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Synthesis of Simplified Tedanolide Analogues—Connecting Tedanolide to Myriaporone and Gephyronic Acid

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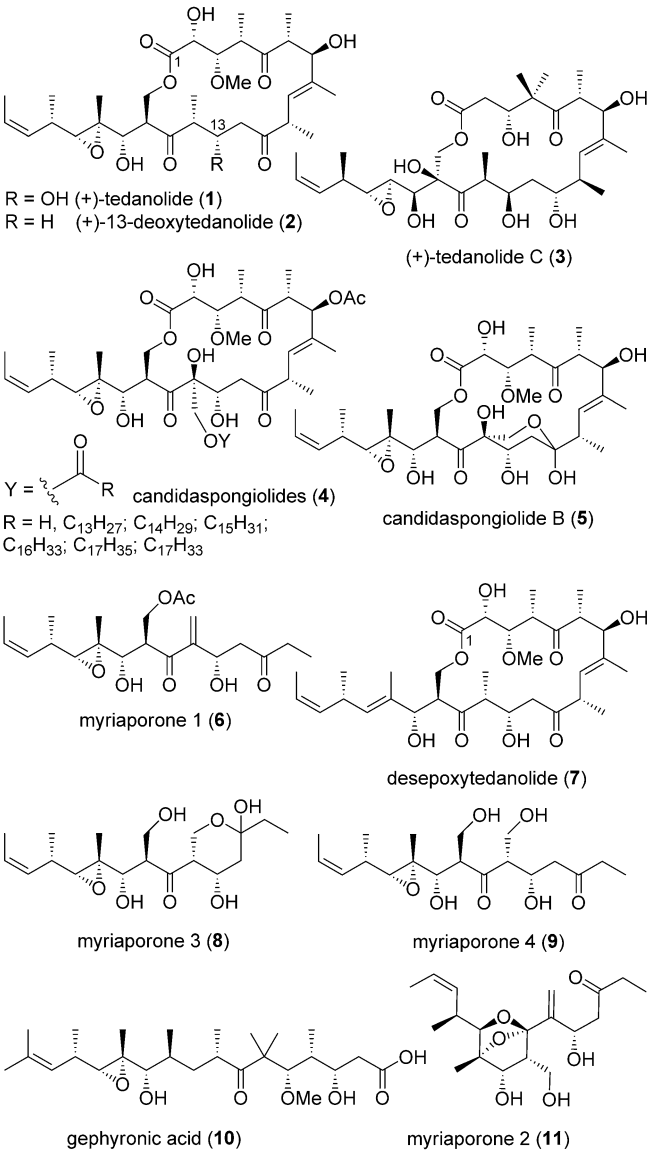
(+)-Tedanolide (**1**) was isolated from the Caribbean sponge *Tedania ignis* by Schmitz et al. in 1984,[1] and this natural product was found to be cytotoxic against KB and PS tumor cell lines in the picomolar range. Importantly, compound **1** was shown to increase significantly the lifespan of mice implanted with lymphocytic leukaemia.[1] A congener of **1**, (+)-13-deoxytedanolide (**2**), was discovered later by Fusetani et al.[2] from *Mycale adhaerens*, and it exhibited similar biological activity in inhibiting the growth of P388 tumors.[2] Furthermore, the isolation of additional metabolites, namely tedanolide C (**3**) and the candidaspongiolides (**4**) was reported by Ireland[3] and McKee.[4] Ten years after tedanolide (**1**) was discovered, Rinehart isolated the myriaporones from *Myriapora truncate*.[5]

It was proposed that myriaporones 1 (**6**) and 2 (**11**) are artificial derivatives obtained through the isolation and purification steps used to obtain myriaporones 3/4 (**8**/**9**). Myriaporones 3/4 exist in dynamic equilibrium between the cyclic hemiketal and the open-chain isomer. The promising biological activity (IC_{50} = 100 ng mL^{-1} against L-1210 murine leukemia cells) as well as the similarities of their structure to the C10 to C23 portion of tedanolide (**1**) suggest that the myriaporones are in fact naturally occurring analogues. The myriaporones would then share the same mode of action as tedanolide, and their simpler structure renders them more attractive as drug candidates and serves as a starting point for more readily available potential lead compounds.

Recently, a study established that like tedanolide (**1**), myriaporones 3/4 (**8**/**9**) are potent protein synthesis inhibitors selective for eukaryotes.[6] A similar natural product, gephyronic acid (**10**), was isolated from the cultivation broth of *Archangium gephyra* (strain Ar 3895).[7a] Initial biological analysis revealed selective inhibition of eukaryotic protein synthesis along with a nanomolar cytostatic effect against a range of mammalian cell lines. For example, compound **10** exhibits an IC_{50} value of 10 ng mL^{-1} against human cervix carcinoma (HeLa) and human myelogenous leukemia (K-562) cell lines. These similar structures prompted us to initiate a program to identify simplified analogues along the lines of our synthesis of the southern hemisphere of tedanolide (**1**).



