Synthesis of (4*R*,12*S*,15*S*,16*S*,19*R*,20*R*,34*S*)-Muricatetrocin and (4*R*,12*R*,15*S*,16*S*,19*R*,20*R*,34*S*)-Muricatetrocin, Two Potent Inhibitors of Mitochondrial Complex I

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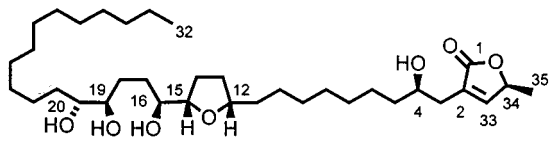
(4*R*,12*S*,15*S*,16*S*,19*R*,20*R*,34*S*)-Muricatetrocin (**1**) and (4*R*,12*R*,15*S*,16*S*,19*R*,20*R*,34*S*)-muricatetrocin (**2**) were synthesized by a modular synthetic strategy. Both compounds act as potent inhibitors of mitochondrial complex I. Compound **1** showed analytical data in agreement with howiicin E and a fit with the data for muricatetrocin A if one reassigns the reported ^{13}C signals for C(13) and C(14). Compound **2** matched muricatetrocin B in respect to all NMR data. However, a lower optical rotation was found for **2** ($[\alpha]_D^{28}$ = +6.7) than was reported for the natural product ($[\alpha]_D^{25}$ = +15.0).

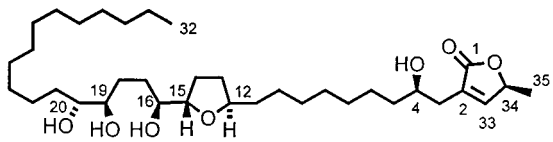
Introduction

Over 250 acetogenins from *Annonaceae* have been isolated and characterized so far.[1] This class of natural products shows remarkable biological properties, e.g. as antitumour agents, immunosuppressants or pesticides.[1] The inhibition of mitochondrial complex I is discussed as one mode of action.[2] Complex I, also known as NADH: ubiquinone oxido reductase, transfers electrons from NADH to ubiquinone and links this process with translocation of protons across the inner membrane. Numerous synthetic routes to the different subtypes of *Annonaceae* acetogenins have been elaborated over the last decade.[3−9]1

In 1993 McLaughlin et al. reported on the isolation of two new monotetrahydrofuran acetogenins from *Annona muricata*.[10] They were named muricatetrocin A and B. Structure **1** was proposed for muricatetrocin A and structure **2** for muricatetrocin B. In 1994 Yang et al. published analytical data for howiicin E isolated from *Goniothalamus howii*, which indicated a constitutional identity and a stereochemical match for muricatetrocin A and howiicin E.[11]



1 (proposed structure[10] for muricatetrocin A)



2 (proposed structure[10] for muricatetrocin B)

Figure 1. Structures of the target molecules **1** and **2**

All three natural products have a C_{35} skeleton, three hydroxyl groups in the left side chain (C-16, C-19, C-20), one hydroxyl group in the right side chain (C-4) and a butenolide moiety at the right end of the molecule. The assignment of the relative and absolute configuration of the seven stereocentres of muricatetrocin A and B was based on NMR measurements including Mosher ester methodology.[10] The relative configuration of the 2,5-disubstituted THF ring was proposed to be *cis* for muricatetrocin A and *trans* for muricatetrocin B. Here we report on the total synthesis of compounds **1** and **2** and the comparison of their analytical data with the data reported for muricatetrocin A, howiicin E and muricatetrocin B.

Results and Discussion

Our retrosynthesis of **1** (Scheme 1) disconnects between C-15 and C-16, and so leads to the addition of an organometallic reagent **3** to the aldehyde **4**. A related coupling has already successfully been used in the total synthesis of mucocin.[4c] The THF aldehyde **4** can be prepared via a Wittig reaction of the ylide **5** and the butenolide aldehyde **6**.

The synthesis of the right half of the target molecule **1** is summarized in Scheme 2. The *cis* THF alcohol **7** was prepared following a known route, using the enantioselective addition of a diorganozinc reagent to an aldehyde following Knochel's procedure.[12] Protection of the primary hydroxyl group in **7** as a triethylsilyl (TES) ether followed by reductive cleavage of the pivalate gave the alcohol **8**. The latter was converted via the corresponding iodide into the phosphonium salt **9**. A Wittig reaction of **9** with the aldehyde **10**[4c] afforded the olefin **11** in 65% yield as a mixture of

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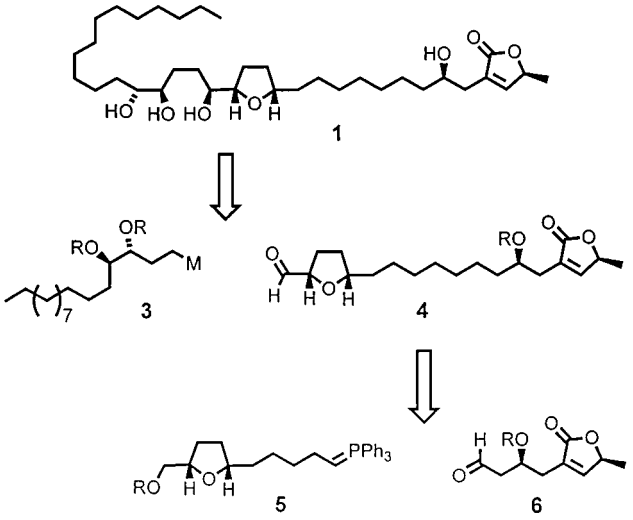
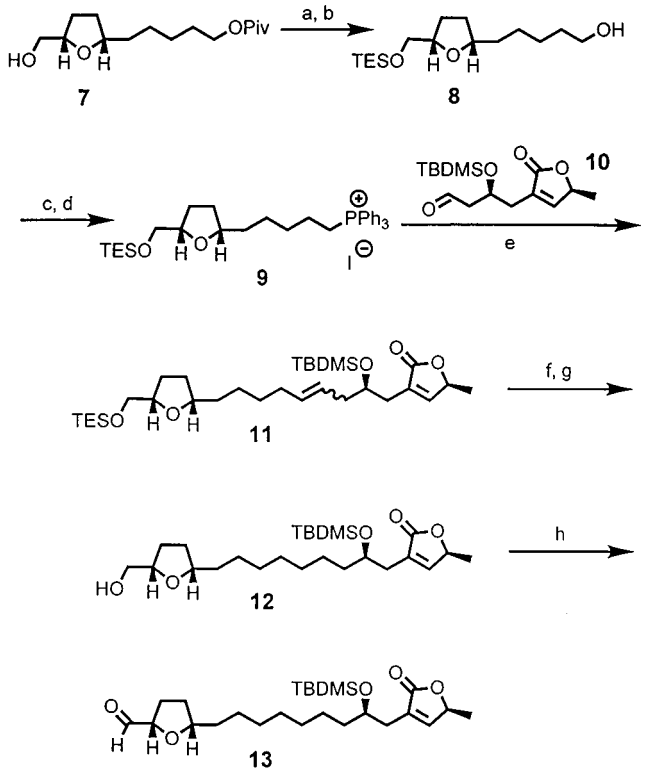
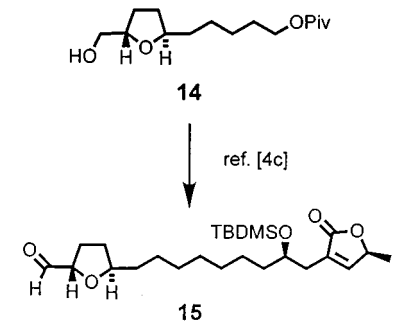


Scheme 1. Retrosynthetic analysis of **1**

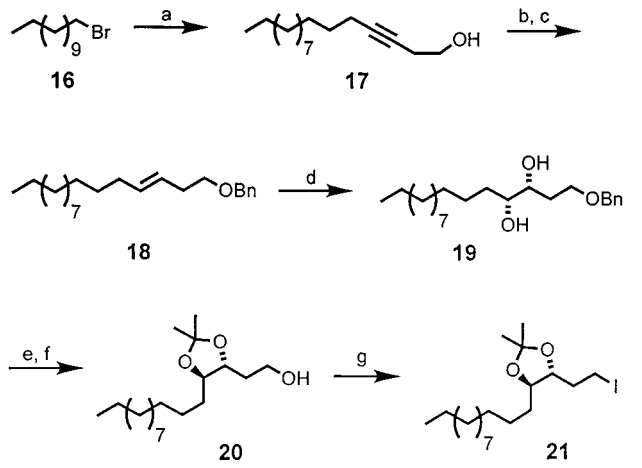


Scheme 2. a) TESCl (2.5 equiv.), imidazole (3.0 equiv.), CH_2Cl_2, room temp., 2 h, 95%; b) DIBAH (2.5 equiv.), THF, −40 °C → −15 °C, 1 h, 86%; c) I_2 (1.2 equiv.), PPh_3 (1.1 equiv.), imidazole (3.0 equiv.), CH_2Cl_2, 0 °C → room temp., 1.5 h, 74%; d) PPh_3 (5.0 equiv.), CH_3CN/toluene 1:1, 70 °C, 20 h; e) NaHMDS (1.0 equiv.), THF, 0 °C, 30 min, then **10**, −70 °C → 0 °C, 20 min, 65%; f) [$(PPh_3)_3RhCl$] (0.15 equiv.), H_2 (1 atm), benzene, room temp., 3 h, 83%; g) CSA (0.03 equiv.), CH_2Cl_2/MeOH 5:1, −20 °C, 10 min, 75%; h) $(COCl)_2$ (2.5 equiv.), DMSO (5.0 equiv.), NEt_3 (7.0 equiv.), CH_2Cl_2, −70 °C → 0 °C, 1.5 h, 87%. TES = triethylsilyl, TBDMS = *tert*-butyldimethylsilyl, NaHMDS = sodium hexamethyldisilazide, CSA = camphorsulfonic acid

(*E*)/(*Z*) isomers. Aldehyde **10** was prepared in 10 steps from acetoacetic acid methyl ester. Key steps were a Noyori hydrogenation to establish the sterogenic centre at C-4 and an alkylation with (*S*)-propylene oxide leading to the lactone



Scheme 3. Preparation of the *trans* THF aldehyde **15** from the *trans* THF alcohol **14**; details are given in ref. [4c]



Scheme 4. a) 3-butyn-1-ol (2.6 equiv.), *n*BuLi (5.0 equiv.), NH_3/THF/DMPU, rfx., 10 h, 50%; b) $LiAlH_4$ (5.8 equiv.), diglyme, 100 °C, 14 h, 83%; c) BnBr (1.3 equiv.), NaH (3.0 equiv.), DMF, 90 °C, 24 h, 91%; d) AD-mix β, $MeSO_2NH_2$ (1.0 equiv.), H_2O/*t*BuOH 1:1 0 °C → room temp., 20 h, 90%, *ee* = 98%; e) 2,2-dimethoxypropane (10 equiv.), CSA (cat.), CH_2Cl_2, room temp., 1 h, 95%; f) H_2 (1 atm), Pd-C (0.5 mol-% Pd), EtOAc, room temp., 20 h, 95%; g) I_2 (1.2 equiv.), PPh_3 (1.1 equiv.), imidazole (3.0 equiv.), CH_2Cl_2, 0 °C → room temp., 5 h, 66%

