Stereoselective Total Synthesis of Passifloricin A[1])

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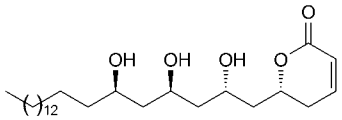
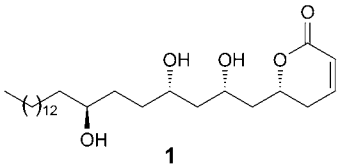
The stereoselective total synthesis of passifloricin A (**1**), a naturally occurring dihydropyranone with leishmanicidal and antiprotozoal activities, has been accomplished starting from protected glyceraldehyde using *Maruoka* asymmetric allylation, diastereoselective iodo-carbonate cyclization, and *Grubbs*' olefin metathesis reactions as the key steps.

Introduction. – Dihydropyranones are an important group of bioactive natural products [1]. They act as *Michael* acceptors to display their biological properties. Passifloricin A, a member of this group, was isolated from *Passiflora foetida* var. *hispida* (Passifloraceae) [2]. The compound was found to possess interesting leishmanicidal and antiprotozoal activities [3].

The structure of passifloricin A was initially assigned as **1a** on the basis of its spectroscopic data [2]. Several syntheses of the compound with this proposed structure, **1a**, were also reported [4]. *Murga et al.* synthesized different isomers of the compound, and after inspection of their NMR spectra, they revised the structure of passifloricin A as **1** [4a][5].



1a



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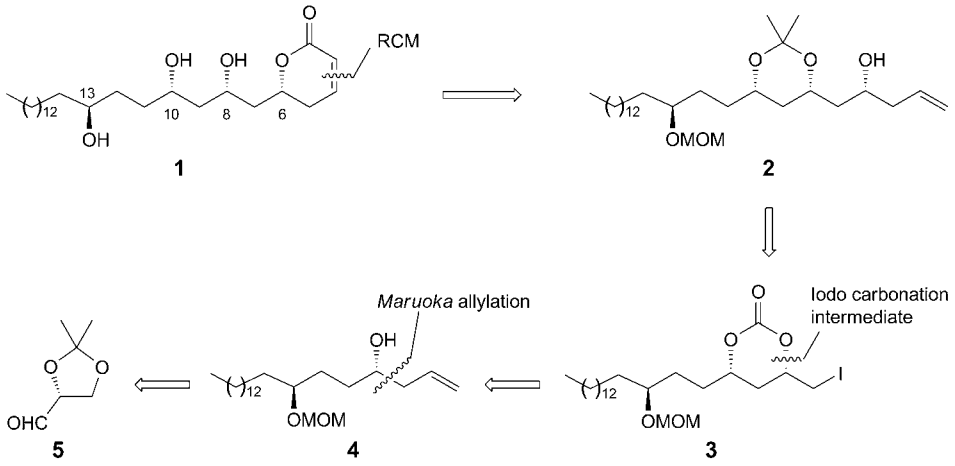
Due to the interesting structure and important biological properties, the synthesis of passifloricin A (**1**) has been an attractive target for the organic chemists [4a][5][6]. In continuation of our work [7] on bioactive natural products, here we report an attractive and efficient new synthesis of compound **1** in a stereoselective manner.

Results and Discussion. – The retrosynthetic analysis (*Scheme 1*) indicates that passifloricin A (**1**) can be synthesized from the homoallylic alcohol **2** [6c], which can be prepared from the iodo-carbonate **3**. The latter can be obtained from another homoallylic alcohol **4**, generated from the protected glyceraldehyde **5**.

[1]) Part 63 in the series, 'Synthetic Studies on Natural Products'.

Scheme 1. *Retrosynthetic Pathway for Passifloricin A* (**1**)



The present synthesis of passifloricin A (**1**) started from (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**5**; *Scheme 2*), which was reacted with 1-bromotetradecane in the presence of Mg to afford a mixture of diastereoisomeric alcohols **6a** and **6b**. The reaction was carried out under different conditions to increase the yield of the desired alcohol **6a** (*Table*). When the reaction was conducted in THF at 70° for 8 h, the total yield was 94%, favoring the *anti*-isomer (*anti*/*syn* 89:11), was separated chromatographically for the next step.