As a consequence of the biological profiles (Table 1) and challenging structures, natural products **1** and **2** have initiated a variety of synthetic studies.[7–10] Thus far, several research groups have investigated the construction of fragments, and the total synthesis of **1** and **2** has been completed by Smith,[8] Roush[9] and Kalesse.[10] More recently, Laschat[7a] and Taylor[7b] reported the structure elucidation and synthesis of gephyronic acid (**10**). Consequently, we initiated a synthesis program to identify simplified tedanolides as potential lead compounds for drug development.

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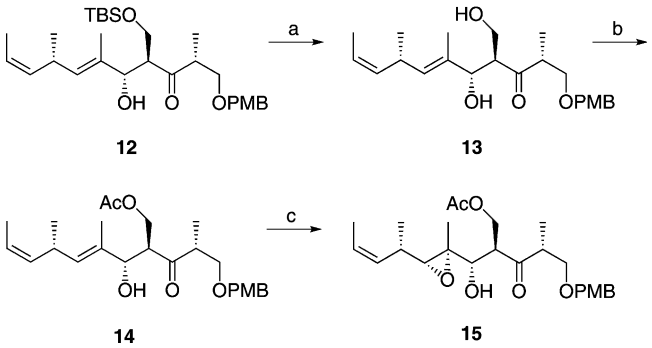
Table 1. Biological activity of tedanolide (**1**) and desepoxytedanolide (**7**).

Compd	Cell line	IC_{50}[a] [nmol mL^{-1}]
1	KB-3-1 (cervix carcinoma)	0.33
1	KB-V1 (mdr KB)	1.64
1	SW-480 (colon cancer)	0.082
1	Primary human fibroblasts	0.15
1	L-929 mouse fibroblasts	0.082
7	L-929 mouse fibroblasts	0.89

[a] Growth inhibitory effects in the given cell lines were measured after five days of incubation using an MTT assay.

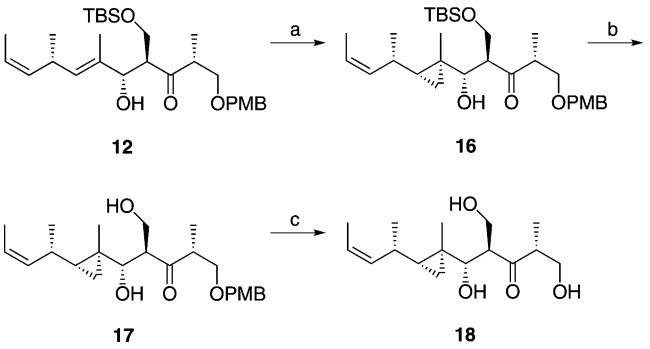
The starting point of our synthetic endeavors was intermediate **12** that serves as a pivotal building block during our total synthesis of tedanolide. Our rational was to incorporate the appropriate functionalities to substitute for the missing elements of the macrocyclic lactone. In particular, those were an acetate group at the primary hydroxy group to compensate for the lactone moiety, and the *p*-methoxybenzyl (PMB) group, which should participate in hydrophobic interactions comparable to the eastern part of tedanolide. Additionally, we planned to probe whether the epoxide would add to the biological activity. Along this line, the first obvious derivatives were compounds **13**–**15**. These compounds were obtained by removal of the *tert*-butyldimethylsilyl (TBS) protecting group, subsequent acylation of the primary alcohol, and finally Henbest epoxidation (Scheme 1).



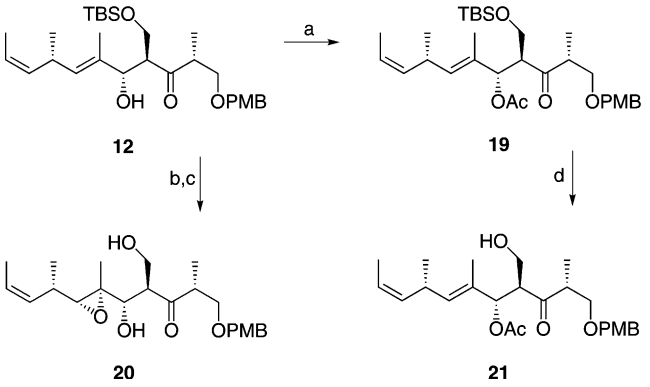
Scheme 1. Synthesis of derivatives **13**, **14** and **15**. *Reagents and conditions*: a) Pyridine, HF–pyridine, THF, 95%; b) AcCl, DIPEA, CH_2Cl_2, 80%; c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 44%.