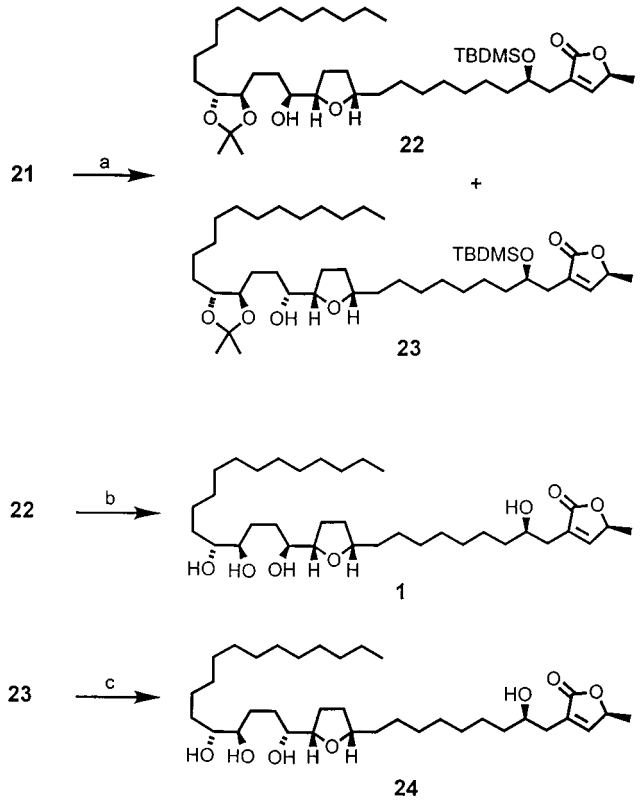
moiety. A chemoselective hydrogenation, using Wilkinson's catalyst,[13] of the isolated double bond in **11**, followed by TES-deprotection, gave the alcohol **12**. The Swern oxidation of **12** provided the aldehyde **13**.

Following the same route, the *trans* THF alcohol **14** was converted into the *trans* THF aldehyde **15** (Scheme 3). This reaction sequence was used for the first time in the context of the mucocin synthesis and is described in ref. 4c.

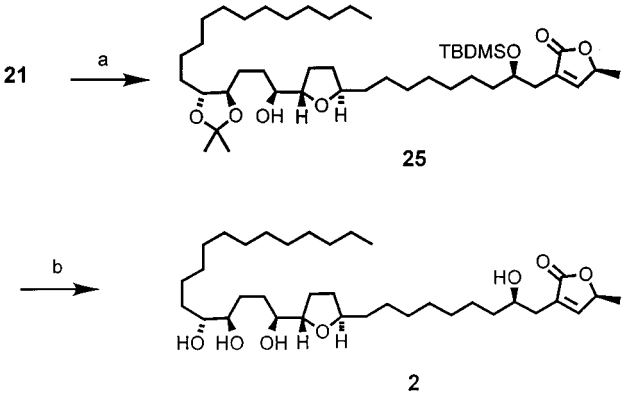
The synthesis of the left side chain, containing the two stereocentres at C-19 and C-20, was addressed next (Scheme 4). To this end, the bromide **16** was allowed to react with the dianion of 3-butyn-1-ol to give the alkylation product **17** in 50% yield. An (*E*)-selective reduction of the triple bond to the corresponding alkene followed by benzylation of the primary hydroxyl function resulted in compound **18**. The Sharpless dihydroxylation[14] of **18** with AD-mix β gave the diol **19** with an *ee* = 98% as determined by HPLC. The vicinal diol was protected as an acetonide. Hydrogenolytic cleavage of the benzyl ether afforded the alcohol **20**, which could be transformed into the iodide **21**.

The final part of the synthesis of **1** required the chelation-controlled addition of an organometallic reagent prepared

from the iodide **21** to the *cis* THF aldehyde **13**. Organomagnesium compounds form the chelation-controlled product with the related *trans* THF aldehyde **15**.[4c] Due to the small scale of the coupling reaction (< 1 mmol), heterogeneous Grignard-type chemistry with magnesium turnings was not very suitable. Instead, the homogeneous generation of the corresponding organolithium compound followed by transmetallation to magnesium was used. The iodide **21** was subjected to an iodine-lithium exchange[15] in Et_2O at − 105 °C and subsequently treated with magnesium bromide in Et_2O at − 100 °C. Addition of the aldehyde **13** gave the two secondary alcohols **22** and **23** as coupling products (60%) with a 1:1 stereoselectivity. Both epimers could be separated by chromatography. The stereochemical assignment[16] was based on ^{13}C NMR data (new chiral centre: δ = 74.5 for **22** and 72.1 for **23**). It should be pointed out that no stereocontrol could be achieved in the addition of the organomagnesium compound to the *cis* THF aldehyde. This stands in contrast to the results obtained in the *trans* case (ref.[4c] and vide infra). Deprotection of the TBDMS group in **22** with HF in CH_3CN and subsequent cleavage of the acetonide function provided compound **1** in 68% yield. The epimeric coupling product **23** yielded the C-16 epimer **24** in 63% yield after the same deprotection sequence (Scheme 5).



Scheme 5. a) **21** (1.3 equiv.), *t*BuLi (2.0 equiv.), Et_2O, −105 °C, 4 min, then $MgBr_2{\cdot}Et_2O$ (4.2 equiv.), −100 → −25 °C, 2 h, → −78 °C, **13** (1.0 equiv.), → −5 °C, 2 h, 60% (1:1 mixture of **22** and **23**, separated by FCC), 28% of aldehyde **13** reisolated; b) $HF{\cdot}CH_3CN$ (3.0 equiv.), CH_2Cl_2, room temp., 1 h, then CSA (0.5 equiv.), MeOH, room temp., 1 h, 68%; c) $HF{\cdot}CH_3CN$ (3.0 equiv.), CH_2Cl_2, room temp., 1 h, then CSA (0.5 equiv.), MeOH, room temp., 1 h, 63%



Scheme 6. a) **21** (1.3 equiv.), *t*BuLi (1.9 equiv.), Et_2O, −105 °C, 4 min, then $MgBr_2{\cdot}Et_2O$ (3.9 equiv.), −100 → −30 °C, 2 h, → −75 °C, **15** (1.0 equiv.), → −10 °C, 2 h, 34% (single isomer), 10% of aldehyde **15** reisolated; b) HF/CH_3CN (3.0 equiv.), CH_2Cl_2, room temp., 30 min, then CSA (0.5 equiv.), MeOH, room temp., 1 h, 84%

Addition of the organomagnesium compound prepared from **21** to the *trans* THF aldehyde **15** gave the chelation-controlled coupling product **25** in 34% yield as a single isomer (Scheme 6). The epimeric product, which in the *cis* series was formed in equimolar amounts, was not observed. TBDMS deprotection and cleavage of the acetonide afforded compound **2**.

Compound **1** was isolated as a waxy solid with $[\alpha]_D^{33}$ = +12.5 (*c* = 1.1 in $CHCl_3$). The reported optical rotation for muricatetrocin A is $[\alpha]_D^{25}$ = +10.3 (*c* = 0.15 in $CHCl_3$). The reported optical rotation for howiicin E is $[\alpha]_D^{18.5}$ = +15.79 (*c* = 0.8 in $CHCl_3$). The MS and IR data for **1** are in agreement with the reported data for muricatetrocin A. Based on the synthesis we assign the following absolute configuration to the seven stereocentres of **1**: 4*R*,12*S*,15*S*, 16*S*,19*R*,20*R*,34*S*. A comparison of the ^1H- and ^{13}C-NMR data for the synthetic compound **1** and the natural products muricatetrocin A and howiicin E is shown in Table 1 and Table 2.

There is a good match for all ^1H- and ^{13}C signals of compound **1** and the reported data for howiicin E. A comparison of the NMR data for muricatetrocin A and compound **1** shows differences for the CH_2 groups in the THF ring at C(13) and C(14). McLaughlin et al. report a ^{13}C resonance for C(13) at 28.43 and for C(14) at 32.43. For compound **1** we see no ^{13}C resonance around 28.43. Based on 2D-experiments (HH and HC COSY) we assign the signal at 27.79 to C(14) and one of the signals in the overlap region between 25 and 30 ppm to C(13) (probably at 26.11 ppm). In the original publication,[10] the same ^{13}C resonances were reported at C(13) and C(14) for muricatetrocin A and muricatetrocin B. Because both natural products differ in their relative configuration at the THF ring one might expect differences for the resonances at C(13) and C(14). Inspection of copies of the NMR spectra of muricatetrocin A, kindly provided by Prof. McLaughlin, allowed no closer analysis of the ^{13}C region between 24 and 34 ppm.[17] Based on the present data it can be stated that howiicin E has the structure of **1** and that after reassignment of the C(13)/C(14) NMR data of muricatetrocin A it is possible that mu-

Table 1. ^{1}H resonances and assignments for compound **1** (600 MHz), muricatetrocin A[10] (500 MHz) and howiicin E[11] (400 MHz)

	δ **1**	δ Muricatetrocin A	δ Howiicin E
H_a−C(3)	2.38 (ddt, J = 15.2, 8.4, 0.9 Hz)	2.38 (ddt, J = 15.1, 8.0, 1.4 Hz)	2.38 (dd, J = 14.5, 8.1 Hz)
H_b−C(3)	2.51 (ddt, J = 15.2, 3.1, 1.5 Hz)	2.51 (ddt, J = 15.1, 4.0, 1.4 Hz)	2.50 (dd, J = 14.5, 3.1 Hz)
H−C(4)	3.77−3.92 (m)	3.82 (m)	3.88 (m)
CH_2(5)	1.2−1.7 (m)	1.45 (m)	1.45 (m)
CH_2(6−11)	1.2−1.7 (m)	1.2−1.5	1.2−1.6
H−C(12)	3.77−3.92 (m)	3.85 (dt, J = 5.9, 6.7 Hz)	3.76 (m)
H_a−C(13)	1.3−1.9 (m)	1.96 (m)	1.97 (m)[a]
H_b−C(13)	1.3−1.9 (m)	1.65 (m)	
H_a−C(14)	1.9 (m)	1.91 (m)	1.69 (m)[a]
H_b−C(14)	1.6 (m)	1.72 (m)	
H−C(15)	3.70 (q, J = 6.8 Hz)	3.70 (q, J = 7.0 Hz)	3.88 (m)
H−C(16)	3.34−3.48 (m)	3.39 (m)	3.43 (m)
CH_2(17)	1.2−1.7 (m)	1.54 (m)	1.4−1.6 (m)
CH_2(18)	1.2−1.7 (m)	1.56 (m)	1.4−1.6 (m)
H−C(19)	3.34−3.48 (m)	3.42 (m)	3.43 (m)
H−C(20)	3.34−3.48 (m)	3.39 (m)	3.43 (m)
CH_2(21)	1.2−1.7 (m)	1.57 (m)	1.4−1.6 (m)
CH_2(22−31)	1.2−1.7 (m)	1.2−1.5	1.2−1.6
CH_3(32)	0.86 (t, J = 7.0 Hz)	0.85 (t, J = 7.0 Hz)	0.88 (t, J = 7.7 Hz)
H−C(33)	7.16 (d, J = 1.1 Hz)	7.17 (d, J = 1.4 Hz)	7.18 (br. s)
H−C(34)	5.04 (dq, J = 7.1, 1.3 Hz)	5.04 (dq, J = 7.1, 1.4 Hz)	5.05 (q, J = 6.7 Hz)
CH_3(35)	1.41 (d, J = 6.8 Hz)	1.41 (d, J = 7.1 Hz)	1.41 (d, J = 6.8 Hz)

[a] Signals may be interchanged.