Scheme 2

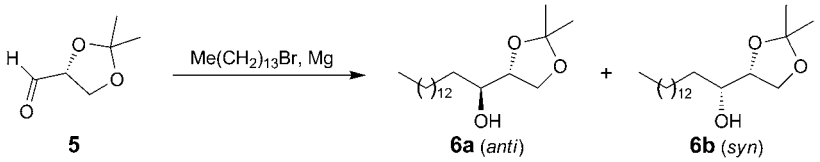
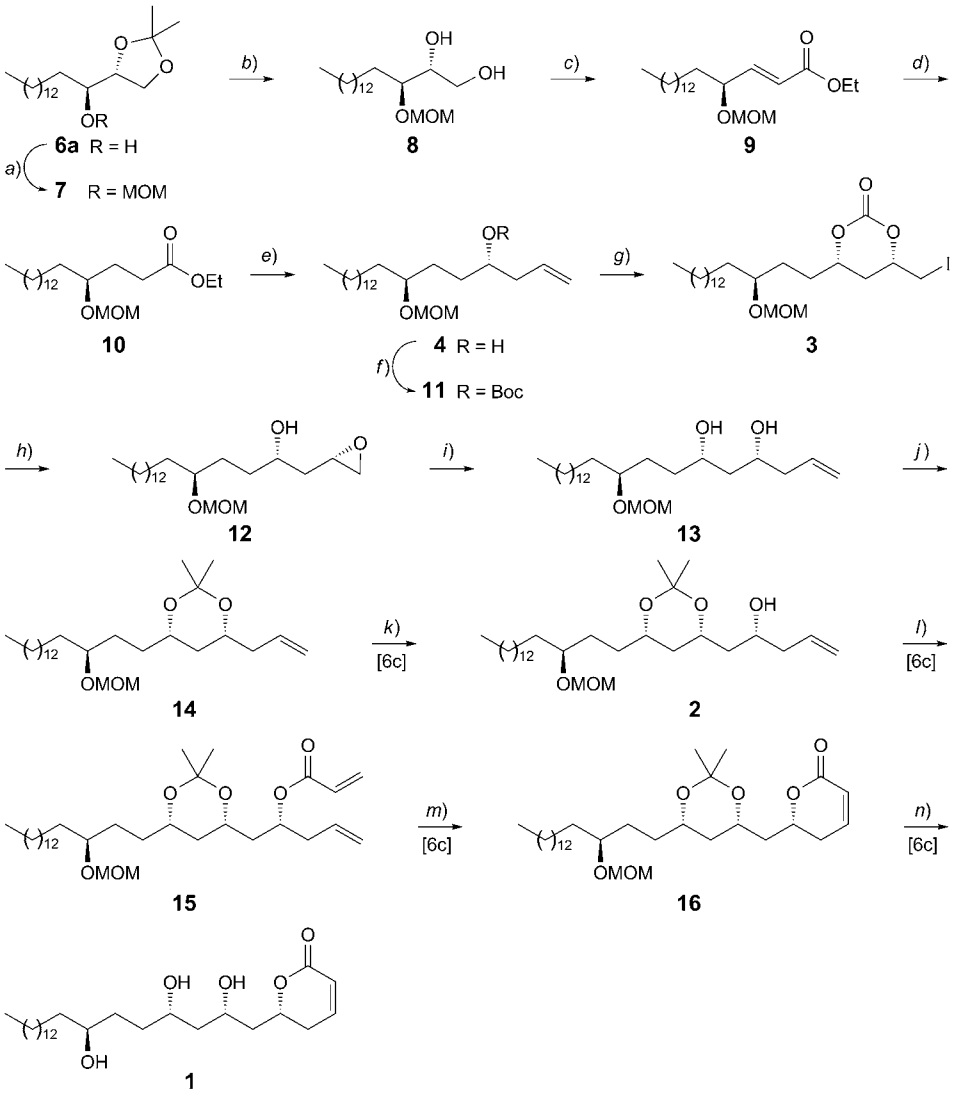


Table. *Reaction Conditions for the Synthesis of* **6a**/**6b** (*anti*/*syn*)

Solvent	Temp. [°]	Time [h]	Yield [%]	*syn*/*anti*
THF	70	8	94	11:89
THF	r.t.	24	74	32:68
Et_2O	r.t.	24	78	37:63

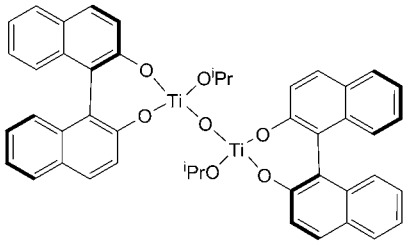
The alcohol **6a** was reacted with MOMCl in the presence of EtN^iPr_2 to give the corresponding MOM-protected alcohol **7** (*Scheme 3*). Acetonide deprotection of **7** with PPTS in MeOH yielded the diol **8**, which was then treated with $NaIO_4$, and the resulting aldehyde underwent *Wittig* homologation with $Ph_3PCHCOOEt$ to furnish the α,β-unsaturated ester **9**. Reduction of **9** with $NiCl_2/NaBH_4$ in MeOH afforded the saturated ester **10**. Further reduction of the latter with DIBAL-H in dry CH_2Cl_2 gave the corresponding aldehyde, which directly underwent the *Maruoka* asymmetric

Scheme 3

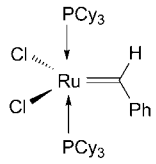


a) Methoxymethyl chloride (MOMCl), EtN^iPr_2, CH_2Cl_2, 0° – r.t., 6 h; 92%. *b*) Pyridinium *p*-toluenesulfonate (PPTS), MeOH, 0° – r.t., 8 h; 89%. *c*) 1. $NaIO_4$, $NaHCO_3$, CH_2Cl_2, 0°, 10 h; 91%; 2. $Ph_3PCHCOOEt$, CH_2Cl_2, r.t., 5 h; 87%. *d*) $NiCl_2 \cdot 6\,H_2O$, $NaBH_4$, MeOH, 0° – r.t., 30 min; 96%. *e*) 1. Diisobutylaluminium hydride (DIBAL-H), CH_2Cl_2, – 78°, 2 h; 79%. 2. **A** (10 mol-%), allyl(tributyl)-stannane, 4-Å molecular sieves (MS), CH_2Cl_2, 0°, 25 h; 81%. *f*) Di(*tert*-butyl) dicarbonate ($(Boc)_2O$), Et_3N, 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 0° – r.t., 4 h; 93%. *g*) *N*-Iodosuccinimide (NIS), MeCN, – 20°, 2 h; 81%. *h*) K_2CO_3, MeOH, 0° – r.t., 5 h; 91%. *i*) CH_2=CHMgBr, CuI, THF, – 20° – r.t., 3 h; 79%. *j*) 2,2-Dimethoxypropane (2,2-DMP), PPTS, CH_2Cl_2, 0° – r.t., 8 h; 96%. *k*) 1. OsO_4, *N*-methylmorpholine *N*-oxide (NMO), $NaIO_4$, acetone/H_2O, 0° – r.t., 6 h; 92%; 2. **A** (10 mol-%), allyl(tributyl)stannane, 4-Å MS, CH_2Cl_2, 0°, 21 h; 69%. *l*) CH_2=CHC(O)Cl, EtN^iPr_2, CH_2Cl_2, 0° – r.t., 6 h; 94%. *m*) *Grubbs*' 1st generation catalyst **B** (10 mol-%), CH_2Cl_2, reflux, 10 h; 71%. *n*) 4N HCl, THF, r.t., 10 h; 88%.