Analogues that exhibit the conformational restriction of epoxides but lack the capability to form hydrogen bonding interactions were derived through cyclopropanation of intermediate **12** and removal of the TBS and PMB groups, respectively (Scheme 2).

Finally, the derivatives positioning the acetyl group at the secondary alcohol instead of the primary hydroxy group and having the epoxide incorporated without any acetyl group present are outlined in Scheme 3. These transformations involved acetylation of intermediate **12**, and its subsequent TBS deprotection or epoxidation followed by TBS removal, respectively (Scheme 3).



Scheme 2. Synthesis of epoxide analogues. *Reagents and conditions*: a) Et_2Zn, CH_2I_2, CH_2Cl_2, −10 °C→RT, 96%; b) Pyridine, HF–pyridine, THF, 40%; c) CAN, CH_3OH/H_2O, 0 °C→RT, 9 h, 26%.

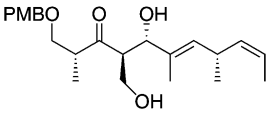
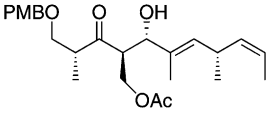
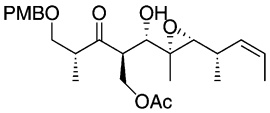
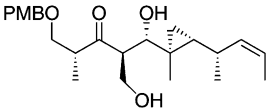
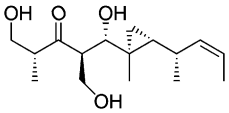
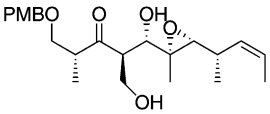
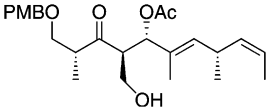


Scheme 3. Synthesis of derivatives **20** and **21**. *Reagents and conditions*: a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, RT, 2.5 h, 62%; b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, −78 °C→−40 °C, 16 h, 41%; c) pyridine, HF–pyridine, THF, 0 °C, 30 min, 73%; d) pyridine, HF–pyridine, THF, 63%.

When these derivatives were subjected to biological evaluation, it became apparent that acylation at the primary hydroxy group would led to simplified analogues, with IC_{50} values of approximately 7 μg mL^{-1}. Remarkably, acylation at the secondary hydroxy group decreases the biological activity compared with compound **14**. Introduction of the epoxide moiety does not significantly alter the activity. However, cyclopropanation and epoxidation does reduce the biological activity for derivatives that do not exhibit acetylation of the primary hydroxy group (Table 2). Active compound **15** was checked for inhibitory effects on protein synthesis in an in vitro translation assay but was found to be inactive.

In conclusion, these first data on simplified tedanolides show that these biologically active compounds are approximately one order of magnitude less active than desirable for promising drug candidates. However, these data show that the decoration, namely the incorporation of acetyl groups, has a more pronounced effect on the biological activity of these derivatives, while epoxidation has only a little contribution, if at all, to the overall activity. While this might not be true of the parent compound, tedanolide, for the simplified analogues this might be pivotal in order to obtain compounds with activities in the low nanomolar range. These first biological evaluations also showed that simplified analogues can potentially

Table 2. Biological activity of tedanolide, desepoxytedanolide and simplified analogues in mammalian cell lines.[a]

Structure	Compd	IC_{50}[a] [μmol mL^{-1}] KB-3-1	L-929
Tedanolide (**1**)		0.00033	0.000082
Desepoxytedanolide (**7**)		n.d.	0.00089
	**13**	23	41
	**14**	25	16
	**15**	20	17
	**17**	20	49
	**18**	> 140	> 140
	**20**	> 100	> 100
	**21**	46	46

[a] Growth inhibitory effect in KB-3-1 cervix carcinoma cells and L-929 mouse fibroblasts were measured after five days of incubation using an MTT assay. n.d. = not determined.

open up a therapeutic window and help identifying new targets even though the mode of action might be different than for the other members of this family, which act through inhibition of translation. Remarkably, compounds **13** and **17** already exhibit selectivity towards tumor cells. This unexpected result will potentially provide access to a new target and provides a promising starting point for further optimization.