Table 2. ^{13}C-NMR resonances and assignments for compound **1** (75 MHz), muricatetrocin A[10] (125 MHz) and howiicin E[11] (100 MHz)

	δ **1**	δ Muricatetrocin A	δ Howiicin E
C(1)	174.62	174.53	174.63
C(2)	131.16	131.10	131.19
C(3)	33.35	33.39	33.37
C(4)	69.92	69.94	69.94
C(5)	37.37	37.41	37.41
C(6−11)	25−29	25−29	25−29
C(12)	80.02	80.03	80.05
C(13)	26.11	28.43	26.14
C(14)	27.79	32.43	27.83
C(15)	82.05	82.01	82.12
C(16)	74.25	74.90	74.29
C(17)	35.94	35.99	35.55
C(18)	33.46	33.48	33.52
C(19)	74.57	74.62	74.57
C(20)	74.88	74.39	74.91
C(21)	31.35	29.95	31.38
C(22−30)	25−30	25−29	25−30
C(31)	22.97	22.71	22.70
C(32)	14.10	14.18	14.10
C(33)	151.82	151.81	151.86
H−C(34)	77.89	77.99	78.00
CH_3(35)	19.10	19.16	19.13

ricatetrocin A has the configuration 4*R*,12*S*,15*S*,16*S*,19*R*,20*R*,34*S*.

Compound **2** was isolated as a waxy solid with $[\alpha]_D^{28}$ = +6.7 (c = 0.4 in $CHCl_3$). The reported optical rotation for muricatetrocin B is $[\alpha]_D^{25}$ = +15.0 (c = 0.43 in $CHCl_3$). The MS and IR data for **2** are in agreement with the reported data for muricatetrocin B. Based on the synthesis we assign the following absolute configuration to the seven stereocentres of **2**: 4*R*,12*R*,15*S*,16*S*,19*R*,20*R*,34*S*. A comparison of the ^{1}H- and ^{13}C-NMR data for the synthetic compound **2** and the natural product muricatetrocin A is shown in Table 3.

There is a good match for all ^{1}H and ^{13}C signals of compound **2** and the reported data for muricatetrocin B. Based on the NMR data it is likely that muricatetrocin B has the 4*R*,12*R*,15*S*,16*S*,19*R*,20*R*,34*S* configuration. However, there is a discrepancy in the magnitude of the optical rotation for the natural product and compound **2**, which prevents us from unequivocally stating that muricatetrocin B and compound **2** are identical.[17]

Biological Evaluation

Compounds **1**, **2**, and **24** were tested as inhibitors of bovine-heart mitochondrial complex I. Bovine-heart mitochondria were prepared as described before.[18] The inhibition of oxygen uptake was measured. The respiratory activities were analyzed with a Clark-type oxygen electrode (100 mM sodium phosphate pH 7.4, 1 mM EDTA, 1 mM $MgCl_2$, 0.2 mg/mL protein).[13] All three compounds exhibited very high activities (**1**: K_i50 = 1.6 nM, **2**: K_i50 = 3.3 nM, **24**: K_i50 = 1.5 nM). These results show that compounds **1**, **2**, and **24** have similar activities in comparison with the known strong inhibitor rotenon (rotenon: K_i50 = 1.0 nM).[2]

Table 3. ^{1}H and ^{13}C NMR resonances and assignments for compound **2** (300 MHz, 75 MHz) and muricatetrocin B[10] (500 MHz, 125 MHz)

	δ(H) **2**	δ(C) **2**	δ(H) Muricatetrocin B	δ(C) Muricatetrocin B
C(1)		174.64		174.53
C(2)		131.12		131.04
H_a−C(3)	2.32 (m)	33.35	2.38 (ddt, J = 15.1, 8.0, 1.4 Hz)	33.39
H_b−C(3)	2.46 (m)		2.51 (ddt, J = 15.1, 4.0, 1.4 Hz)	
H−C(4)	3.75−3.93 (m)	69.93	3.82 (m)	69.88
CH_2(5)	1.21−1.78 (m)	37.36	1.45 (m)	37.28
CH_2(6−11)	1.21−1.78 (m)	25−29	1.2−1.5	25−29
H−C(12)	3.75−3.93 (m)	79.3	3.85 (dt, J = 5.9, 6.7 Hz)	79.27
H_a−C(13)	1.90−2.08 (m)	28.39	2.00 (m)	28.43
H_b−C(13)	1.21−1.78 (m)		1.63 (m)	
H_a−C(14)	1.90−2.08 (m)	32.39	1.97 (m)	32.43
H_b−C(14)	1.21−1.78 (m)		1.71 (m)	
H−C(15)	3.75−3.93 (m)	81.72	3.78 (q, J = 7.0 Hz)	81.73
H−C(16)	3.35−3.51 (m)	74.43	3.40 (m)	74.43
CH_2(17)	1.21−1.78 (m)	35.49	1.40 (m)	35.43
CH_2(18)	1.21−1.78 (m)	33.44	1.57 (m)	33.48
H−C(19)	3.35−3.51 (m)	74.58	3.42 (m)	74.56
H−C(20)	3.35−3.51 (m)	74.24	3.40 (m)	74.23
CH_2(21)	1.21−1.78 (m)	29.92	1.57 (m)	29.95
CH_2(22−30)	1.21−1.78 (m)	25−29	1.2−1.5	25−29
CH_3(32)	0.86 (t, J = 7.0 Hz)	14.12	0.85 (t, J = 7.0 Hz)	14.17
H−C(33)	7.16 (d, J = 1.1 Hz)	151.85	7.17 (d, J = 1.4 Hz)	151.81
H−C(34)	5.04 (dq, J = 6.8, 1.5 Hz)	77.99	5.04 (dq, J = 7.1, 1.4 Hz)	77.99
CH_3(35)	1.41 (d, J = 6.8 Hz)	19.10	1.41 (d, J = 7.1 Hz)	19.14

It should be noticed that all three different stereoisomers display comparable activity. This observation is in agreement with recent results from Miyoshi et al., who found that the stereochemistry around the THF rings was of minor importance.[2b] It has been stated that bis-THF acetogenins like bullatacin and squamocin A are more potent complex I inhibitors than mono-THF acetogenins.[1c] Our data for the mono-THF acetogenins **1**, **2**, and **24** are comparable with the data for the bis-THF acetogenin squamocin A (K_i50 = 1.0 nM). Therefore, we see no remarkable difference in complex I inhibition for both groups of compounds. The high selectivities reported for the cytotoxicity of Annonaceae acetogenins in different cancer cell lines may reflect the different degrees of uptake and transport by the tumor cells. Once the acetogenins reach complex I, most of them strongly inhibit the enzyme.

Conclusion

A modular synthetic strategy was used for the stereoselective synthesis of (4*R*,12*S*,15*S*,16*S*,19*R*,20*R*,34*S*)-muricatetrocin **1** and (4*R*,12*R*,15*S*,16*S*,19*R*,20*R*,34*S*)-muricatetrocin **2**. Both compounds are very strong inhibitors of bovine heart mitochondrial complex I. Based on the present data we can suggest the identity of howiicin E and compound **1**. In the case of muricatetrocin A a reassignment of NMR data at C(13) and C(14) is proposed. The analytical data for compound **2** and muricatetrocin B are identical except for a difference in the magnitude of the optical rotation.

Experimental Section

General: All b.p.s and m.p.s are uncorrected values. − IR: Perkin−Elmer FT-IR 1600, Biorad FTS 3000MX. − NMR: Bruker AC-300, DPX-300, and AMX-600. For ^{1}H NMR, $CHCl_3$ impurity in $CDCl_3$ solvent δH = 7.24; for ^{13}C NMR, $CDCl_3$ as solvent δC = 77.0. − Elemental analysis: CHNS-932 Analysator (Leco). − HRMS: Finnigan MAT 95. All reactions were performed under an Ar-atmosphere in oven- or flame-dried glassware except where otherwise stated. − HPLC: Rainin-Dynamax, SD-200 and SD-1, PDA1. Dry solvents: THF, Et_2O, benzene, and xylene were distilled from sodium benzophenone. Pyridine, triethylamine, 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 visualized with UV light and/or heat-gun treatment with 5% phosphomolybdic acid in ethanol. Column chromatography (CC) and flash column chromatography (FCC) 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. DMPU: *N*,*N*′-Dimethylpropyleneurea.

5-[(2′*S*,5′*S*)-5′-(Hydroxymethyl)tetrahydrofuran-2′-yl]pentyl Pivalate (7): For the preparation of **7** see ref.[12] R_f = 0.19 (*n*-hexane/MTBE 1:1); HPLC: R_t = 22.9 min (Superspher Si 60, *n*-hexane/

*i*PrOH 96/4, 1.0 mL·min^{-1}); $[\alpha]_D^{20}$= −6.5, (*c* = 0.94, $CHCl_3$, pure *cis*-isomer). − IR (film): $\tilde{\nu}$ = 3445 m br (OH), 2937/2864 s (CH), 1728 s (C=O), 1481 m, 1398/1366 w (*t*Bu), 1285 s, 1159 s, 1058 s, 1038 w. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13 (s, 9 H, *t*Bu), 1.24−1.48 and 1.49−1.70 and 1.77−1.97 (m, 12 H, 3′-H_2, 4′-H_2, 2-H_2, 3-H_2, 4-H_2, 5-H_2), 2.28 (s, br, 1 H, OH), 3.42 (dd, *J* = 11.3/5.7 Hz, 1 H, 1′′-H_a), 3.61 (dd, *J* = 11.5/3.6 Hz, 1 H, 1′′-H_b), 3.64−3.75 (m, 1 H, 2′-H), 3.85−4.00 (m, 1 H, 5′-H),3.99 (t, *J* = 6.6 Hz, 2 H, 1-H_2). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.76, 25.84, 27.0, 28.5, 31.3, 35.7 (C-3′,4′,2−5), 27.1 [C(CH_3)$_3$], 38.6 [*C*(CH_3)$_3$], 64.2 (C-1), 65.2 (C-1′′), 79.2 (C-5′), 79.9 (C-2′), 178.5 (*C*O*t*Bu). − $C_{15}H_{28}O_4$ (272.38): calcd. C 66.14, H 10.36; found C 66.22, H 10.71.