allylation [4] with allyl(tributyl)stannane in the presence of the Ti complex of (*R*,*R*)-BINOL (=(*R*,*R*)-1,1′-binaphthalene-2,2′-diol), **A**, to yield the chiral allylic alcohol **4** (ee 97% determined by chiral HPLC). The OH group of **4** was protected by using Boc_2O, and the resulting product **11** was subjected to the iodo-carbonate cyclization [8] by treatment with NIS in MeCN. The diastereoselectivity of the reaction was greater than 95% favoring the *syn*-isomer **3**; the other isomer was separated by column chromatography. The iodo-carbonate **3** was then treated with K_2CO_3 in MeOH to give the 1,3-*syn*-epoxy alcohol **12** in high yield [8]. The epoxy moiety was opened with vinyl *Grignard* reagent in the presence of a catalytic amount of CuI in THF to furnish the allylic 1,3-diol **13**. The two OH groups of **13** were protected by using 2,2-dimethoxypropane (2,2-DMP) and PPTS to afford the acetonide **14**. The compound **14** was treated with OsO_4 and NMO in acetone/H_2O and then with $NaIO_4$ to form an aldehyde, which was immediately reacted with allyl(tributyl)stannane and the titanium complex of (*R*,*R*)-BINOL (**A**) to yield the homoallylic alcohol **2**. In analogy to [6c], the alcohol **2** was acrylated with CH_2=CHC(O)Cl and EtN^iPr_2 to afford the unsaturated ester **15**, required for ring-closing metathesis (RCM) [6c][9]. The ring-closing metathesis of **15** was successfully achieved by treatment with *Grubbs*' 1st generation catalyst, **B**, to furnish the lactone **16**. Here, we used another catalyst, **B**, compared with [6c]. The lactone **16** was subsequently treated with 4N HCl in THF, resulting in the cleavage of the MOM-ether and simultaneous deprotection of the acetonide group to afford the trihydroxy lactone **1**, whose physical and spectroscopic properties were identical to those reported for the natural passifloricin A [2].



A



Grubbs' catalyst (1st generation)

B

In conclusion, we have developed an asymmetric total synthesis of the bioactive natural product passifloricin A (**1**) starting from the protected (*R*)-glyceraldehydes **5** by applying *Maruoka* asymmetric allylation, iodo-carbonate cyclization , and *Grubbs*' olefin metathesis reaction as the key steps. The preparation of iodo-carbonate and its conversion to an epoxy alcohol have been employed here for the first time to synthesize this compound. The method can conveniently be applied to the preparation of different analogs of passifloricin A.

The authors thank *CSIR* and *UGC*, New Delhi, for financial support.

Experimental Part

General. All commercially available reagents were used directly without further purification unless otherwise stated. The solvents used were all of anal. grade and were distilled under dry N_2 where necessary. All reactions were performed in pre-dried apparatus unless otherwise stated. The progress of the reactions was monitored by anal. TLC performed on *Merck* silica gel *60 F_{254}* plates. Yields were of purified compounds unless otherwise stated. Column chromatography (CC): silica gel 60–120 mesh (*Qingdao Marine Chemical*, China). Optical rotations: *JASCO DIP 300* digital polarimeter. NMR Spectra: *Gemini 200* MHz spectrometer in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, J in Hz. ESI-MS: *VG-Autospec-micromass* instrument; in m/z. HR-MS: *QSTAR-XL-Hybrid* MS system (*Applied Biosystems*); in m/z.

(αS,4R)-2,2-Dimethyl-α-tetradecyl-1,3-dioxolane-4-methanol (**6a**). To a stirred soln. of $Me(CH_2)_{13}Br$ (10 g, 36.10 mmol) in THF was added Mg (1.3 g, 54.15 mmol), and the temp. was slowly raised to 70°. The mixture was stirred for 8 h. After quenching the reaction with sat. NH_4Cl soln. (15 ml), the mixture was extracted with AcOEt (3 × 30 ml). After evaporation of the solvent, the residue was purified by CC to afford pure **6a** (8.9 g, 75%). Clear yellow liquid. $[\alpha]_D^{20} = +35.3$ ($c = 0.2$, $CHCl_3$). IR: 3368, 1464, 1375, 1215. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.96–3.80 (*m*, 3 H); 3.66–3.72 (*m*, 1 H); 3.91 (br. *s*, 1 H); 1.38–1.19 (*m*, 32 H); 0.87 (*t*, $J = 7.0$, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 108.9; 79.0; 70.8; 64.6; 32.9; 32.0; 29.8; 29.5; 27.9; 26.6; 25.8; 25.2; 22.8; 14.2. ESI-MS: 351 ($[M + Na]^+$).