Experimental Section

Chemistry

(2*R*,4*R*,5*S*,6*E*,8*S*,9*Z*)-5-Hydroxy-4-(hydroxymethyl)-1-((4-methoxybenzyl)oxy)-2,6,8-trimethylundeca-6,9-dien-3-one (13): A solution of **12** (78 mg, 0.15 mmol) in THF (8 mL) was treated dropwise at 0 °C with pyridine (8.1 mL, 0.1 mol) and then HF–pyridine (5.26 mL, 70%). The mixture was warmed to RT and stirred for 4 h. The reaction was quenched by addition to saturated aq $NaHCO_3$, the layers were separated, and the aqueous layer was extracted with EtOAc (3×15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography (PE/EtOAc, 3:1) afforded compound **13** as colorless oil (58 mg, 95%): $[\alpha]_D^{23} = +11.0$ ($c = 1.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.19$ (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 5.37–5.31 (m, 1H), 5.30 (dd, $J = 4.9$, 4.0 Hz, 1H), 5.23–5.14 (m, 1H), 4.41 (d, $J = 11.5$ Hz, 1H), 4.38 (d, $J = 11.5$ Hz, 1H), 4.26 (d, $J = 8.6$ Hz, 1H), 3.79 (s, 3H), 3.65–3.55 (m, 2H), 3.49 (dd, $J = 8.7$, 4.5 Hz, 1H), 3.41–3.31 (m, 1H), 3.19–3.09 (m, 2H), 2.55 (br s, 2H), 1.66 (d, $J = 1.3$ Hz, 3H), 1.62 (dd, $J = 6.8$, 1.7 Hz, 3H), 1.01 (d, $J = 3.3$ Hz, 3H), 1.00 ppm (d, $J = 3.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 218.1$, 159.6, 134.8, 133.9, 132.8, 129.6, 129.3, 122.3, 114.0, 76.9, 73.4, 72.9, 62.5, 57.9, 55.4, 47.7, 30.6, 21.4, 13.1, 12.9, 11.5 ppm; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{23}H_{34}O_5Na$: 413.5028, found 413.1573.

(2*R*,3*S*,4*E*,6*S*,7*Z*)-3-Hydroxy-2-((*R*)-3-((4-methoxybenzyl)oxy)-2-methylpropanoyl)-4,6-dimethylnona-4,7-dien-1-yl acetate (14): A solution of compound **13** (57 mg, 0.14 mmol) in CH_2Cl_2 (7 mL) was cooled to −78 °C and treated with DIPEA (46 μL, 0.26 mmol) and acetyl chloride (12.2 μL, 0.17 mmol). The mixture was stirred for 1 h and again DIPEA (46 μL, 0.26 mmol) and acetyl chloride (12.2 μL, 0.17 mmol) were added and stirred for 5 h at −78 °C, and then at −50 °C for 16 h. Water (10 mL) and saturated aq $NaHCO_3$ (10 mL) were added. The mixture was allowed to warm to RT, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The organic layers are combined, dried (Na_2SO_4), filtered and concentrated. Purification by column chromatography on silica gel (PE/EtOAc, 3:1) gave compound **14** as colorless oil (45 mg, 80%): $[\alpha]_D^{23} = +13.2$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.21$ (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 5.34 (dqd, $J = 10.7$, 6.7, 0.9 Hz, 1H), 5.27 (d, $J = 9.0$ Hz, 1H), 5.18 (ddq, $J = 10.8$, 9.2, 1.7 Hz, 1H), 4.44 (d, $J = 11.8$ Hz, 1H), 4.40 (d, $J = 11.7$ Hz, 1H), 4.19 (d, $J = 8.5$ Hz, 1H), 4.03 (qd, $J = 11.3$, 6.8 Hz, 1H), 3.79 (s, 3H), 3.64 (dd, $J = 9.1$, 7.8 Hz, 1H), 3.41–3.30 (m, 2H), 3.27 (td, $J = 8.3$, 5.4 Hz, 1H), 3.09–2.98 (m, 1H), 2.58 (br s, 1H), 1.91 (s, 3H), 1.67 (d, $J = 1.3$ Hz, 3H), 1.62 (dd, $J = 6.8$, 1.7 Hz, 3H), 1.05 (d, $J = 7.0$ Hz, 3H), 1.03 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 214.3$, 170.6, 159.4, 134.6, 134.1, 132.5, 129.8, 129.4, 122.5, 113.9, 76.8, 73.1, 71.6, 62.9, 55.4, 53.6, 47.1, 30.5, 21.3, 20.8, 13.2, 13.1, 11.4 ppm; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{25}H_{36}O_6Na$: 455.5395, found 455.3230.