5-[(2′*S*,5′*S*)-5′-(Triethylsilyloxymethyl)tetrahydrofuran-2′-yl]-pentan1-ol (8). − 1. TES Protection: To a solution of the alcohol **7** (488 mg, 1.79 mmol) in CH_2Cl_2 (20 mL) were added imidazole (366 mg, 5.37 mmol) and powdered molecular sieves (4 Å, 50 mg). The mixture was treated with TESCl (0.75 mL, 4.48 mmol) at 0 °C. After stirring at room temp. for 2 h, the reaction mixture was filtered through a pad of celite and diluted with MTBE (20 mL), phosphate buffer solution (10 mL) and water (5 mL). The aqueous layer was extracted with MTBE (3× 7 mL) and the combined organic layers were washed with sat. aqueous NaCl (2× 20 mL) and dried with $MgSO_4$. The solvents were evaporated and the residue was purified by CC (25 g silica, PE/MTBE 2:1) to yield the TES-protected alcohol (657 mg, 95%) as a colourless liquid. − **5-[(2′*S*,5′*S*)-5′-(Triethylsilyloxymethyl)tetrahydrofuran-2′-yl]pentyl Pivalate:** R_f = 0.68 (*n*-hexane/MTBE 1:1); $[\alpha]_D^{20}$ = −3.6 (*c* = 1.0, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2956/2938/2912/2876 s (CH), 1731 s (C=O), 1285 m, 1156 s, 1100 m, 744 m. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.57 (q, *J* = 7.9 Hz, 6 H, 3× SiCH_2CH_3), 0.93 (t, *J* = 7.7 Hz, 9 H, 3× SiCH_2CH_3), 1.16 (s, 9 H, *t*Bu), 1.28−1.49 (m, 6 H, 3× alkyl-CH_2), 1.50−1.75 (m, 4 H, 2× alkyl-CH_2), 1.81−1.95 (m, 2 H, alkyl-CH_2), 3.48 (dd, *J* = 10.4/5.8 Hz, 1 H, 1′′-H_a), 3.60 (dd, *J* = 10.5/4.9 Hz, 1 H, 1′′-H_b), 3.75−3.84 (m, 1 H, 2′-H), 3.86−3.95 (m, 1 H, 5′-H), 4.01 (t, *J* = 6.6 Hz, 2 H, 1-H_2). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.4 (Si*C*H_2CH$_3$)$_3$, 6.7 (SiCH$_2$*C*H$_3$)$_3$, 25.9, 26.1, 28.0, 28.6, 30.9, 35.8 (C-3′,4′,2−5), 27.2 [C(*C*H_3)$_3$], 38.7 [*C*(CH_3)$_3$], 64.3 (C-1), 65.8 (C-1′′), 79.4 (C-5′), 79.8 (C-2′), 178.6 (*C*O*t*Bu). − $C_{21}H_{42}O_4Si$ (386.64): calcd. C 65.23, H 10.95; found C 65.15, H 10.97. − **2. Cleavage of the Pivalate:** A solution of the pivalate (651 mg, 1.68 mmol) in THF (20 mL) was treated with DIBAH (4.21 mL, 4.21 mmol, 1 M in hexanes) at −40 °C. The reaction mixture was allowed to warm up to −15 °C during 1 h. The reaction was quenched by addition of MeOH (2 mL), sat. aqueous $NaHCO_3$ (4 mL), and ethyl acetate (15 mL). The mixture was stirred 30 min at room temp., solid Na_2SO_4 (10 g) was then added and the mixture was stirred vigorously for 1 h. The mixture was filtered through a pad of celite and the solvents were removed in vacuo. The crude product was purified by CC (25 g silica gel, PE/MTBE 2:1) to obtain alcohol **8** (438 mg, 86%) as a colourless oil. **8**: R_f = 0.19 (*n*-hexane/MTBE 1:1); $[\alpha]_D^{23}$ = −5.7, (*c* = 0.28, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3429 m br (OH), 2936/2913/2875 s (CH), 1673 w, 1458 w, 1096 m, 1015 w, 742 m. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.58 (q, *J* = 8.2 Hz, 6 H, 3× SiCH_2CH_3), 0.93 (t, *J* = 7.7 Hz, 9 H, 3× SiCH$_2$CH_3), 1.27−1.76 (m, 11 H, OH and 5× alkyl-CH_2), 1.83−1.95 (m, 2 H, alkyl-CH_2), 3.48 (dd, *J* = 10.4/5.8 Hz, 1 H, 1′′-H_a), 3.55−3.66 (m, 3 H, 1′′-H_b, 1-H_2), 3.75−3.86 (m, 1 H, 2′-H), 3.87−3.97 (m, 1 H, 5′-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.4 (Si*C*H_2CH$_3$)$_3$, 6.7 (SiCH$_2$*C*H$_3$)$_3$, 25.8, 26.1, 28.0, 30.9, 32.7, 36.9 (C-3′,4′,2−5), 62.9 (C-1), 65.8 (C-1′′), 79.4 (C-5′), 79.9 (C-2′). − $C_{16}H_{34}O_3Si$ (302.52): calcd. C 63.52, H 11.33; found C 63.20, H 11.26.

Phosphonium Salt 9. − 1. Iodination: To a solution of imidazole (283 mg, 4.16 mmol) and PPh_3 (399 mg, 1.52 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added first a solution of iodine (421 mg, 1.66 mmol) in CH_2Cl_2 (7 mL) and then a solution of alcohol **8** (419 mg, 1.39 mmol) in CH_2Cl_2 (3 mL). The reaction mixture was stirred at room temp. for 1.5 h, $Na_2S_2O_3$ solution (5% in water, 30 mL) was then added and the mixture was stirred until the brown colour disappeared. The phases were separated and the aqueous layer was extracted with MTBE (3× 15 mL). The combined organic layers were washed with sat. aqueous NaCl (2× 20 mL) and dried with $MgSO_4$. The solvents were evaporated in vacuo and the residue was purified by CC (45 g silica gel, PE/MTBE 1:1) to yield the iodide as a colourless oil (420 mg, 74%). **(2*S*,5*S*)-2-(5′-Iodopentyl)-5-(triethylsilyloxymethyl)tetrahydrofuran:** R_f = 0.72 (*n*-hexane/MTBE 1:1); $[\alpha]_D^{22}$ = −4.1 (*c* = 0.48, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2953/2935/2911/2875 s (CH), 1460 w, 1238 w, 1094 m, 1012 w, 798 w, 744/728 s. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.52−0.63 (m, 6 H, 3× SiCH_2CH_3), 0.88−0.97 (m, 9 H, 3× Si CH$_2$CH_3), 1.23−1.93 (m, 12 H, 6× alkyl-CH_2), 3.16 (t, *J* = 7.2 Hz, 2 H, 5′-H_2), 3.44−3.52 (m, 1 H, 1′′-H_a), 3.55−3.64 (m, 1 H, 1′′-H_b), 3.75−3.86 (m, 1 H, 2-H), 3.87−3.97 (m, 1 H, 5-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.4 (Si*C*H_2CH$_3$)$_3$, 6.7 (SiCH$_2$*C*H$_3$)$_3$, 7.1 (C-5′), 25.2, 27.9, 30.58, 30.9, 33.5, 35.7 (C-3,4,1′-4′), 65.8 (C-1′′), 79.5 (C-5), 79.8 (C-2). − $C_{16}H_{33}IO_2Si$ (412.42). − **2. Preparation of the Triphenylphosphonium Salt 9:** The iodide (293 mg, 0.71 mmol) and PPh_3 (932 mg, 3.5 mmol) were dissolved in toluene (1 mL) and CH_3CN (4 mL). The solution was stirred at 70 °C for 48 h. The mixture was concentrated in vacuo and washed with Et_2O several times until the rinsing liquid was free of PPh_3 (checked by TLC). The phosphonium salt **9** was dried in vacuo (ca. 0.1 mbar) and was used for the Wittig reaction without further purification.

(5*S*)-3-{(2′*R*,4′*Θ*)-*tert*-Butyldimethylsilyloxy-9′-{(2′′*S*,5′′*S*)-5′′-[(triethylsilyl)oxymethyl]tetrahydrofuran-2′′-yl}non-4′-enyl}-5-methylfuran-2(5*H*)-one (11): The phosphonium salt **9** was dissolved in THF (5 mL) and treated with NaHMDS (0.55 mL 1 M in THF, 0.55 mmol) at 0 °C. The orange solution was stirred at 0 °C for 30 min, and was then cooled to −70 °C and a solution of aldehyde **10** (165 mg, 0.55 mmol) in THF (3 mL) was added dropwise. The cooling bath was replaced by an ice bath and the now light brown-yellow solution was stirred 20 min at 0 °C. The reaction was quenched by the addition of phosphate buffer solution (1 M, pH 7, 7 mL). The mixture was diluted with MTBE (10 mL) and water (8 mL). The aqueous layer was extracted with MTBE (3× 7 mL) and the combined organic layers were washed with sat. aqueous NaCl (2× 10 mL) and dried with $MgSO_4$. The solvents were removed in vacuo and the residue was purified by FCC (35 g silica gel, *c*HexH/MTBE 5:1) to yield olefin **11** (200 mg, 65%) as a colourless oil. **11**: R_f = 0.61 (*n*-hexane/MTBE 1:1). − IR (film): $\tilde{\nu}$ = 2954/2933 s (CH), 2876/2858 m (CH), 1761 m (C=O), 1463 w, 1373/ 1357 w (*t*Bu), 1252 w, 1079 m, 1005 w, 836 w, 775 w. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.01 (s, 3 H, SiCH_3), 0.03 (s, 3 H, SiCH_3), 0.58 (q, *J* = 8.2 Hz, 6 H, 3× SiCH_2CH_3), 0.84 [s, 9 H, SiC(CH_3)$_3$], 0.93 (t, *J* = 7.7 Hz, 9 H, 3× SiCH$_2$CH_3), 1.39 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.24−1.76 (m, 8 H, 4× alkyl-CH_2), 1.81−2.03 (m, 4 H, 2× alkyl-CH_2), 2.09−2.29 (m, 2 H, alkyl-CH_2), 2.30−2.50 (m, 2 H, alkyl-CH_2), 3.48 (dd, *J* = 10.4/5.8 Hz, 1 H, 1′′′-H_a), 3.60 (dd, *J* = 10.4/5.1 Hz, 1 H, 1′′′-H_b), 3.74−3.84 (m, 1 H, 2′′-H), 3.84−4.08 (m, 2 H, 4-H, 5′′-H), 4.97 (dq, *J* = 6.8/1.1 Hz, 1 H, 5-H), 5.27−5.52 (m, 2 H, 4′-H, 5′-H), 7.09 (d, *J* = 1.5 Hz, 1 H, 4-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.6, −4.4 (2 Si*C*H_3), 4.4 (2 Si*C*H_2CH$_3$), 6.7 (2 SiCH$_2$*C*H$_3$), 18.0 [Si*C*(CH_3)$_3$], 18.9 (CH_3), 25.8 [SiC(*C*H_3)$_3$], 26.0, 27.5, 27.9, 29.7, 31.8, 32.6, 35.0, 35.9 (C-

1′,3′,6′-9′,3′′,4′′), 65.8 (C-1′′′), 70.00 (C-2′), 77.4 (C-5), 79.4 (C-5′′), 79.9 (C-2′′), 124.8 (C-5′), 130.9 (C-3), 132.1 (C-4′), 151.5 (C-4), 173.9 (C-2). − HRMS (EI): $C_{31}H_{58}O_5Si_2$ calcd. 567.3901, found 567.3909 ([M + H]$^+$).

