; 13-H_2 and OH), 3.55 – 3.71 (m, 3H; 1-H, 1‴-H, 5‴-H), 3.74 – 4.00 (m, 16H; 2′-H, 5′-H, 2″-H, 5″-H, 4 × OCH_3); ^{13}CNMR (75 MHz, $CDCl_3$): δ = – 4.6, – 4.44, – 4.38, – 4.3 ($SiCH_3$), 11.6 (CH_3Ph), 14.1 (C-11‴), 18.1, 18.2 ($SiC(CH_3)_3$), 25.9 ($SiC(CH_3)_3$), 21.9 (C-3‴), 22.6 (C-10‴), 25.2, 26.1, 27.0, 28.5, 29.50, 29.54, 29.6, 29.65, 29.68, 29.7, 30.1, 30.4, 31.9 (C-2 to C-13, C-3′, C-4′, C-3″, C-4″, C-7‴ to C-9‴), 32.4 (C-2‴), 37.0, 37.6 (C-4‴, C-6‴), 60.6, 61.0, 61.08, 61.1 (4 × OCH_3), 71.3 (C-1), 72.4 (C-5‴), 74.5 (C-1‴), 82.2, 82.3, 82.45, 82.51 (C-2′, C-5′, C-2″, C-5″), 124.9, 130.4 (C-1‴, C-6‴), 144.7, 147.7 (C-2‴, C-3‴, C-4‴, C-5‴).

Hydroquinone – squamocin D dimethyl ether (29): Alcohol **28** (14.8 mg, 15.3 μmol) was dissolved in CH_2Cl_2 (300 μL). HF (5% in MeCN, 500 μL) was added and the mixture was stirred for 1 h, 30 min at 0 °C. The reaction was quenched with phosphate buffer solution (pH = 7, 2 mL). The aqueous layer was extracted four times with $CHCl_3$/*i*PrOH (10 mL). The combined organic layers were dried with $MgSO_4$. Removal of the solvents in vacuo and purification by column chromatography (4 g silica, MTBE/MeOH 50:1) afforded triol **29** (8.7 mg, 11.8 μmol, 77%) as a colorless oil. R_f = 0.34 (silica, MTBE/MeOH 50:1); $[\alpha]_D^{23}$ = + 5.3 (c = 0.17, $CHCl_3$); IR (film): $\tilde{\nu}$ = 3402(br m) (OH), 2927(s)/ 2856(s) (CH), 1463(m), 1413(w), 1352(w), 1262(w), 1195(w), 1108(w), 1062(m), 964(w), 878(w), 802(w) cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$): δ = 0.86 (t, J = 6.6 Hz, 3H; 34-H_3), 1.20 – 1.68 (m, 42H; 4-H_2 to 14-H_2, 17-H′, 18-H′, 21-H′, 22-H′, 25-H_2 to 27-H_2, 29-H_2 to 33-H_2), 1.88 – 2.00 (m, 4H; 17-H″, 18-H″, 21-H″, 22-H″), 2.13 (s, 3H; 39-H_3), 2.53 (t, J = 6.4 Hz, 2H; 3-H_2), 3.33 – 3.43 (m, 2H; 15-H, 24-H), 3.54 – 3.62 (m, 1H; 28-H), 3.74 – 3.89 (m, 16H; 16-H, 19-H, 20-H, 23-H, 4 × OCH_3); ^{13}CNMR (75 MHz, $CDCl_3$): δ = 11.6 (C-39), 14.1 (C-34), 21.7 (C-26), 22.6 (C-33), 25.6, 27.0, 28.4, 28.9, 29.0, 29.4, 29.5, 29.61, 29.63, 29.67, 29.73, 30.1, 30.3, 31.8 (C-3 to C-13, C-17, C-18, C-21, C-22, C-30 to C-32), 33.2 (C-25), 33.4 (C-14), 37.3, 37.5 (C-27, C-29), 60.6, 61.0, 61.08, 61.09 (4 × OCH_3), 71.7 (C-28), 73.9, 74.1 (C-15, C-24), 81.77, 81.84, 83.1, 83.2 (C-16, C-19, C-20, C-23), 124.9, 130.4 (C-2, C-35), 144.6, 144.7, 147.6, 147.7 (C-1, C-36, C-37, C-38); HR-MS (EI): found: 736.5492 $[M]^+$; calcd: 736.5489.