(2*R*,4*R*)-2-((*S*)-Hydroxy((2*R*,3*R*)-2-methyl-3-((*S*,*Z*)-pent-3-en-2-yl)-oxiran-2-yl)methyl)-5-((4-methoxybenzyl)oxy)-4-methyl-3-oxopentyl acetate (15): A solution of **14** (14 mg, 0.03 mmol) in CH_2Cl_2 (0.6 mL) at −78 °C was treated with $NaHCO_3$ (9.5 mg, 0.113 mmol) and *m*-CPBA (5.6 mg, 0.03 mmol). The reaction was stirred for 1 h at −78 °C, warmed to −40 °C and stirred for 16 h at this temperature. Saturated aq $NaHCO_3$ (2 mL) and CH_2Cl_2 (3 mL) were added, and the reaction was warmed to RT. The layers was separated, and the aqueous layer was extracted with CH_2Cl_2 (2×3 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 6:1) afforded compound **15** as a colorless oil (6.5 mg, 44%): $[\alpha]_D^{23} = +4.5$ ($c = 0.35$ in MeOH); ^{1}H NMR (400 MHz, [D_6]benzene): $\delta = 7.19$ (d, $J = 8.7$ Hz, 2H), 6.80 (d, $J = 8.7$ Hz, 2H), 5.49–5.38 (m, 1H), 5.20–5.10 (m, 1H), 4.37 (dd, $J = 11.0$, 4.9 Hz, 1H), 4.27 (s, 2H), 4.22 (dd, $J = 10.9$, 8.8 Hz, 1H), 3.66 (dd, $J = 9.1$,7.4 Hz, 1H), 3.47 (dd, $J = 8.8$, 4.6 Hz, 1H), 3.40–3.34 (m, 1H), 3.29 (s, 3H), 3.12–3.02 (m, 1H), 2.55–2.51 (m, 1H), 2.50 (s, 1H), 2.41–2.31 (m, 1H), 1.58 (s, 3H), 1.43 (dd, $J = 6.9$, 1.8 Hz, 3H), 1.31 (s, 3H), 1.17 (d, $J = 6.9$ Hz, 3H), 1.08 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, [D_6]benzene): $\delta =$

212.5, 169.9, 159.8, 130.8, 130.5, 129.5, 124.9, 114.1, 76.5, 73.1, 71.9, 66.4, 62.9, 62.3, 54.7, 52.8, 48.4. 31.6, 20.3, 18.7, 13.3, 13.3, 12.0 ppm; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{26}H_{36}O_7Na$: 471.5389, found 471.2265.

(1*S*,2*R*,4*R*)-2-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-hydroxy-5-((4-methoxybenzyl)oxy)-4-methyl-1-((1*S*,2*R*)-1-methyl-2-((*S*,*Z*)-pent-3-en-2-yl)cyclopropyl)pentan-3-one (16): A solution of allylalcohol **12** (30 mg, 0.06 mmol) in CH_2Cl_2 (0.6 mL) was cooled to −10 °C and treated slowly with Et_2Zn (0.3 mL, 0.3 mmol, 1 M in hexane) and CH_2I_2 (24 μL, 0.3 mmol). After the addition was completed, the mixture was stirred for 2.5 h at RT. The reaction was stopped by the addition of saturated aq NH_4Cl (0.3 mL). The organic layer was diluted with methyl *tert*-butyl ether (2.5 mL) and treated with 10% aq HCl (0.3 mL), then washed consecutively with saturated aq Na_2SO_3 (0.3 mL), saturated aq $NaHCO_3$ (1 mL) and brine (1 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by column chromatography (petroleum ether (PE)/EtOAc, 8:1) provided **16** as a colorless oil (30.4 mg, 0.058 mmol, 96%): $[\alpha]_D^{23} = +9.2$ ($c = 1.0$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.22$ (d, $J = 8.5$ Hz, 2H), 6.86 (d, $J = 8.5$ Hz, 2H), 5.39–5.27 (m, 2H), 4.44 (d, $J = 11.6$ Hz, 1H), 4.39 (d, $J = 11.6$ Hz, 1H), 3.84 (dd, $J = 9.9$, 5.1 Hz, 1H), 3.79 (s, 3H), 3.75–3.66 (m, 2H), 3.35 (dd, $J = 8.9$, 6.8 Hz, 1H), 3.24 (m, 1H), 3.05–2.99 (m, 1H), 2.87 (d, $J = 8.8$ Hz, 1H), 2.08–2.04 (m, 1H), 1.58 (dd, $J = 6.1$, 1.4 Hz, 3H), 1.13 (d, $J = 7.2$ Hz, 3H), 1.06 (s, 3H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.84 (s, 9H), 0.60–0.54 (m, 1H), 0.51 (dd, $J = 8.8$, 13.3 Hz, 2H), −0.01 (s, 3H), −0.01 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 215.9$, 159.4, 136.3, 130.2, 129.5 121.8, 113.9, 78.5, 73.0, 71.5, 62.2, 57.8, 55.4, 47.1, 32.2, 29.6, 26.0, 24.7, 21.5, 18.3, 16.8, 13.8, 13.1, 12.7, −5.3, −5.4 ppm; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{30}H_{50}O_5SiNa$: 541.3325, found: 541.3330.