(5*S*)-3-{(2′*R*)-*tert*-Butyldimethylsilyloxy-9′-{(2′′*S*,5′′*S*)-5′′-(hydroxymethyl)tetrahydrofuran-2′′-yl}nonyl}-5-methylfuran-2(5*H*)-one (12). − 1. Wilkinson Hydrogenation: A solution of $(PPh_3)_3RhCl$ (61 mg, 0.07 mmol) in benzene (4 mL, spectroscopy grade) was degassed and stirred under hydrogen for 15 min. A solution of olefin **11** (258 mg, 0.44 mmol) in benzene (2 mL) was added and the mixture was stirred under hydrogen (1 atm) for 3 h at room temp. The solution was concentrated in vacuo and the residue was purified by FCC (18 g silica gel, cyclohexane/MTBE 2:1) to yield the hydrogenation product as a light brown oil (207 mg, 83%). − **(5*S*)-3-{(2′*R*)-*tert*-Butyldimethylsilyloxy-9′-[(2′′*S*,5′′*S*)-5′′-{(triethylsilyl)oxymethyl}tetrahydrofuran-2′′-yl]nonyl}-5-methylfuran-2(5*H*)-one:** R_f = 0.46 (silica gel, treated with 1 M $AgNO_3$, *n*-hexane/MTBE 2:1); $[\alpha]_D^{22}$ = 7.2, (*c* = 0.16, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2953/2931 s (CH), 2877/2857 m (CH), 1759 s (C=O), 1462 w, 1253 w, 1075 m, 836 w, 776 w. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.03−0.09 (m, 6 H, 2× $SiCH_3$), 0.58 (q, *J* = 7.8 Hz, 6 H, 3× $SiCH_2CH_3$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 0.93 (t, *J* = 7.9 Hz, 9 H, 3× $SiCH_2CH_3$), 1.39 (d, *J* = 7.2 Hz, 3 H, CH_3), 1.17−1.76 (m, 16 H, 8× alkyl-CH_2), 1.81−2.02 (m,2 H, alkyl-CH_2), 2.37−2.43 (m, 2 H,1′-H_2), 3.48 (dd, *J* = 10.4/5.8 Hz, 1 H, 1′′′-H_a), 3.61 (dd, *J* = 10.4/5.1 Hz, 1 H, 1′′′-H_b), 3.67−4.06 (m, 3 H, 2′-H, 2′′-H, 5′′-H), 4.93−5.03 (m, 1 H, 5-H), 7.09 (d, *J* = 1.5 Hz, 1 H, 4-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.5 (2 $SiCH_3$), 4.4 (2 $SiCH_2CH_3$), 6.7 (2 $SiCH_2CH_3$), 18.0 [$SiC(CH_3)_3$], 19.0 (CH_3), 26.9 [$SiC(CH_3)_3$], 25.1, 25.8, 26.2, 28.0, 29.5, 29.6, 30.8, 32.7, 36.0, 36.9 (C-1′,3′-9′,3′′,4′′), 65.8 (C-1′′′), 70.2 (C-2′), 77.4 (C-5), 79.4 (C-5′′), 80.0 (C-2′′), 130.8 (C-3), 151.5 (C-4), 174.0 (C-2). − HRMS (EI): $C_{31}H_{60}O_5Si_2$ calcd. 569.4058, found 569.4057 ([M + H]$^+$). − **2. TES-Deprotection:** At −20 °C a solution of camphorsulfonic acid (CSA) (2.4 mg, 10 μmol) in MeOH (1 mL) was added to a solution of the protected alcohol (194 mg, 340 μmol) in CH_2Cl_2 (5 mL). The mixture was stirred at −20 °C for 10 min, and then phosphate buffer solution (1 M, pH 7) (3 mL) and water (2 mL) were added. The aqueous layer was extracted with MTBE (4× 5 mL) and the combined organic layers were washed with sat. aqueous NaCl (2× 7 mL) and dried with $MgSO_4$. The solvents were evaporated in vacuo and the residue was purified by FCC (12 g silica gel, MTBE) to yield the primary alcohol **12** (117 mg, 75%) as a colourless liquid. R_f = 0.48 (MTBE); $[\alpha]_D^{24}$ = 12.4 (*c* = 1.2, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3455 w br (OH), 2930 s (CH), 2857 m (CH), 1756 m (C=O), 1464 w, 1373 w, 1318 w, 1255 w, 1204 w, 1078 m, 837 m, 775 w. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.04−0.04 (m, 6 H, 2× $SiCH_3$), 0.84 [s, 9 H, $SiC(CH_3)_3$], 1.38 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.18−2.04 (m, 18 H, 9× alkyl-CH_2), 2.39 (d, *J* = 5.6 Hz, 2 H, 1′-H_2), 3.39−3.50 (m, 1 H, 1′′′-H_a), 3.61−3.70 (m, 1 H, 1′′′-H_b), 3.77−4.02 (m, 3 H, 4-H, 12-H, 5′′-H), 4.92−5.02 (m, 1 H, 5-H), 7.09 (d, *J* = 1.1 Hz, 1 H, 4-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.5 (2 $SiCH_3$), 18.0 [$SiC(CH_3)_3$], 18.9 (CH_3), 25.8 [$SiC(CH_3)_3$], 25.1, 26.2, 26.9, 27.0, 29.5, 29.6, 31.4, 32.7, 35.9, 36.9 (C-1′,3′-9′,3′′,4′′), 65.3 (C-1′′′), 70.1 (C-2′), 77.4 (C-5), 79.8 (C-5′′), 80.2 (C-2′′), 130.8 (C-3), 151.5 (C-4), 174.0 (C-2). − HRMS (EI): $C_{25}H_{46}O_5Si$ calcd. 455.3193, found 455.3194 ([M + H]$^+$).

(2*S*,5*S*)-5-{(8′*R*)-8′-*tert*-Butyldimethylsilyloxy-9′-[{(5′′*S*)-5′′-methyl-2′′-oxo-2′′,5′′-dihydrofuran-3′′-yl}nonyl]tetrahydrofuran}-2-carbaldehyde (13): To a solution of oxalyl chloride (0.06 mL, 0.64 mmol) in CH_2Cl_2 (6 mL) was added DMSO (0.09 mL, 1.28 mmol) dropwise at −70 °C. After 15 min of stirring a solution of alcohol **12** (116 mg, 255 μmol) in CH_2Cl_2 (1 mL) was added at −65 °C. After another 20 min of stirring, the solution was treated at −50 °C with NEt_3 (0.25 mL, 1.79 mmol). The mixture was stirred for 30 min at −50 °C and a further 60 min at 0 °C. Then the reaction was quenched by the addition of phosphate buffer solution (2 mL, 1 M, pH 7), water (3 mL) and CH_2Cl_2 (5 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3× 4 mL). The combined organic layers were washed with water (2× 5 mL) and dried with $MgSO_4$. The solution was concentrated in vacuo and the residue was purified by FCC (20 g silica gel, cyclohexane/MTBE 1:1) to afford aldehyde **13** (101 mg, 87%) as a colourless oil. R_f = 0.33 (*n*-hexane/MTBE 1:2); $[\alpha]_D^{27}$ = −9.7 (*c* = 0.98, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2930/2857 s (CH), 1757 s (C=O), 1735 m (C=O) 1463 w, 1258 w, 1076 m, 836 m, 775 w. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.03−0.04 (m, 6 H, 2× $SiCH_3$), 0.84 [s, 9 H, $SiC(CH_3)_3$], 1.39 (d, *J* = 6.8 Hz, 3 H, CH_3), 1.20−2.24 (m, 18 H, 3,4,1′-7′-CH_2), 2.39 (d, *J* = 5.7 Hz, 2 H, 9′-H_2), 3.88−4.04 (m, 2 H, 5-H, 8′-H), 4.21 (ddd, *J* = 8.5/5.5/1.7 Hz, 1 H, 2-H), 4.93−5.02 (m, 1 H, 5′′-H), 7.09 (d, *J* = 1.1 Hz, 1 H, 4′′-H), 9.65 (d, *J* = 1.9 Hz, 1 H, CHO). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.5 (2 $SiCH_3$), 18.0 [$SiC(CH_3)_3$], 18.9 (CH_3), 25.8 [$SiC(CH_3)_3$], 25.1, 26.1, 27.8, 29.46, 29.51, 29.6, 31.0, 32.7, 35.6, 36.9 (C-3,C-4,C-1′-7′,C-9′), 70.1 (C-8′), 77.4 (C-5′′), 81.5 (C-2), 82.9 (C-5), 130.8 (C-3′′), 151.5 (C-4′′), 174.0 (C-2′′), 203.3 (CHO). − HRMS (EI): $C_{25}H_{44}O_5Si$ calcd. 453.3036, found 453.3038 ([M + H]$^+$).