(4R)-4-[(1S)-1-(Methoxymethoxy)pentadecyl]-2,2-dimethyl-1,3-dioxolane (**7**). To a soln. of **6a** (9.5 g, 28.96 mmol) in anh. CH_2Cl_2 (10 ml) at 0° under N_2 was added EtN^iPr_2 (4.17 g, 31.85 mmol) dropwise, and after 5 min MOMCl (2.63 ml, 34.75 mmol) was added dropwise. The mixture was stirred at r.t. for 6 h. After quenching the reaction with sat. NH_4Cl soln. and brine, the mixture was extracted with CH_2Cl_2 (3 × 30 ml). After evaporation of the solvent, the residue was purified by CC to afford pure **7** (9.9 g, 92%). Clear liquid. $[\alpha]_D^{20} = +9.5$ ($c = 0.2$, $CHCl_3$). IR: 1462, 1374, 1264, 1215, 1155, 1036. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.69 (*d*, $J = 12.0$, 1 H); 4.61 (*d*, $J = 12.0$, 1 H); 4.02–3.94 (*m*, 2 H); 3.79–3.84 (*m*, 1 H); 3.57–3.63 (*m*, 1 H); 3.34 (*s*, 3 H); 1.53–1.45 (*m*, 2 H); 1.38–1.21 (*m*, 30 H,); 0.87 (*t*, $J = 7.0$, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 109.0; 96.2; 78.9; 77.7; 66.2; 55.8; 32.1; 31.8; 29.9; 29.7; 26.9; 25.5; 25.0; 23.8; 14.2. ESI-MS: 395 ($[M + Na]^+$).

(2R,3S)-3-(Methoxymethoxy)heptadecane-1,2-diol (**8**). To a stirred soln. of **7** (7.0 g, 18.8 mmol) in MeOH (30 ml) at 0° was added a cat. amount of PPTS. The mixture was stirred at r.t. for 8 h. After quenching the reaction with solid $NaHCO_3$ under ice cooling and evaporation of the solvent, the residue was purified by CC to afford pure **8** (5.55 g, 89%). Liquid. $[\alpha]_D^{20} = +8.7$ ($c = 0.4$, $CHCl_3$). IR: 3421, 1463, 1213, 1100, 1033. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.72 (*d*, $J = 12.0$, 1 H); 4.64 (*d*, $J = 12.0$, 1 H); 3.71–3.65 (*m*, 2 H); 3.62–3.57 (*m*, 2 H); 3.44 (*s*, 3 H); 3.32 (br. *s*, 1 H); 2.71 (br. *s*, 1 H); 1.61–1.43 (*m*, 2 H); 1.30 (br. *s*, 24 H); 0.90 (*t*, $J = 7.0$, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 98.0; 83.2; 73.1; 63.0; 56.0; 32.2; 31.8; 29.9; 29.2; 25.9; 22.9; 14.2. ESI-MS: 355 ($[M + Na]^+$).

Ethyl (2E,4S)-4-(Methoxymethoxy)octadec-2-enoate (**9**). To a stirred soln. of **8** (5.4 g, 16.26 mmol) in dry CH_2Cl_2 (20 ml) at 0°, aq. $NaHCO_3$ soln. (2.5 ml) was added, followed by careful addition of $NaIO_4$ (8.74 g, 40.66 mmol). The mixture was allowed to reach slowly r.t., and stirred for 10 h. After quenching the reaction with Na_2SO_4 (2.0 g), the mixture was stirred vigorously for 30 min and then filtered through sintered funnel with CH_2Cl_2 (2 × 50 ml). The combined org. extracts were washed with brine (30 ml), dried (Na_2SO_4), and concentrated under reduced pressure, the residue was purified by CC (AcOEt/hexane 1:9) to afford pure aldehyde (4.43 g, 91%). Liquid.

To a stirred soln. of the aldehyde (4.43 g, 14.76 mmol) in CH_2Cl_2 was added $Ph_3PCHCOOEt$ (6.16 g, 17.72 mmol). The mixture was stirred at r.t. for 5 h. After quenching the reaction with ice, the mixture was extracted with CH_2Cl_2 (3 × 20 ml). After evaporation of the solvent, the residue was purified by CC to afford pure **9** (4.75 g, 87%) as a clear liquid. $[\alpha]_D^{20} = -90.6$ ($c = 0.4$, $CHCl_3$). IR: 1724, 1657, 1463, 1161. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.75 (*dd*, $J = 16$, 8.0,1 H); 5.92 (*d*, $J = 16.0$, 1 H); 4.61 (*d*, $J = 12.0$, 1 H); 4.52 (*d*, $J = 12.0$, 1 H); 4.22–4.11 (*m*, 3 H); 3.34 (*s*, 3 H); 1.62–1.50 (*m*, 2 H); 1.34–1.18 (*m*, 27 H); 0.89 (*t*, $J = 7.0$, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 173.5; 148.2; 122.0; 96.4; 75.1; 60.2; 55.9; 35.2; 32.0; 29.9; 29.8; 25.3; 22.8; 14.2. ESI-MS: 393 ($[M + Na]^+$).

Ethyl (4S)-4-(Methoxymethoxy)octadecanoate (**10**). To a stirred soln. of **9** (4.5 g, 12.16 mmol) in dry MeOH (30 ml) under N_2 at 0°, $NiCl_2 \cdot 6\,H_2O$ (0.575 g, 2.43 mmol) was added. After stirring for 5 min, $NaBH_4$ (0.899 g, 24.32 mmol) was added slowly (intermittently), and the mixture was stirred for 30 min. After quenching the reaction with sat. NH_4Cl soln. (5 ml), the mixture was extracted with AcOEt (3 × 10 ml). The combined org. extracts were dried (Na_2SO_4). After evaporation of the solvent, the residue was purified by CC using AcOEt/hexane to afford pure **10** (4.33 g, 96%). Liquid. $[\alpha]_D^{20} = +19.2$ ($c = 0.4$, $CHCl_3$). IR: 1738, 1463, 1250, 1152. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.59 (*s*, 2 H); 4.11 (*q*, *J* = 7.0, 2 H); 3.46–3.59 (*m*, 1 H); 3.34 (*s*, 3 H); 2.35 (*t*, *J* = 7.0, 2 H); 1.91–1.79 (*m*, 1 H); 1.79–1.69 (*m*, 1 H); 1.53–1.40 (*m*, 2 H); 1.34–1.16 (*m*, 27 H); 0.89 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 173.3; 96.5; 76.0; 60.3; 55.7; 34.1; 31.9; 30.2; 29.8; 29.2; 25.3; 22.2; 14.2; 14.0. ESI-MS: 395 ($[M + Na]^+$).