(1*S*,2*R*,4*R*)-1-Hydroxy-2-(hydroxymethyl)-5-((4-methoxybenzyl)oxy)-4-methyl-1-((1*S*,2*R*)-1-methyl-2-((*S*,*Z*)-pent-3-en-2-yl)cyclopropyl)pentan-3-one (17): A solution of **16** (15 mg, 0.029 mmol) in THF (1.5 mL) was cooled to 0 °C and treated slowly with pyridine (1.5 mL, 0.018 mol) and HF–pyridine (0.95 mL, 70%). The reaction was stirred for 15 min at 0 °C, then transferred to an EtOAc/buffer (pH 7) mixture (2 mL). The slurry was stirred for 5 min and the layers were separated. The aqueous layer was extracted with EtOAc (3×2 mL), and the combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 2:1) provided cyclopropane **17** as a colorless oil (4.6 mg, 0.011 mmol, 40%): $[\alpha]_D^{23} = +12.6$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.19$ (d, $J = 8.5$ Hz, 2H), 6.87 (d, $J = 8.5$ Hz, 2H), 5.42–5.32 (m, 2H), 4.43 (d, $J = 11.6$ Hz, H), 4.39 (d, $J = 11.6$ Hz, 1H), 3.91–3.82 (m, 2H), 3.79 (s, 3H), 3.65 (dd, $J = 11.8$ Hz, 2H), 3.50 (dd, $J = 8.8$, 4.4 Hz, 1H), 3.20–3.16 (m, 1H), 3.13–3.10 (m, 1H), 3.10 (m, 1H), 2.13–2.04 (m, 2H), 1.58 (dd, $J = 6.1$, 1.4 Hz, 3H), 1.57 (s, 3H), 1.05 (d, $J = 5.8$ Hz, 3H), 1.02 (d, $J = 6.8$ Hz, 3H), 0.79–0.72 (m, 1H), 0.52 (dd, $J = 8.8$, 13.6 Hz, 1H), 0.02 ppm (dd, $J = 7.2$, 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 218.8$, 159.5, 136.1, 129.6, 129.4, 121.6, 114.0, 78.7, 73.3, 72.7, 61.3, 57.8, 55.4, 47.6, 32.2, 29.5, 24.3, 21.4, 16.6, 13.2, 13.0, 12.5 ppm; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{24}H_{36}O_5Na$: 427.2460, found: 427.2462.

(1*S*,2*R*,4*R*)-1,5-Dihydroxy-2-(hydroxymethyl)-4-methyl-1-((1*S*,2*R*)-1-methyl-2-((*S*,*Z*)-pent-3-en-2-yl)cyclopropyl)pentan-3-one (18): A solution of cyclopropane **17** (13.5 mg, 0.026 mmol) in MeOH/water (2:1, 1.5 mL) was cooled to 0 °C and treated with ammonium cerium(IV) nitrate (31 mg, 0.056 mmol) to give an orange solution. The reaction was stirred for 3 h at 0 °C, and the treated with an additional aliquot of ammonium cerium(IV) nitrate (14.3 mg, 0.026 mmol). The reaction was stirred for 16 h. The layers were separated, and the aqueous phase was extracted with EtOAc (3× 2 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 3:1→1:1) provided triol **18** as a colorless oil (2 mg, 7.0 μmol, 26%): $[\alpha]_D^{23} = +7.6$ ($c = 0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.41$ (m, 2H), 3.88 (d, $J = 5.5$ Hz, 2H), 3.80 (dd, $J = 5.5$ Hz, 2H), 3.55 (br s, 1H), 3.35–3.30 (m, 1H), 3.10–3.02 (m, 2H), 1.61 (d, $J = 5.1$ Hz, 3H), 2.16–2.10 (m, 1H), 1.94 (br s, 1H), 1.28 (s, 3H), 1.11 (d, $J = 6.1$ Hz, 3H), 1.04 (d, $J = 6.8$ Hz, 3H), 0.94–0.85 (m, 1H), 0.79–0.73 (m, 1H), 0.52 ppm (dd, $J = 9.2$, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 207.7$, 136.0, 121.9, 79.7, 65.4, 61.7, 55.2, 51.0, 32.1, 29.7, 24.7, 21.4, 16.4, 13.8, 13.2, 12.5 ppm; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{16}H_{28}O_4Na$: 307.1885, found: 307.1883.