Hexadec-3-yn-1-ol (17): Ammonia (50 mL, predried with sodium) was condensed in a 150 mL three-neck flask at −78 °C under argon atmosphere. A solution of *n*BuLi (13 mL, 32 mmol, 2.46 M in hexanes) was added. The obtained suspension was stirred for 15 min, then it was treated with a solution of butynol (1.17 g, 16.7 mmol) in THF (25 mL). The cooling bath was removed and the mixture was allowed to reflux for 30 min. After the addition of bromododecane (1.60 g, 6.42 mmol) in THF (25 mL) and a further 15 min of stirring, DMPU (20 mL, freshly distilled) was added. The mixture was allowed to reflux for another 15 min, then kept at −40 °C overnight (cryostat) and then refluxed for further 8 h. The reaction was quenched by the addition of solid NH_4Cl. The ammonia was allowed to evaporate and then water (50 mL) and MTBE (50 mL) were added and the phases were separated. The aqueous layer was extracted with MTBE (3× 50 mL) and the combined organic layers were washed with sat. aqueous NaCl (100 mL) and dried with $MgSO_4$. The solvents were removed in vacuo and the residue was purified by CC (100 g silica gel, hexane/MTBE 1:1) to afford 771 mg (50%) of alkynol **17** as a white waxy solid. **17**: R_f = 0.38 (*n*-hexane/MTBE 1:1). − IR (film): $\tilde{\nu}$ = 3221 br m (OH), 2953 m/2917/2849 s (CH), 1468 m (CH_2), 1044 w, 720 w. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.68 (t, *J* = 6.2 Hz, 3 H, 16-H_3), 1.18−1.40 (m, 18 H, 7−15-H_2), 1.78 (t, *J* = 6.2 Hz, 2 H, OH), 1.39−1.51 (m, 2 H), 2.10−2.16 (m, 2 H), 2.37−2.43 (m, 2 H) (2,5,6-H_2), 3.65 (dt, *J* = 6.2 Hz, 1-H_2). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-16), 18.7, 22.7, 23.2, 28.9, 29.0, 29.2, 29.3, 29.5, 29.6, 29.7, 31.9 (C-2, 5−15), 61.4 (C-1), 76.2, 82.8 (C-3, C-4). − $C_{16}H_{30}O$ (238.41): calcd. C 80.61, H 12.68; found C 80.77, H 12.40.

***O*-Benzyl-(*E*)-hexadec-3-en-1-ol (18). − 1. (*E*)-Selective Reduction:** Alkynol **17** (771 mg, 6.42 mmol), dissolved in diglyme (8 mL), was treated with $LiAlH_4$ (350 mg, 9.22 mmol). The mixture was stirred for 14 h at 100 °C. After cooling to 0 °C, MTBE (25 mL) was added and then water (0.35 mL), NaOH (0.35 mL, 15% in water), and again water (1 mL) were added dropwise. After 1 h of stirring at 50 °C the precipitate was removed by filtration through a pad of celite. The precipitate was washed with MTBE and water. The phases of the filtrate were separated and the aqueous layer was

extracted with MTBE (3× 30 mL). The combined organic layers were washed with sat. aqueous NaCl (50 mL) and dried with $MgSO_4$. The solvents were removed in vacuo. The precipitate was dissolved with hydrochloric acid (2 M, 20 mL), the solution was extracted with MTBE (3× 20 mL) and the combined organic layers were washed with sat. aqueous $NaHCO_3$ (20 mL) and dried with $MgSO_4$. The solvents were removed in vacuo. The combined crude products were purified by CC (90 g silica gel, PE/MTBE 1:1) to afford 649 mg (83%) of the desired (*E*)-alkenol as a white waxy solid. − **(*E*)-Hexadec-3-en-1-ol:** R_f = 0.38 (*n*-hexane/MTBE 1:1). − IR (film): $\tilde{\nu}$ = 3336 br m (OH), 2956 m/ 2921 s/2852 s (CH), 1467 w, 1049 w, 966 w, 721 w. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.6 Hz, 3 H, 16-H_3), 1.15−1.60 (m, 20 H, 6−15-H_2), 1.95−2.02 (m, 2 H), 2.20−2.27 (m, 2 H) (2,5-H_2), 3.53−3.68 (m, 2 H, 1-H_2), 5.29−5.40 (m, 1 H), 5.48−5.59 (m, 1 H), (3,4-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-16), 22.7, 29.2, 29.3, 29.5, 29.5, 29.6, 29.6, 29.7, 29.7, 31.9, 32.7 (C-5−15), 36.0 (C-2), 62.0 (C-1), 125.6 (C-4), 134.5 (C-3). − $C_{16}H_{32}O$ (240.42). − **2. Benzyl Protection:** (*E*)-Hexadec-3-en-1-ol (630 mg, 2.62 mmol) was dissolved in DMF (25 mL) and treated with NaH (190 mg, 7.9 mmol). Two drops of DMSO were added and the mixture was stirred for 30 min at 50 °C. Then benzyl bromide (590 mg, 3.4 mmol) was added dropwise and the suspension was stirred for another 24 h at 90 °C. After cooling to room temp., solid NH_4Cl and water (30 mL) were added and after 10 min stirring the phases were separated. The aqueous layer was extracted with MTBE (3× 20 mL) and the combined organic layers were washed with sat. aqueous NaCl (2× 25 mL) and dried with $MgSO_4$. The solvents were removed in vacuo and the crude product was purified by CC (50 g silica gel, *c*HexH/MTBE 20:1) to obtain 789 mg (91%) of benzyl ether **18** as a colourless oil. R_f = 0.40 (*c*HexH/MTBE 20:1). − IR (film): $\tilde{\nu}$ = 2925/2854 s (CH), 1362 w, 1101 m (COC), 909 m, 734 s/697 m (Ar). − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.8 Hz, 3 H, 16-H_3), 1.13−1.39 (m, 20 H, 6−15-H_2),1.97 (dt, *J* = 6.7 Hz, 6.7 Hz, 2 H, 5-H_2), 2.31 (dt, *J* = 6.6 Hz, 6.6 Hz, 2 H, 2-H_2), 3.47 (t, *J* = 7.0 Hz, 2 H, 1-H_2), 4.51 (s, 2 H, PhCH_2O), 5.33−5.58 (m, 2 H, 3,4-H), 7.17−7.47 (m, 5 H, Ar). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-16), 22.7, 29.2, 29.4, 29.5, 29.5, 29.6, 29.7, 29.7, 29.7, 31.9, 32.7, 33.1 (C-2, C-5−15), 70.3 (C-1), 72.8 (Ph*C*H_2), 126.1 (C-4), 127.5, 127.6, 128.2, 128.3, 128.7, 138.6 (Ph), 132.7 (C-3). − $C_{23}H_{38}O$ (330.55): calcd. C 83.57, H 11.59; found C 83.77, H 11.61.

(3*R*,4*R*)-1-*O*-Benzylhexadecane-1,3,4-triol (19): Alkene **18** (789 mg, 2.38 mmol) was dissolved in *t*BuOH/H_2O 1:1 (20 mL), cooled to 0 °C and treated with AD-mix β (3.34 g) and methanesulfonamide (226 mg, 2.38 mmol). The mixture was allowed to warm to room temp. and was stirred for 20 h. The colour changed from orange to yellow. The reaction was quenched by the addition of sodium thiosulfate pentahydrate (3.48 g, 14 mmol). After 15 min, MTBE (20 mL) was added and the phases were separated. The aqueous layer was extracted with MTBE (3× 15 mL), the combined organic layers were washed with sat. aqueous NaCl (2× 15 mL) and dried with $MgSO_4$. The solvents were evaporated in vacuo and the residue was purified by CC (80 g silica gel, PE/MTBE 3:1) to yield 782 mg (90%) of the dihydroxylated product **19** as a colourless solid. The enantiomeric ratio was determined by chiral HPLC to be 98:2. m.p.: 62 °C; R_f = 0.34 (*n*-hexane/MTBE 1:3); HPLC: R_t (*R*,*R*-isomer) = 11.2 min, R_t (*S*,*S*-isomer) = 14.8 min, (Chiralcel-OD-H, *n*-hexane/*i*PrOH 96:4, 1.0 mL·min^{-1}); $[\alpha]_D^{21}$ = 7.5 (*c* = 1.0, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3414/3032 br. s (OH), 2957 w/2919/2850 s (CH), 1471 m, 1372 m, 1105 m, 1072 m, 859 w, 729 m/695 w. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.6 Hz, 3 H, 16-H_3), 1.11−1.45 (m, 22 H, 5−15-H_2), 2.42 (d, 1 H, *J* = 5.7 Hz, 1 H, OH), 3.12 (d, 1 H, *J* = 3.8 Hz, 1 H, OH), 1.70−1.96 (m, 2 H), 3.34−3.47 (m, 1 H), 3.59−3.79 (m, 3 H) (1-H_2, 2-H_2, 3-H, 4-H), 4.51 (s, 2 H, PhCH_2O), 7.20−7.39 (m, 5 H, Ph). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-16), 22.7, 25.8, 29.3 29.6, 29.6, 29.6, 29.7, 29.7, 31.9, 33.2, 33.5 (C-2, 5−15), 68.6 (C-1), 73.4 (Ph*C*H_2), 73.7, 74.3 (C-3, C-4), 127.7, 127.9, 128.5, 137.7 (Ph). − $C_{23}H_{40}O_3$ (364.56): calcd. C 75.77, H 11.06; found C 75.69, H 11.30.

(3*R*,4*R*)-3,4-*O*-Isopropylidenehexadecane-1,3,4-triol (20). − 1. Acetonide Protection: Compound **19** (152 mg, 0.42 mmol) was dissolved in CH_2Cl_2 (10 mL) and 2,2-dimethoxypropane (152 mg, 0.42 mmol) and CSA (ca. 5 mg) was added at room temp. After 50 min of stirring, phosphate buffer solution (5 mL, pH 7, 1 M) and water (5 mL) were added and the phases were separated. The aqueous layer was extracted with MTBE (3× 10 mL) and the combined organic layers were washed with sat. aqueous NaCl (2× 15 mL) and dried with $MgSO_4$. The solvents were removed in vacuo and the residue was filtered with *c*HexH/MTBE 20:1 over silica gel to afford 161 mg (95%) of the protected triol as a colourless oil. − **(3*R*,4*R*)-1-*O*-Benzyl-3,4-*O*-isopropylidenehexadecane-1,3,4-triol:** R_f = 0.33 (*c*HexH/MTBE 20:1); $[\alpha]_D^{29}$ = 23.6 (*c* = 1.0, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 2926/2855 s, 1456 m, 1368 m, 1241 m, 1171 w, 1094 s, 1029 w, 872 w, 734 m/697 w. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 6.9 Hz, 3 H, 16-H_3), 1.20−1.34 (m, 20 H, 6−15-H_2), 1.36 (d, *J* = 2.3 Hz, 6 H, acetonide-CH_3), 1.37−1.58 (m, 2 H, 5-H_2), 1.72−1.95 (m, 2 H, 2-H_2), 3.53−3.69 (m, 3 H, 1-H_a, 3,4-H), 3.73 (dt, *J* = 8.1/3.8 Hz, 1 H, 1-H_b), 4.50 (s, 2 H, PhCH_2O), 7.21−7.35 (m, 5 H, Ph). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-16), 22.7, 26.1, 27.2, 27.3, 29.3, 29.5, 29.6, 29.7, 29.7, 29.8, 31.9, 32.7, 33.2 (C-2, 5−15, acetonide-CH_3), 67.3 (C-1), 73.0 (Ph*C*H_2), 78.1, 81.0 (C-3, C-4), 107.9 (OCO), 127.5, 127.6, 128.3, 138.4 (Ph). − $C_{26}H_{44}O_3$ (404.63): calcd. C 77.18, H 10.96; found C 77.06, H 10.98. − **2. Cleavage of the Benzyl Ether:** Palladium on activated carbon (15 mg, 10% Pd) was suspended in a solution of the benzyl-protected alcohol (132 mg, 0.33 mmol) in EtOAc (20 mL, HPLC-grade). The mixture was degassed at 0 °C and then vigorously stirred under hydrogen (1 atm) for 20 h at room temp. Then the suspension was filtered through a pad of celite and the solvent was evaporated in vacuo. The alcohol **20** was obtained in 95% yield (98 mg) as a colourless oil which needed no further purification. **20**: R_f = 0.29 (*n*-hexane/MTBE 2:1); $[\alpha]_D^{23}$ = 20.5 (*c* = 1.0, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3430 br. m (OH), 1056 s, 874 w. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 6.9 Hz, 3 H, 16-H_3), 1.15−1.23 (m, 20 H, 6−15-H_2), 1.36 (s, 6 H, acetonide-CH_3), 1.40−1.58 (m, 2 H, 5-H_2), 1.64−1.87 (m, 2 H, 2-H_2), 2.46 (br. s, 1 H, OH), 3.59−3.74 (m, 2 H, 3,4-H), 3.78 (t, *J* = 5.7 Hz, 2 H, 1-H_2). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-16), 22.7, 26.0, 27.2, 27.3, 29.3, 29.5, 29.5, 29.6, 29.6, 29.7, 31.9, 32.5, 34.7 (C-2, 5−15, acetonide-CH_3), 60.9 (C-1), 80.2, 81.0 (C-3, C-4), 108.3 (OCO). − $C_{19}H_{38}O_3$ (314.50): calcd. C 72.56, H 12.18; found C 72.41, H 12.35.