(4S,7S)-7-(Methoxymethoxy)henicos-1-en-4-ol (**4**). To a stirred soln. of **10** (4.3 g, 11.55 mmol) in dry CH_2Cl_2 (20 ml) at −78°, DIBAL-H (1.0M, 13.87 ml, 13.87 mmol) was added dropwise, and the mixture was stirred at r.t. for 2 h. After quenching the reaction by slow addition of dry MeOH (10 ml), the mixture was allowed to reach r.t. Sat. sodium potassium tartrate (10 ml) was added and stirred for 1 h. Then, the mixture was diluted with H_2O (10 ml) and extracted with Et_2O (2 × 50 ml). The org. layer was separated and dried (Na_2SO_4), and concentrated *in vacuo*. The crude aldehyde (2.99 g, 79%) thus obtained was used further without purification.

To a stirred soln. of $TiCl_4$ (0.097 ml, 0.91 mmol) in CH_2Cl_2 (6 ml) was added dried $Ti(O^iPr)_4$ (774 mg, 2.73 mmol) at 0° under N_2, and the mixture was allowed to warm to r.t. After 1 h, Ag_2O (506 mg, 2.18 mmol) was added at the same temp., and the mixture was stirred for 5 h under exclusion of direct light. The mixture was diluted with CH_2Cl_2 (10 ml) and treated with (*R*,*R*)-BINOL (1.24 g, 4.37 mmol) at r.t. for 2 h to furnish chiral bis-Ti^{IV} oxide **A**. The *in situ* generated **A** was cooled to −15°, and treated sequentially with the aldehyde (2.99 g, 9.11 mmol) and allyl(tributyl)stannane (3.35 ml, 10.93 mmol) at the same temp. The mixture was allowed to warm to 0° and stirred for 25 h. After quenching the reaction with sat. aq. $NaHCO_3$ (25 ml), the mixture was extracted with Et_2O (3 × 30 ml). The org. extracts were dried (Na_2SO_4). After evaporation of solvent, the residue was purified by CC (petroleum ether/AcOEt 7:3) to afford pure **4** (2.73 g, 81% yield). Liquid. $[\alpha]_D^{20} = +7.5$ ($c = 0.2$, $CHCl_3$). IR: 3447, 1640, 1459, 1147. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.71–5.84 (*m*, 1 H); 5.18–5.07 (*m*, 2 H); 4.61 (*s*, 2 H); 3.68–3.50 (*m*, 2 H); 3.35 (*m*, 2 H); 2.30–2.10 (*m*, 2 H); 1.65–1.42 (*m*, 4 H); 1.29 (br. *s*, 28 H), 0.88 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 134.9; 118.0; 95.5; 77.4; 71.1; 55.9; 42.1; 34.5; 32.2; 30.0; 29.9; 29.8; 28.0; 25.4; 22.8; 14.2. ESI-MS: 393 ($[M + Na]^+$).

1,1-Dimethylethyl (4S,7S)-7-(Methoxymethoxy)henicos-1-en-4-yl Carbonate (**11**). Compound **4** (2.6 g, 7.02 mmol) was dissolved in 15 ml of dry CH_2Cl_2, and the mixture was stirred at 0°. $(Boc)_2O$ (2.41 ml, 10.54 mmol) was added, followed by addition of 1.27 ml (9.12 mmol) of Et_3N and 85 mg (0.70 mmol) of DMAP. The mixture was stirred from 0° to r.t. for 4 h and then extracted with CH_2Cl_2 (2 × 15 ml). The combined org. layers were dried (Na_2SO_4) and concentrated *in vacuo*. After evaporation of the solvent, the residue was purified by CC to afford pure **11** (3.07 g, 93%). Liquid. $[\alpha]_D^{20} = +5.5$ ($c = 0.2$, $CHCl_3$). IR: 1738, 1461, 1367, 1279, 1166, 1040. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.69–5.84 (*m*, 1 H); 5.12–5.03 (*m*, 2 H); 4.65 (*s*, 1 H); 4.57 (*s*, 2 H); 3.42–3.55 (*m*, 1 H); 3.32 (*s*, 3 H); 2.33 (*t*, *J* = 7.0, 2 H); 1.68–1.42 (*m*, 15 H); 1.29 (br. *s*, 24 H); 0.89 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 153.1; 134.0; 118.1; 95.2; 81.6; 77.4; 55.7; 39.1; 34.5; 31.9; 30.0; 29.9; 29.7; 27.8; 25.2; 23.0; 14.2. ESI-MS: 493 ($[M + Na]^+$).

(4S,6S)-4-(Iodomethyl)-6-[(3S)-3-(methoxymethoxy)heptadecyl]-1,3-dioxan-2-one (**3**). To a stirred soln. of **11** (2.9 g, 6.17 mmol) in dry MeCN (15 ml) under N_2 at −20° was added NIS (5.55 g, 24.68 mmol), and the temp. was raised to 0°. The mixture was stirred for 2 h. After quenching the reaction with $Na_2S_2O_3$ (15 ml), the mixture was extracted with AcOEt (3 × 20 ml) and H_2O (15 ml). The org. layer were dried (Na_2SO_4) and concentrated *in vacuo*. After evaporation of the solvent, the residue purified by CC to afford pure **3** (2.69 g, 81%). Light-yellow liquid. $[\alpha]_D^{20} = +64.5$ ($c = 0.4$, $CHCl_3$). IR: 1712, 1463, 1382, 1125, 1027. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.61 (*d*, *J* = 12.0, 1 H); 4.58 (*d*, *J* = 12.0, 1 H); 4.52–4.40 (*m*, 2 H); 3.46–3.58 (*m*, 1 H); 3.36–3.45 (*m*, 1 H); 3.34 (*s*, 3 H); 3.24–3.33 (*m*, 1 H); 1.82–1.60 (*m*, 3 H); 1.46–1.59 (*m*, 1 H); 1.25 (br. *s*, 28 H); 0.88 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 150.8; 96.2; 76.9; 76.0; 72.1; 55.2; 37.9; 33.1; 32.5; 30.0; 29.9; 28.6; 25.9; 23.0; 14.2; 7.8. ESI-MS: 551 ($[M + Na]^+$).