(2*R*,4*R*,5*S*,6*E*,8*S*,9*Z*)-4-(((*tert*-Butyldimethylsilyl)oxy)methyl)-1-((4-methoxybenzyl)oxy)-2,6,8-Trimethyl-3-oxoundeca-6,9-dien-5-yl acetate (19): A solution of alcohol **12** (14.6 mg, 0.029 mmol) in CH_2Cl_2 (1 mL) was cooled to 0 °C and treated slowly with Et_3N (24 μL, 0.17 mmol) and acetic acid anhydride (8.2 μL, 0.87 mmol). DMAP (0.37 mg, 0.003 mmol) was then added, and the reaction was stirred for 2.5 h. The reaction was quenched with saturated aq $NaHCO_3$ (1 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×1 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 2:1) provided compound **19** as a colorless oil (10.0 mg, 0.018 mmol, 62%): $[\alpha]_D^{23} = +15.6$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.24$ (d, $J = 8.5$ Hz, 2H), 6.85 (d, $J = 8.5$ Hz, 2H), 5.38 (dd, $J = 8.5$ Hz, 1H), 5.30 (ddq, $J = 13.7$, 7.5, 2.0 Hz, 1H), 5.22 (d, $J = 10.2$ Hz, 1H), 5.19 (ddq, $J = 10.6$, 9.2, 1.7 Hz, 1H), 4.44 (d, $J = 11.3$ Hz, 1H), 4.40 (d, $J = 11.6$ Hz, 1H), 3.8 (s, 3H), 3.70 (dd, $J = 9.2$, 5.12 Hz, 1H), 3.61 (dd, $J = 9.1$, 6.5 Hz, 1H) 3.42 (dd, $J = 9.9$, 4.8 Hz, 1H), 3.35–3.28 (m, 3H), 2.98–2.92 (m, 1H), 1.91 (s, 3H), 1.83 (s, 3H), 1.14 (d, $J = 6.8$ Hz, 3H), 1.63 (d, $J = 1.0$ Hz, 3H), 1.60 (dd, $J = 6.8$, 1.7 Hz, 3H), 1.00 (d, $J = 6.8$ Hz, 3H), 0.83 (s, 9H), −0.04 (s, 3H), 0.05 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 212.9$, 169.2, 159.3, 136.2, 134.7, 130.6, 129.4, 128.8, 122.2, 114.0, 78.1, 73.0, 70.5, 62.8, 55.4, 54.3, 48.3, 30.6, 26.0, 21.2, 21.1, 18.4, 13.5, 13.1, 11.6, −5.5, −5.7 ppm; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{31}H_{50}O_6SiNa$: 569.8004, found: 569.8001.

(1*S*,2*R*,4*R*)-1-Hydroxy-2-(hydroxymethyl)-5-((4-methoxybenzyl)oxy)-4-methyl-1-((2*R*,3*R*)-2-methyl-3-((*S*,*Z*)-pent-3-en-2-yl)oxiran-2-yl)pentan-3-one (20): A solution of allylalcohol **12** (53.4 mg, 0.11 mmol) in CH_2Cl_2 (1.9 mL) was cooled to −78 °C and treated with $NaHCO_3$ (32 mg, 0.38 mmol) and *m*-CPBA (18 mg, 0.11 mmol). The reaction was stirred at −40 °C for 16 h, quenched with saturated aq $NaHCO_3$ (3 mL) and warmed to RT. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×1.5 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 6:1) gave the intermediate as a yellow oil (22.5 mg, 0.05 mmol, 41%): $[\alpha]_D^{23} = +21.8$ ($c = 1.03$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.23$ (d, $J = 8.9$ Hz, 2H), 6.86 (d, $J = 8.5$ Hz, 2H), 5.50 (ddq, $J = 10.8$, 6.8, 0.6 Hz, 1H), 5.23 (ddq, $J = 10.8$, 10.3, 1.6 Hz, 1H), 4.44 (d, $J = 11.6$ Hz, 1H), 4.41 (d, $J = 11.6$ Hz, 1H), 3.79 (s, 3H,), 3.73 (dd, $J = 9.4$, 5.5 Hz, 1H), 3.71 (dd, $J = 9.2$, 5.5 Hz, 1H), 3.64 (dd, $J = 9.9$, 5.5 Hz, 1H), 3.45 (dd, $J = 8.2$, 4.4 Hz, 1H), 3.36 (dd, $J = 9.2$, 7.2 Hz, 1H), 3.17 (dd, $J = 8.7$, 5.3 Hz, 1H), 3.04 (d, $J = 4.8$ Hz, 1H), 2.91 (d, $J = 9.2$ Hz, 1H), 2.41 (m, 1H), 1.65 (dd, $J = 6.8$, 1.7 Hz, 3H), 1.31 (s, 3H), 1.16 (d, $J = 7.2$ Hz, 3H), 1.13 (d, $J = 6.8$ Hz, 3H), 0.84 (s, 9H), −0.01 (s, 3H), −0.02 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 214.7$, 159.2, 130.5, 130.0, 129.6, 124.6, 113.7, 75.2, 72.8, 71.1, 66.2, 63.0, 61.6, 55.8, 55.2, 47.8, 31.4, 25.8, 18.7, 18.6, 13.4,

13.2, 12.1, −5.6, −5.7 ppm; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{29}H_{48}O_6NaSi$: 543.3118, found: 543.3123.