Quinone – squamocin D (Quinone – asiminacin): The triol **29** (4.0 mg, 5.4 μmol) and pyridine-2,6-dicarboxylic acid (5.5 mg, 33 μmol) were dissolved in MeCN (0.4 mL) and water (0.4 mL). CAN (36 mg, 66 μmol) was added at 0 °C. The reaction mixture was stirred for 4 h. The reaction was quenched by adding $CHCl_3$/*i*PrOH (2 mL) and water (1 mL). The aqueous layer was extracted five times with $CHCl_3$/*i*PrOH (2 mL). The combined organic layers were dried with $MgSO_4$. Removal of the solvents and purification by column chromatography (2 g silica, *n*-hexane/*i*PrOH 5:1) afforded quinone – squamocin D (2.7 mg, 3.8 μmol, 70%) as a yellow oil. R_f = 0.28 (silica, *n*-hexane/*i*PrOH 5:1); $[\alpha]_D^{22}$ = + 3.1 (c = 0.13, $CHCl_3$); ^{1}HNMR (300 MHz, $CDCl_3$): δ = 0.86 (t, J = 6.6 Hz, 3H; 34-H_3), 1.20 – 1.67 (m, 42H; 4-H_2 to 14-H_2, 17-H′, 18-H′, 21-H′, 22-H′, 25-H_2 to 27-H_2, 29-H_2 to 33-H_2), 1.89 – 2.10 (m, 4H; 17-H″, 18-H″, 21-H″, 22-H″), 1.99 (s, 3H; 39-H_3), 2.42 (t, J = 6.4 Hz, 2H; 3-H_2), 3.37 – 3.53 (m, 2H; 15-H, 24-H) overlap with 3.53 – 3.62 (m, 1H; 28-H), 3.84 – 3.98 (m, 10H; 16-H, 19-H, 20-H, 23-H, 2 × OCH_3); ^{13}CNMR (75 MHz, $CDCl_3$): δ = 11.9 (CH_3 – 39), 14.1 (C-34), 21.4 (C-26), 22.6 (C-33), 25.4, 25.7, 26.4, 28.67, 28.74, 29.4, 29.5, 29.6, 29.7, 29.9, 31.9 (C-3 to C-13, C-17, C-18, C-21, C-22, C-30 to C-32), 32.6 (C-25), 33.1 (C-14), 36.8, 37.7 (C-27, C-29), 61.2 (OCH_3), 71.7 (C-28), 74.4, 74.7 (C-15, C-24), 81.7, 81.8, 82.9, 83.0 (C-16, C-19, C-20, C-23), 138.7, 143.1, 144.2 (C-2, C-35, C-37, C-38), 184.2, 184.7 (C-1, C-36); HRMS (EI): found: 708.5177 $[M + 2 \times H]^+$; calcd: 708.5176.

Compound 35: This compound was prepared from (3*S*)-3-(*tert*-butyldimethylsilyloxy)-4-[(5′*S*)-5′-methyl-2′-oxo-2′,5′-dihydro-furan-3′-yl]butanal[6a,b] by side chain elongation by means of a Wittig reaction. R_f = 0.66 ($CHCl_3$/MeOH 10:1); ^{1}HNMR (300 MHz, $CDCl_3$): δ = 0.85 (t, J = 7.0 Hz, 3H; 14′-H_3), 1.40 (d, J = 7.2 Hz, 3H; CH_3), 1.11 – 1.52 (m, 20H; 4′-13′-H_2), 1.87 – 2.32 (m, 2H; 3′-H_2), 2.32 – 2.60 (m, 2H; 1′-H_2), 3.73 – 3.91 (m, 1H; 2′-H_2), 4.93 – 5.09 (m, 1H; 5-H), 7.10 – 7.19 (m, 1H; 4-H); ^{13}CNMR (75 MHz, $CDCl_3$): δ = 14.1 (C-14′), 19.1 (CH_3), 22.7, 25.6, 29.3, 29.6, 29.7, 31.9, 33.3, 37.4 (C-1′,3′-13′), 70.0 (C-2′), 77.9 (C-5), 124.2 (C-3), 151.8 (C-4), 174.8 (C-2); HRMS (EI): found 311.2581 $[M - H]^+$; calcd: 311.2586.

Acknowledgement

This work was supported by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, and ASTA-Medica AG.