(αS,2S)-α-[(3S)-3-(Methoxymethoxy)heptadecyl]oxirane-2-ethanol (**12**). K_2CO_3 (1.91 g, 13.86 mmol) was added to a soln. of **3** (2.5 g, 4.62 mmol) in anh. MeOH (15 ml) at r.t., and the resulting mixture was stirred for 5 h. Then, the mixture was diluted with Et_2O (15 ml), and the reaction was quenched with a mixture of $Na_2S_2O_3$/sat. aq. $NaHCO_3$ 1:1. The aq. phase was extracted with Et_2O (3 × 30 ml), and the org. extracts were washed with brine, dried (Na_2SO_4), and then concentrated. After evaporation of the solvent, the residue was purified by CC to afford pure **12** (1.61 g, 91%). Yellow liquid. $[\alpha]_D^{20} = +9.4$ ($c = 0.4$, $CHCl_3$). IR: 3374, 1465, 1374, 1245, 1033. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.62 (*s*, 2 H); 3.83 (br. *s*, 1 H); 3.48–3.59 (*m*, 1 H); 3.37 (*s*, 3 H); 3.18–3.26 (*m*, 1 H); 3.0–3.80 (*m*, 1 H); 2.69–2.75 (*m*, 1 H); 2.47 (*m*, 1 H); 1.82–1.63 (*m*, 2 H); 1.62–1.41 (*m*, 6 H); 1.28 (br. *s*, 24 H); 0.90 (*t*, $J = 7.0$, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 96.2; 75.5; 2.8; 55.8; 50.9; 47.8; 42.0; 34.5; 32.0; 30.2; 29.3; 25.2; 22.5; 14.2. ESI-MS: 409 ($[M + Na]^+$).

(4R,6S,9S)-9-(Methoxymethoxy)tricos-1-ene-4,6-diol (**13**). To a soln. of **12** (1.55 g, 4.01 mmol) in dry THF (10 ml) under N_2, a cat. amount of CuI was added, and the resulting mixture was stirred at 25° for 30 min. It was cooled to −20°, CH_2=CHMgBr (2.68 ml, 1.0M in THF) was slowly added, and stirring was continued at the same temp. for 30 min. The mixture was slowly warmed to r.t. After 3 h (monitored by TLC), the reaction was quenched with sat. NH_4Cl soln. (15 ml), and the mixture was diluted with AcOEt (20 ml). The org. layer was separated, and the aq. layer was extracted with AcOEt (3 × 15 ml). The combined org. layer was washed with brine (2 × 15 ml), dried (Na_2SO_4), and concentrated under reduced pressure to afford the crude product which, by CC (hexane/AcOEt 5:5) furnished **13** (1.31 g, 79%). Liquid. $[\alpha]_D^{20} = +11.6$ ($c = 0.2$, $CHCl_3$). IR: 3362, 1546, 1472, 1275, 1063. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.80 (*m*, 1 H); 5.18–5.07 (*m*, 2 H); 4.62 (*s*, 2 H); 3.91–3.77 (*m*, 2 H); 3.51–3.59 (*m*, 1 H); 3.37 (*s*, 3 H); 2.22 (*t*, $J = 7.0$, 2 H); 1.68–1.40 (*m*, 8 H); 1.23 (br. *s*, 24 H); 0.89 (*t*, $J = 7.0$, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 144.6; 135.0; 118.7; 95.4; 79.6; 76.4; 72.5; 55.4; 42.5; 42.0; 34.6; 31.9; 31.2; 29.6; 25.4; 22.6; 14.4. ESI-MS: 437 ($[M + Na]^+$).

(4S,6R)-4-[(3S)-3-(Methoxymethoxy)heptadecyl]-2,2-dimethyl-6-(prop-2-en-1-yl)-1,3-dioxane (**14**). Compound **13** (1.25 g, 3.01 mmol) was dissolved in 10 ml of dry CH_2Cl_2 at 0°, and cat. amount of PPTS and 2,2-DMP (0.74 ml, 6.03 mmol) were added. The mixture was stirred from 0° to r.t. for 8 h. After quenching the reaction with ice, the mixture was extracted with CH_2Cl_2 (2 × 15 ml). The combined org. layers were dried (Na_2SO_4) and concentrated *in vacuo*. After evaporation of the solvent, the residue was purified by CC (petroleum ether/AcOEt 9:1) to afford pure **14** (1.31 g, 96%). Liquid. $[\alpha]_D^{20} = +8.4$ ($c = 0.2$, $CHCl_3$). IR: 1638, 1462, 1379, 1257, 1040. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.72–5.81 (*m*, 1 H); 5.10–4.98 (*m*, 2 H); 4.59 (*s*, 2 H); 3.84–3.68 (*m*, 2 H); 3.46–3.54 (*m*, 1 H); 3.34 (*s*, 3 H); 2.28 (*m*, 1 H); 2.08–2.14 (*m*, 1 H); 1.54–1.20 (*m*, 38 H); 0.88 (*t*, $J = 7.0$, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 134.0; 117.2; 98.8; 96.2; 77.3; 69.2; 69.0; 55.5; 41.1; 36.8; 34.5; 32.0; 30.2; 30.0; 29.7; 25.8; 23.0. ESI-MS: 477 ($[M + Na]^+$).