(3*R*,4*R*)-1-Iodo-3,4-*O*-isopropylidenehexadecane-3,4-diol (21): To a solution of imidazole (58 mg, 0.84 mmol) and PPh_3 (81 mg, 0.31 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added first a solution of iodine (87 mg, 0.34 mmol) in CH_2Cl_2 (3 mL) and then a solution of alcohol **20** (89 mg, 0.28 mmol) in CH_2Cl_2 (1.5 mL). The reaction mixture was stirred at room temp. for 5 h, and then sat. aqueous $Na_2S_2O_3$ was added dropwise until the brown colour disappeared. The phases were separated and the aqueous layer was extracted with MTBE (3× 10 mL). The combined organic layers were washed with sat. aqueous NaCl (2× 15 mL) and dried with $MgSO_4$. The solvents were evaporated in vacuo and the residue was purified by CC (30 g silica gel, PE/MTBE 2:1) to yield iodide **21**

(79 mg, 66%) as a colourless oil. **21**: R_f = 0.67 (*n*-hexane/MTBE 2:1). − IR (film): $\tilde{\nu}$ = 2986 w/2925 s/2854 s, 1466 w, 1378 m, 1369 m, 1237 m, 1173 w, 1088 w, 857 w, 563 w. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83−0.89 (m, 3 H, 16-H_3), 1.17−1.34 (m, 20 H, 6−15-H_2), 1.35 (d, J = 5.3 Hz, 6 H, acetonide-CH_3), 1.43−1.61 (m, 2 H, 5-H_2), 1.96−2.11 (m, 2 H, 2-H_2), 3.16−3.37 (m, 2 H, 3,4-H), 3.57−3.72 (m, 2 H, 1-H_2). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 1.8 (C-1), 14.1 (C-16), 22.7, 26.0, 27.2, 27.3, 29.3, 29.5, 29.6, 29.6, 29.7, 29.7, 31.9, 32.8 (C-5−15, acetonide-CH_3), 37.5 (C-2), 80.3, 80.6 (C-3, C-4), 108.4 (OCO). − $C_{19}H_{37}IO_2$ (424.40): calcd. C 53.77, H 8.79; found C 53.92, H 9.10.

(4*R*,12*S*,15*S*,16*S*,19*R*,20*R*,34*S*)-4-*O*-(*tert*-Butyldimethylsilyl)-19,20-*O*-isopropylidenemuricatetrocin (22) and (4*R*,12*S*,15*S*,16*R*,19*R*,20*R*,34*S*)-4-*O*-(*tert*-butyldimethylsilyl)-19,20-*O*-isopropylidenemuricatetrocin (23): In a 10-mL Schlenk tube a solution of iodide **21** (73 mg, 172 μmol) in Et_2O (3 mL) was cooled to −105 °C and treated with *tert*-butyllithium (0.23 mL, 1.48 M in pentane, 422 μmol). After 4 min at −100 °C, $MgBr_2{\cdot}Et_2O$ (0.14 mL, 543 μmol) was added. The formation of a colourless solid was observed. The reaction mixture was allowed to warm up to −25 °C over 2 h. Then the mixture was cooled to −78 °C and a solution of aldehyde **13** (60 mg, 133 μmol) in cold Et_2O (2 mL) was added. The solution was allowed to warm up to −5 °C over 2 h. The reaction was quenched by the addition of phosphate buffer solution (1 M, pH 7, 2 mL). The mixture was diluted with water (5 mL) and MTBE (10 mL). The aqueous layer was extracted with MTBE (4× 5 mL) and CH_2Cl_2 (1× 5 mL). The combined organic layers were washed with sat. aqueous NaCl (2× 6 mL) and dried with $MgSO_4$. The solvents were removed in vacuo and the residue was purified by FCC (20 g silica gel, gradient PE/MTBE 1:1 to 1:2) to yield the coupling products **22** and **23** (60 mg, 60%) as a colourless oil. Aldehyde **13** (28%, 17 mg) was reisolated. The 1:1 mixture (^{13}C NMR) of the C-16 epimers **22** and **23** was separated by optimized flash chromatography (40 g silica gel, PE/MTBE 2:1 to MTBE). − **22**: R_f = 0.50 (*n*-hexane/MTBE 1:2); $[\alpha]_D^{22}$ = 10.7 (c = 0.37, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3501 w br (OH), 2928 s/2856 m (CH), 1760 m (C=O), 1463 w, 1376 w, 1251 w, 1073 m, 836 w, 775 w. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.02−0.06 [m, 6 H, Si(CH_3)], 0.81−0.90 [m, 12 H, SiC(CH_3)$_3$, 32-H_3], 1.19−2.12 (m, 44 H, alkyl), 1.39 (d, J = 6.8 Hz, 3 H, 35-H_3), 2.36−2.43 (m, 2 H, 3-H_2), 2.51 (d, J = 4.1 Hz, 1 H, OH), 3.31−3.42 (m, 1 H), 3.51−3.62 (m, 2 H), 3.62−3.75 (m, 1 H), 3.76−3.88 (m, 1 H), 3.88−4.06 (m, 1 H) (4,12,15,16,19,20-H), 4.98 (dq, J = 6.8/1.3 Hz, 1 H, 34-H), 7.10 (d, J = 1.1 Hz, 1 H, 33-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.5, (2 SiCH_3), 14.1 (C-32), 18.0 [SiC(CH_3)$_3$], 19.0 (C-35), 29.6 [SiC(CH$_3$)$_3$], 22.7, 25.1, 25.9, 26.1, 26.2, 27.3, 27.8, 29.3, 29.5, 29.6, 29.7, 29.8, 31.3, 31.9, 32.7, 36.0, 36.9 (C-3,5−11,13,14,17,18,21−31, acetonide-CH_3), 70.2 (C-4), 74.5 (C-16), 77.5 (C-34), 79.9 (C-15), 81.2, 81.3, 82.3 (C-12, C-19, C-20), 107.8 (OCO), 130.8 (C-2), 151.5 (C-33), 174.0 (C-1). − HRMS (EI): $C_{44}H_{82}O_7Si$ calcd. 750.5830, found 750.5834 ([M]$^+$). − **23**: R_f = 0.46 (*n*-hexane/MTBE 1:2); $[\alpha]_D^{22}$ = 11.9 (0.42, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3488 w br (OH), 2927 s/2856 m (CH), 1761 s (C=O), 1464 w, 1376 w, 1254 w, 1076 m, 836 w, 775 w. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = −0.02−0.05 [m, 6 H, Si(CH_3)], 0.82−0.90 [m, 12 H, SiC(CH_3)$_3$, 32-H_3], 1.18−2.07 (m, 44 H, alkyl), 1.39 (d, J = 6.8 Hz, 3 H, 35-H_3), 2.40 (d, J = 5.7 Hz, 2 H, 3-H_2), 2.65 (br. s, 1 H, OH), 3.53−3.63 (m, 2 H), 3.65−3.87 (m, 3 H), 3.87−4.02 (m, 1 H) (4,12,15,16,19,20-H), 4.98 (dq, J = 6.8/1.2 Hz, 1 H, 34-H), 7. 90 (d, J = 1.1 Hz, 1 H, 33-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.6, (2 SiCH_3), 14.1 (C-32), 18.0 [SiC(CH_3)$_3$], 19.0 (C-35), 29.6 [SiC(CH$_3$)$_3$], 22.7, 24.8, 25.1, 25.8, 25.9, 26.1, 26.2, 27.2, 27.3, 29.3, 29.5, 29.5, 29.6, 29.7, 29.8, 31.3, 31.9, 32.7, 32.8 (C-3,5−11,13,14,17,18,21−31, acetonide-CH_3), 70.1 (C-4), 72.1 (C-16), 77.4 (C-34), 79.7 (C-15), 80.8 (C-12), 80.9, 82.1 (C-19, C-20), 107.9 (OCO), 130.8 (C-2), 151.5 (C-33), 174.0 (C-1). − HRMS (EI): $C_{44}H_{82}O_7Si$ calcd. 750.5830, found 750.5823 ([M]$^+$).