[1] a) F. Q. Alali, X.-X. Liu, J. L. McLaughlin, *J. Nat. Prod.* **1999**, *62*, 504 – 540; b) M. C. Zafra-Polo, B. Figadère, T. Gallardo, J. R. Tormo, D. Cortes, *Phytochemistry* **1998**, *48*, 1087 – 1117; c) G. Cassiraghi, F. Zanardi, L. Battistini, G. Rassu, G. Aappendino, *Chemtracts: Org. Chem.* **1998**, *11*, 803 – 827; d) A. Cavé, B. Figadère, A. Laurens, D. Cortes, *Progress in the Chemistry of Organic Natural Products*, (Eds.: W. Herz, G. W. Kirby, R. E. Moore, W. Steglich, C. Tamm), Springer, New York, **1997**, 81 – 288.

[2] Total syntheses of annonaceous acetogenins: a) Z.-M. Wang, S.-K. Tian, M. Shi, *Eur. J. Org. Chem.* **2000**, 349 – 356; b) W. Q. Yang, T. Kitahara, *Tetrahedron* **2000**, *56*, 1451 – 1461; c) S. C. Sinha, S. C. Sinha, E. Keinan, *J. Org. Chem.* **1999**, *64*, 7067 – 7073; d) Q. Wu, Z.-J. Yao, X.-G. Chen, Y.-L. Wu, *J. Org. Chem.* **1999**, *64*, 2440 – 2445; e) A. Sinha, S. C. Sinha, S. C. Sinha, E. Keinan, *J. Org. Chem.* **1999**, *64*, 2381 – 2386; f) P. Li, J. Yang, K. Zhao, *J. Org. Chem.* **1999**, *64*, 2259 – 2263; g) J. A. Marshall, H. Jiang, *J. Org. Chem.* **1999**, *64*, 971 – 975; h) Z.-M. Wang, S. K. Tian, M. Shi, *Tetrahedron Lett.* **1999**, *1*, 977 – 980; i) T.-S. Hu, Q. Yu, Q. Lin, Y.-L. Wu, Y. Wu, *Org. Lett.* **1999**, *1*, 399 – 401; for work prior to 1999 including the important contributions from the groups of T. R. Hoye, B. Figadère, and B. M. Trost see refs. [1] and [6b].

[3] a) G.-X. Zhao, L. R. Miesbauer, D. L. Smith, J. L. McLaughlin, *J. Med. Chem.* **1994**, *37*, 1971 – 1974; b) M. Sahai, S. Singh, M. Singh, Y. K. Gupta, S. Akashi, R. Yuji, K. Hirayama, H. Asaki, H. Araya, N. Hara, T. Eguchi, K. Kakimuma, Y. Fujimoto, *Chem. Pharm. Bull.* **1994**, *42*, 1163 – 1174.

[4] G. Shi, D. Alfonso, M. O. Fatope, L. Zeng, Z.-M. Gu, G.-X. Zhao, K. He, J. M. MacDougal, J. L. McLaughlin, *J. Am. Chem. Soc.* **1995**, *117*, 10409 – 10410.

[5] a) U. Emde, U. Koert, *Tetrahedron Lett.* **1999**, *40*, 5979 – 5982; b) U. Emde, U. Koert, *Eur. J. Org. Chem.* **2000**, 1889 – 1904.

[6] a) S. Bäurle, S. Hoppen, U. Koert, *Angew. Chem.* **1999**, *111*, 1341 – 1344; *Angew. Chem. Int. Ed.* **1999**, *38*, 1263 – 1266; b) S. Hoppen, S. Bäurle, U. Koert, *Chem. Eur. J.* **2000**, *6*, 2382 – 2396; c) P. Neogi, T. Doundoulakis, A. Yazbak, S. C. Sinha, S. C. Sinha, E. Keinan, *J. Am. Chem. Soc.* **1998**, *120*, 11279—11284; d) S. Takahashi, T. Nakata, *Tetrahedron Lett.* **1999**, *40*, 723 – 726; e) S. Takahashi, T. Nakata, *Tetrahedron Lett.* **1999**, *40*, 727 – 730; f) P. A. Evans, V. S. Murthy, *Tetrahedron Lett.* **1998**, *39*, 9627 – 9628; g) P. A. Evans, V. S. Murthy, *Tetrahedron Lett.* **1999**, *40*, 1253 – 1256.