(αR,4R,6S)-6-[(3S)-3-(Methoxymethoxy)heptadecyl]-2,2-dimethyl-α-prop-2-en-1-yl-1,3-dioxane-4-ethanol (**2**). To a stirred soln. of **14** (1.3 g, 2.86 mmol) in aq. acetone (10 ml) was added NMO (1.0 g, 8.59 mmol), followed by OsO_4 (2.5 wt% in ^{i}BuOH) and $NaIO_4$ (1.22 g, 5.72 mmol). The mixture was stirred for 6 h. After quenching the reaction with sat. $NaHSO_3$ (5 ml), the mixture was stirred for 30 min and then filtered through sintered funnel with CH_2Cl_2 (2 × 30 ml). The org. extracts were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. After evaporation of the solvent, the residue was purified by CC (AcOEt/hexane) to afford an aldehyde (1.2 g, 92%) as a liquid.

To a stirred soln. of $TiCl_4$ (48 mg, 0.263 mmol) in CH_2Cl_2 (3 ml) was added dried $Ti(O^iPr)_4$ (224 mg, 0.789 mmol) at 0° under N_2, and the mixture was allowed to warm to r.t. After 1 h, Ag_2O (121 mg, 0.526 mmol) was added at r.t., and the mixture was stirred for 5 h under exclusion of direct light. The mixture was diluted with CH_2Cl_2 (6 ml), and treated with (*R,R*)-BINOL (298 mg, 1.05 mmol) at r.t. for 2 h to furnish chiral bis-Ti^{IV} oxide **A**. The *in situ* generated **A** was cooled to −15° and treated sequentially with the aldehyde (1.2 g, 2.63 mmol) and allyl(tributyl)stannane (0.96 ml, 3.15 mmol) at 15°. The mixture was allowed to warm to 0° and stirred for 21 h. The reaction was quenched with sat. aq. $NaHCO_3$ (20 ml), and the mixture was extracted with Et_2O (3 × 20 ml). The org. extracts were dried (Na_2SO_4). After evaporation of solvent, the residue was purified by CC (petroleum ether/AcOEt 8:2) gave **2** (904 mg, 69% yield). Liquid. $[\alpha]_D^{20} = +8.6$ ($c = 0.4$, $CHCl_3$). IR: 3447, 1640, 1459, 1147, 1039. ^{1}H-NMR (200 MHz, $CDCl_3$): 5.76–5.85 (*m*, 1 H); 5.18–5.04 (*m*, 2 H); 4.11 (br. *s*, 1 H); 3.90–3.67 (*m*, 2 H); 3.58–3.47 (*m*,

2 H); 3.36 (*s*, 3 H); 2.35–2.12 (*m*, 2 H); 1.61–1.18 (*m*, 42 H); 0.88 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 135.1; 117.3; 98.8; 96.8; 77.2; 71.1; 70.3; 69.2; 42.2; 37.4; 34.4; 32.1; 30.0; 29.8; 29.6; 25.1; 22.5; 14.0. ESI-MS: 521 ($[M+Na]^+$).

*(1*R*)-1-({(4*S*,6*S*)-6-[(3*S*)-3-(Methoxymethoxy)heptadecyl]-2,2-dimethyl-1,3-dioxan-4-yl}methyl)-but-3-en-1-yl Prop-2-enoate* (**15**). CH_2=CHC(O)Cl (188 mg 2.08 mmol) was added dropwise under N_2 to a soln. of **2** (0.80 g, 1.60 mmol), and EtN^iPr_2 (0.33 ml, 1.92 mmol) in dry CH_2Cl_2 (8 ml) at 0°. The mixture was stirred for 6 h at r.t. The reaction was quenched with sat. aq. NH_4Cl (10 ml) and org. layer was separated. The aq. layer was extracted with CH_2Cl_2 (3 × 15 ml), and the combined org. layer was washed with brine (20 ml), dried (Na_2SO_4), and concentrated. After evaporation of the solvent, the residue was purified by CC (petroleum hexane/AcOEt 8:2) to afford **15** (0.83 g, 94% yield). $[\alpha]_D^{20} = +7.2$ (*c* = 0.4, $CHCl_3$). IR: 1725, 1640, 1459, 1147, 1039. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.46 (*dd*, *J* = 16.0, 2.0, 1 H); 6.15–6.02 (*m*, 2 H); 5.79–5.86 (*m*, 1 H); 5.16–5.03 (*m*, 3 H); 4.64 (*s*, 2 H); 3.90–3.72 (*m*, 2 H); 3.48–3.56 (*m*, 1 H); 3.34 (*s*, 3 H); 2.34–2.15 (*m*, 2 H); 1.62–1.11 (*m*, 40 H); 0.82 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 166.2; 134.4; 128.9; 128.0; 118.1; 99.7; 97.2; 77.2; 71.0; 70.2; 68.6; 55.8; 42.0; 39.1; 37.3; 34.1; 32.0; 30.1; 29.9; 29.2; 22.8; 20.2; 14.0. ESI-MS: 553 ($[M+Na]^+$).