(4*R*,12*S*,15*S*,16*S*,19*R*,20*R*,34*S*)-Muricatetrocin (1): The protected compound **22** (20 mg, 26.6 μmol) was dissolved in CH_2Cl_2 (1 mL) and HF·CH_3CN (0.24 mL, 80 μmol) was added dropwise at room temp. After 1 h of stirring, a solution of CSA (3 mg, 12 μmol) in MeOH (0.5 mL) was added and the solution was stirred for a further 60 min. Then phosphate buffer solution (pH 7, 1 M, 0.5 mL), water (2 mL) and CH_2Cl_2 (3 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (4× 2 mL) and $CHCl_3$/*i*PrOH 1:1 (2× 2 mL). The combined organic layers were dried with $MgSO_4$. The solvents were evaporated in vacuo and the residue was purified by FCC (8 g silica gel, first *n*-hexane/MTBE 1:2, then $CHCl_3$/MeOH 10:1) to yield 10.8 mg (68%) of the product **1** as a colourless solid. Final impurities were removed by preparative HPLC (Rainin Si 60, 21.4 × 250 mm, *n*-hexane/*i*PrOH 80:20, 20 mL·min^{-1}). R_f = 0.31 ($CHCl_3$/MeOH 10:1); R_t = 18.4 min (Superspher Si 60, *n*-hexane/*i*PrOH 75:25, 1.0 mL·min^{-1}); UV: λ_{max} = 215 nm; $[\alpha]_D^{32}$ = 12.5 (c = 1.1, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3408 m br (OH), 2919 s /2850 m (CH), 1746 m (C=O), 1467 w, 1322 w, 1202 w, 1067 w, 1025 w, 853 w. − ^{1}H NMR (300 MHz, $CDCl_3$): see Table 1. − ^{13}C NMR (75 MHz, $CDCl_3$): see Table 2. − MS (EI): m/z = 597 [M + H]$^+$, 379 [M − (C-20−32) − H_2O]$^+$, 361 [M − (C-20−32) − 2 H_2O]$^+$, 309 [M − (C-16−32)]$^+$, 291 [M − (C-16−32) − H_2O]$^+$, 269 [(C-16−32) − H_2O]$^+$, 141 [(C-1−4/C-33−35)]$^+$. − HRMS (EI): $C_{35}H_{64}O_7$ calcd. 597.4730, found 597.4736 ([M + H]$^+$).

(4*R*,12*S*,15*S*,16*R*,19*R*,20*R*,34*S*)-Muricatetrocin (24): The protected compound **23** (20 mg, 26.6 μmol) was dissolved in CH_2Cl_2 (1 mL) and HF·CH_3CN (0.24 mL, 80 μmol) was added dropwise at room temp. After 1 h of stirring, a solution of CSA (3 mg, 12 μmol) in MeOH (0.5 mL) was added and the solution was stirred for a further 60 min. Then phosphate buffer solution (pH 7, 1 M, 0.5 mL), water (2 mL) and CH_2Cl_2 (3 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (4 × 2 mL) and $CHCl_3$/*i*PrOH 1:1 (2 × 2 mL). The combined organic layers were dried with $MgSO_4$. The solvents were evaporated in vacuo and the residue was purified by FCC (8 g silica gel, first *n*-hexane/MTBE 1:2, then $CHCl_3$/MeOH 10:1) to yield 10.0 mg (63%) of **24** as a colourless solid which needed no further purification. R_f = 0.28 ($CHCl_3$/MeOH 10:1); R_t = 16.4 min (Superspher Si 60, *n*-hexane/*i*PrOH 75:25, 1.0 mL·min^{-1}); UV: λ_{max} = 216 nm; $[\alpha]_D^{32}$ = 12.4 (c = 0.5, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3395 m br (OH), 2922 s /2853 m (CH), 1744 m (C=O), 1453 w, 1322 w, 1205 w, 1076 w, 1028 w. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (t, J = 6.8 Hz, 3 H, 32-H_3), 1.41 (d, J = 6.8 Hz, 3 H, 35-H_3), 1.21−1.34, 1.35−2.07 (m, 44 H, alkyl), 2.28−2.58 (m, 2 H, 3-H_2), 3.30−3.50 (m, 3 H, 19,20-H), 3.70−3.92 (m, 4 H, 4,12,15,16-H), 5.03 (dq, J = 6.8/1.4 Hz, 1 H, 34-H), 7.16 (d, J = 1.5 Hz, 1 H, 33-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-32), 19.1 (C-35), 22.7 (C-31), 24.4, 25.5, 25.7, 26.1, 27.0, 29.32, 29.35, 29.37, 29.5, 29.60, 29.62, 29.64, 29.66, 29.70, 31.0, 31.2, 33.7, 35.7 (C-6−11,13,14,17,18,21−30), 33.3 (C-3), 37.4 (C-5), 69.9 (C-4), 72.3 (C-16), 74.5, 74.8 (C-19, C-20), 78.0 (C-34), 79.7 (C-12), 82.0 (C-15), 131.2 (C-2), 151.8 (C-33), 174.6 (C-1). − MS (EI): m/z = 597 [M + H]$^+$, 379 [M − (C-20−32) − H_2O]$^+$, 361 [M − (C-20−32) − 2H_2O]$^+$, 309 [M − (C-16−32)]$^+$, 291 [M − (C-16−32) − H_2O]$^+$, 269 [(C-16−32) − H_2O]$^+$, 199 [(C-20−32)]$^+$, 141 [(C-1−4/C-33−35)]$^+$. − HRMS (EI): $C_{35}H_{64}O_7$ calcd. 597.4730, found 597.4736 ([M + H]$^+$).

(4*R*,12*R*,15*S*,16*S*,19*R*,20*R*,34*S*)-4-*O*-(*tert*-Butyldimethylsilyl)-19,20-*O*-isopropylidenemuricatetrocin (25): In a 10-mL Schlenk tube a solution of iodide **21** (27 mg, 63.2 μmol) in Et_2O (1 mL) was cooled to −105 °C and treated with *tert*-butyllithium (0.08 mL, 1.48 M in pentane, 120 μmol). After 4 min at −100 °C, $MgBr_2{\cdot}Et_2O$ (0.05 mL, 190 μmol) was added. The formation of a colourless solid was observed. The reaction mixture was allowed to warm up to −30 °C over 2 h. The precipitate redissolved at that temperature. Then the mixture was cooled to −75 °C and a solution of aldehyde **14** (22 mg, 48.6 μmol) in cold Et_2O (1 mL) was added. The solution was allowed to warm up to −10 °C over 2 h. The reaction was quenched by the addition of phosphate buffer solution (1 M, pH 7, 1 mL). The mixture was diluted with water (5 mL) and MTBE (10 mL). The aqueous layer was extracted with MTBE (4× 5 mL) and CH_2Cl_2 (1× 5 mL). The combined organic layers were washed with sat. aqueous NaCl (2× 6 mL) and dried with $MgSO_4$. The solvents were removed in vacuo and the residue was fractionated by FCC (15 g silica gel, gradient PE/MTBE 1:1 to 1:2) to afford a crude coupling product (25 mg), which was purified by optimized flash chromatography (18 g silica gel, gradient PE/MTBE 1:1 to 1:2) to yield 12.3 mg (34%) of the desired product **25** as a colourless solid. The C-16-epimer was not observed. Aldehyde **14** (2.1 mg, 10%) was reisolated. R_f = 0.52 (*n*-hexane/MTBE 1:2); $[\alpha]_D^{24}$ = 4.5 (c = 0.25 ($CHCl_3$). − IR (film): $\tilde{\nu}$ = 3480 w br (OH), 2928 s/2856 m (CH), 1760 m (C=O), 1463 w, 1373 w, 1251 w, 1071 m, 836 w, 777 w. − ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03−0.07 (m, 6 H, $Si(CH_3)$), 0.80−0.90 (m, 12 H, $SiC(CH_3)_3$, 32-H_3), 1.18−2.10 (m, 44 H, alkyl), 1.39 (d, J = 6.8 Hz, 3 H, 35-H_3), 2.40 (d, J = 5.7 Hz, 2 H, 3-H_2), 2.57 (d, J = 3.4 Hz, 1 H, OH), 3.32−3.43 (m, 1 H), 3.50−3.62 (m, 2 H), 3.66−3.80 (m, 1 H), 3.76 (m, 1 H, 15-H), 3.81−3.98 (m, 1 H) (4,12,15,16,19,20-H), 4.98 (dq, J = 6.8/1.3 Hz, 1 H, 34-H), 7.10 (d, J = 1.1 Hz, 1 H, 33-H). − ^{13}C NMR (75 MHz, $CDCl_3$): δ = −4.5, (2 Si*C*H_3), 14.1 (C-32), 19.0 [Si*C*$(CH_3)_3$], 19.2 (C-35), 29.6 [SiC(*C*$H_3)_3$], 22.7, 25.1, 25.8, 25.8, 25.9, 26.1, 27.0, 27.3, 28.4, 29.3, 29.5, 29.6, 29.7, 29.8, 30.3, 31.9, 32.4, 32.8, 35.6 (C-3,5−11,13,14,17,18,21−31, acetonide-CH_3), 70.1 (C-4), 74.2 (C-16), 77.5 (C-34), 79.3 (C-15), 81.2, 81.3, 82.0 (C-12, C-19, C-20), 107.9 (OCO), 130.8 (C-2), 151.5 (C-33), 174.0 (C-1). − HRMS (EI): $C_{44}H_{82}O_7Si$ calcd. 751.5908, found 751.5911 ($[M + H]^+$).

(4*R*,12*R*,15*S*,16*S*,19*R*,20*R*,34*S*)-Muricatetrocin (2): The protected compound **25** (12 mg, 16 μmol) was dissolved in CH_2Cl_2 (1 mL) and $HF{\cdot}CH_3CN$ (0.14 mL, 48 μmol) was added dropwise at room temp. After 30 min of stirring, a solution of CSA (2 mg, 8 μmol) in MeOH (0.5 mL) was added and the solution was stirred for a further 60 min. Then phosphate buffer solution (pH 7, 1 M, 0.5 mL), water (2 mL) and CH_2Cl_2 (3 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (4× 2 mL) and $CHCl_3$/*i*PrOH 1:1 (2× 2 mL). The combined organic layers were dried with $MgSO_4$. The solvents were evaporated in vacuo and the residue was purified by FCC (6 g silica gel, first *n*-hexane/MTBE 1:2, then $CHCl_3$/MeOH 10:1) to yield 8.0 mg (84%) of the product **2** as a colourless solid. Final impurities were removed by preparative HPLC (Rainin Si 60, 21.4 × 250 mm, *n*-hexane/*i*PrOH 80:20, 20 mL·min^{-1}). R_f = 0.24 ($CHCl_3$/MeOH 10:1); R_t = 17.6 min (Superspher Si 60, *n*-hexane/*i*PrOH 75:25, 1.0 mL·min^{-1}); UV: λ_{max} = 214 nm; $[\alpha]_D^{28}$ = 6.7 (c = 0.4, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3449/3305 m br (OH), 2954 w/ 2919 vs/2849 s (CH), 1742 m (C=O), 1066 m, 1026 w, 853 w. − ^{1}H NMR (300 MHz, $CDCl_3$): see Table 3. − ^{13}C NMR (75 MHz, $CDCl_3$): see Table 3. − MS (EI): m/z = 597 $[M + H]^+$, 397 $[M - (C\text{-}20\text{-}32)]^+$, 379 $[M - (C\text{-}20\text{-}32) - H_2O]^+$, 361 $[M - (C\text{-}20\text{-}32) - 2\ H_2O]^+$, 343 $[M - (C\text{-}20\text{-}32) - 3\ H_2O]^+$, 309 $[M - (C\text{-}16\text{-}32)]^+$, 291 $[M - (C\text{-}16\text{-}32) - H_2O]^+$. − HRMS (EI): $C_{35}H_{64}O_7$ calcd. 597.4730, found 597.4736 ($[M + H]^+$).

Acknowledgments

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