[7] a) M. Londershausen, W. Leicht, F. Lieb, H. Moeschler, H. Weiss, *Pestic. Sci.* **1991**, *33*, 427 – 438; b) T. Friedrich, P. Van Heek, H. Leif, T. Ohnishi, E. Forche, B. Kunze, R. Jansen, W. Trowitzsch-Kienast, G. Höfle, H. Reichenbach, H. Weiss, *Eur. J. Biochem.* **1994**, *219*, 691 – 698; c) M. Degli Esposti, *Biochim. Biophys. Acta* **1998**, *1364*, 222 – 235; c) E. Estronell, J. R. Tormo, D. Cortes, *Biochem. Biophys. Res. Commun.* **1997**, *240*, 234 – 238; d) M. C. González, J. R. Tormo, A. Bermejo, M. C. Zafra-Polo, E. Estornell, D. Cortes, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1113 – 1118; e) J. R. Tormo, M. C. Gonzáles, D. Cortes, E. Estornell, *Arch. Biochem. Biophys.* **1999**, *369*, 119 – 126; f) H. Miyoshi, M. Ohshima, H. Shimada, T. Akagi, H. Iwamura, J. L. McLaughlin, *Biochim. Biophys. Acta* **1998**, *1365*, 443 – 452; g) H. Shimada, J. B. Grutzner, J. F. Kozlowski, J. L. McLauglin, *Biochemistry* **1998**, *37*, 854 – 866.

[8] a) R. M. Hollingworth, K. I. Ahammadsahib, G. Gadelhak, J. L. McLaughlin, *Biochem. Soc. Trans.* **1994**, *22*, 230 – 233; b) M. Degli Esposti, A. Ghelli, M. Ratta, D. Cortes, E. Estornell, *Biochem. J.* **1994**, *301*, 161 – 167.

[9] E. Keinan, D. Eren, *J. Org. Chem.* **1987**, *52*, 3872 – 3875.

[10] a) J. L. Fry, M. Orfanopoulos, M. G. Adlington, W. R. Dittmann, S. B. Silverman, *J. Org. Chem.* **1978**, *43*, 374 – 375; b) I. Fleming, A. Barbero, D. Walter, *Chem. Rev.* **1997**, *97*, 2063 – 2192.

[11] U. Koert, M. Stein, H. Wagner, *Liebigs Ann.* **1995**, 1415 – 1426.

[12] L. Syper, K. Kloc, J. Mlochowski, Z. Szulc, *Synthesis* **1979**, 521 – 522.

[13] G. E. Keck, D. Krishnamurthy, *Org. Synth.* **1997**, *75*, 12 – 18.

 © WILEY-VCH Verlag GmbH, D-69451 Weinheim, 2001 0947-6539/01/0705-1004 $ 17.50+.50/0

[14] B. Figadère, J.-C. Harmange, L. X. Hui, A. Cavé, *Tetrahedron Lett.* **1992**, *33*, 5189 – 5192.
[15] T. Komatsu, K. Nakao, H. Nishide, E. Tsuchida, *J. Chem. Soc. Chem. Commun.* **1993**, 728 – 730.
[16] P.-E. Sum, L. Weiler, *Can. J. Chem.* **1978**, *56*, 2700 – 2702.
[17] A. L. Smith, *Methods Enzymol.* **1967**, *10*, 81 – 86.
[18] P. C. Hinkle, M. L. Yu, *J. Biol. Chem.* **1979**, *254*, 2450 – 2455.
[19] D. Alfonso, H. A. Johnson, T. Colman-Saizarbitoria, C. P. Presley, G. P. McCabe, J. R. McLaughlin, *Nat. Tox.* **1996**, *4*, 181 – 188.
[20] H. Shimada, J. B. Grutzner, J. F. Kozlowski, J. L. McLaughlin, *Biochemistry* **1998**, *37*, 854 – 866.
[21] C. R. Lancaster, H. Michel, *Structure* **1997**, *5*, 1339 – 1359.
[22] The cyclic voltammograms of various quinones and butenolide samples are given in the Supporting Information.
[23] a) B.-B. Zeng, Y. Wu, Q. Y. Y.-L. Wu, Y. Li, X.-G. Chen, *Angew. Chem.* **2000**, *112*, 2010 – 2013; *Angew. Chem. Int. Ed.* **2000**, *39*, 1934 – 1937; b) Y. L. Huérou, J. Doyon, R. L. Grée, *J. Org. Chem.* **1999**, *64*, 7682 – 6790.
[24] M. Ohishima, H. Miyoshi, K. Sakamoto, K. Takegami, J. Iwata, K. Kuwabara, H. Iwamura, T. Yagi, *Biochemistry* **1998**, *37*, 6436 – 6445.
[25] Compound **35** was prepared during the total synthesis of mucocin.[6a,b] Analytical data for **35** are given at the end of the Experimental Section.

Received: August 9, 2000 [F2660]