*(6*R*)-5,6-Dihydro-6-[(2*S*,4*S*,7*S*)-2,4,7-trihydroxyhenicosyl]-2*H*-pyran-2-one* (**1**). A flame-dried round-bottomed flask was charged with **15** (0.60 g, 1.13 mmol) in CH_2Cl_2 (40 ml), and *Grubbs*' catalyst **B** (1st generation, 93 mg, 0.11 mmol) was added as a solid. The mixture was heated at reflux for 10 h at r.t. After completion of the reaction (by TLC), the mixture was concentrated *in vacuo* to provide a residue, which was purified by CC (petroleum hexane/AcOEt 7:3) to give **16** (0.40 g, 71% yield).

To a soln. of **16** (0.40 g, 0.79 mmol) in THF (10 ml) was added aq. HCl (4N, 10 ml). The resulting mixture was stirred 10 h at r.t., and then solid $NaHCO_3$ was added. The mixture was filtered through a pad of *Celite* and washed with AcOEt (25 ml). The filtrate was dried (Na_2SO_4) and concentrated. The product was purified by CC ($CHCl_3$/MeOH 8:2) to afford **1** (0.29 g, 88% yield). Liquid. $[\alpha]_D^{20} = +31.2$ (*c* = 0.4, $CHCl_3$). IR: 3357, 1719, 1605, 1421, 1251. ^{1}H-NMR (200 MHz, $CDCl_3$): 6.89–6.97 (*m*, 1 H); 6.02 (*d*, *J* = 10.0, 1 H); 4.68–4.75 (*m*, 1 H); 4.11–4.19 (*m*, 1 H); 3.96–4.04 (*m*, 1 H); 3.64–3.73 (*m*, 1 H); 2.49–2.41 (*m*, 2 H); 1.99–2.08 (*m*, 1 H); 1.76–1.85 (*m*, 1 H); 1.70–1.42 (*m*, 8 H); 1.28 (br. *s*, 24 H); 0.89 (*t*, *J* = 7.0, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 164.8; 145.5; 121.4; 75.0; 72.6; 71.8; 63.4; 43.2; 37.4; 34.1; 32.8; 32.2; 30.0; 29.9; 29.6; 25.9; 22.8; 14.4. ESI-MS: 463 ($[M+Na]^+$).

REFERENCES

[1] S. D. Rychnovsky, *Chem. Rev.* **1995**, *95*, 2021; L. D. Juliawaty, M. Kitajima, H. Takayama, S. A. Achmad, N. Aimi, *Phytochemistry* **2000**, *54*, 989; S. Hagen, J. V. N. V. Prasad, B. D. Tait, *Adv. Med. Chem.* **2000**, *5*, 159; J. Jodynis-Liebert, M. Murias, E. Błoszyk, *Planta Med.* **2000**, *66*, 199; R. Pereda-Miranda, M. Fragoso-Serrano, C. M. Cerda-García-Rojas, *Tetrahedron* **2001**, *57*, 47; J. Murga, E. Falomir, J. García-Fortanet, M. Carda, J. A. Marco, *Org. Lett.* **2002**, *4*, 3447; D. M. Boalino, J. D. Connolly, S. McLean, W. F. Reynolds, W. F. Tinto, *Phytochemistry* **2003**, *64*, 1303; S. H. Inayat-Hussain, B. O. Annuar, L. B. Din, A. M. Ali, D. Ross, *Toxicol. in Vitro* **2003**, *17*, 433; T. Grkovic, J. S. Blees, N. H. Colburn, T. Schmid, C. L. Thomas, C. J. Henrich, J. B. McMohan, K. R. Gustafson, *J. Nat. Prod*. **2010**, *74*, 1015.

[2] F. Echeverri, V. Arango, W. Quiñones, F. Torres, G. Escobar, Y. Rosero, R. Archbold, *Phytochemistry* **2001**, *56*, 881.

[3] W. G Cardona, W. F. Quinones, F. L. Echeverri, *Molecules* **2004**, *9*, 666; C. G. Wilson, S. V. Jairo, *Trop. J. Pharm. Res.* **2011**, *10*, 671.

[4] a) J. Murga, J. Garcia-Fortanet, M. Carda, J. A. Marco, *Tetrahedron Lett.* **2003**, *44*, 7909; b) J. Garcia-Fortanet, J. Murga, M. Carda, J. A. Marco, *Org. Lett.* **2003**, *5*, 1447; c) J. Cossy, S. BouzBouz, M. Popkin, *Chimie* **2003**, *6*, 547; d) S. BouzBouz, J. Cossy, *Tetrahedron Lett.* **2003**, *44*, 4471.

[5] J. Murga, J. García-Fortanet, M. Carda, J. A. Marco, *J. Org. Chem.* **2004**, *69*, 7277, and refs. cit. therein.

[6] a) S. Chandrasekhar, C. Rambabu, A. S. Reddy, *Tetrahedron Lett.* **2008**, *49*, 4476; b) G. Sabitha, M. N. Prasad, K. Shankaraiah, N. M. Reddy, *Synthesis* **2010**, 3891; c) P. Kumar, M. Pandey, P. Gupta, D. D. Dhavale, *Org. Biomol. Chem*. **2012**, *10*, 1820.

[7] B. Das, D. N. Kumar, *Synlett* **2011**, 1285; G. C. Reddy, P. Balasubramanyam, N. Salvanna, T. S. Reddy, B. Das, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2415; C. Sudhakar, P. R. Reddy, C. G. Kumar, P. Sujitha, B. Das, *Eur. J. Org. Chem*. **2012**, *5*, 1253.

[8] P. A. Bartlett, J. D. Meadows, E. G. Brown, A. Morimoto, K. K. Jernstedt, *J. Org. Chem.* **1982**, *47*, 4013; J. J.-W. Duan, A. B. Smith III, *J. Org. Chem*. **1993**, *58*, 3703; R. E. Taylor, M. Jin, *Org. Lett*. **2003**, *5*, 4959.

[9] R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413; R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117.

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