A solution of epoxide (18.4 mg, 0.035 mmol) in THF (1.8 mL) was cooled to 0 °C and treated slowly with pyridine (1.84 mL, 0.22 mol) and HF–pyridine (1.2 mL, 70%). The reaction was stirred at 0 °C for 30 min, and then transferred to a mixture of EtOAc/buffer (pH 7) solution (2 mL) and stirred for 5 min. The layers were separated, and the aqueous layer was extracted with EtOAc (3×2 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 4:1→2:1) provided epoxide **19** as a colorless oil (10.4 mg, 0.025 mmol, 73%): $[\alpha]_D^{23} = +9.2$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.19$ (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.5$ Hz, H), 5.51 (ddq, $J = 10.6$, 6.8, 2.4 Hz, 1H), 5.26 (ddq, $J = 10.2$, 8.8, 1.7 Hz, 1H), 4.42 (d, $J = 11.6$ Hz, 1H), 4.38 (d, $J = 11.6$ Hz, 1H), 3.80 (s, 3H), 3.74 (dd, $J = 11.3$, 3.4 Hz, 1H), 3.68–3.62 (m, 2H), 3.55–3.50 (m, 2H), 3.17 (m, 1H), 3.03 (m, 1H), 2.76 (d, $J = 9.2$ Hz, 1H), 2.46–2.39 (m, 1H), 1.63 (dd, $J = 6.8$, 1.7 Hz, 3H), 1.31 (s, 3H), 1.12 (d, $J = 6.5$ Hz, 3H), 1.03 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 217.3, 159.4, 130.3, 129.5, 129.3, 124.6, 113.9, 76.1, 73.2, 72.7, 66.6, 62.7, 60.9, 56.5, 55.3, 47.8, 31.4, 18.6, 14.1, 13.3, 12.7 ppm; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{23}H_{34}O_6Na$: 429.2252, found: 429.2254. 6.9

(2*R*,4*R*,5*S*,6*E*,8*S*,9*Z*)-4-(Hydroxymethyl)-1-((4-methoxybenzyl)-oxy)-2,6,8-trimethyl-3-oxoundeca-6,9-dien-5-yl acetate (21): A solution of ether **19** (4.5 mg, 8.2 μmol) in CH_3CN/water (1.5:1, 0.5 mL) at RT was treated with ammonium cerium(IV) nitrate (9.2 mg, 0.016 mmol) and stirred for 3 h. The reaction was quenched with saturated aq $NaHCO_3$, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3×1 mL), and the combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification by column chromatography (PE/EtOAc, 2:1) provided acetate **21** as a colorless oil (4.0 mg, 9.2 μmol, 89%): $[\alpha]_D^{23} = +11.9$ ($c = 0.4$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.18$ (d, $J = 8.5$ Hz, 2H), 6.85 (d, $J = 8.5$ Hz, 2H), 5.45 (d, $J = 8.8$ Hz, 1H), 5.35 (d, $J = 10.5$ Hz, 1H), 5.31 (ddq, $J = 13.3$, 6.5, 4.4 Hz, 1H), 5.16, (ddq, $J = 10.6$, 8.8, 1.7 Hz, 1H), 4.41 (d, $J = 11.6$ Hz, 1H), 4.37 (d, $J = 11.6$ Hz, 1H), 3.80 (s, 3H), 3.62 (dd, $J = 12.0$, 6.5 Hz, 1H), 3.51 (dd, $J = 11.6$, 7.5 Hz, 1H), 3.47 (dd, $J = 8.8$, 4.1 Hz, 1H), 3.38–3.29 (m, 2H), 3.17–3.12 (m, 1H), 2.83–2.79 (m, 1H), 1.93 (s, 3H), 1.63 (d, $J = 0.9$ Hz, 3H), 1.62 (dd, $J = 6.8$, 1.7 Hz, 3H), 1.01 (d, $J = 6.8$ Hz, 3H), 1.00 ppm (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 215.4$, 169.2, 160.7, 136.9, 134.5, 129.6, 129.4, 128.7, 122.4, 114.0, 78.0, 73.5, 72.8, 62.1, 56.4, 55.4, 48.2, 30.6, 21.2, 21.2, 13.1, 12.7, 11.6 ppm; HRMS-ESI: *m/z* $[M+Na]^+$ calcd for $C_{25}H_{36}O_6Na$: 455.5395, found: 455.5397.

Biology

The in vitro translation assay was carried out with Flexi rabbit reticulocyte lysate (Promega). In brief, rabbit reticulocyte lysate (20 μL) was mixed with amino acid mixture minus leucine and amino acid mixture minus methionine (0.5 μL), KCl (1 μL), RNasin ribonuclease inhibitor (0.5 μL), luciferase mRNA (0.5 μL), water (10 μL) and **15** to a final concentration of 15 μg mL^{-1}. The mixture was incubated at 30 °C for 90 min. Then an aliquot of reaction mixture (5 μL) was mixed with luciferase assay buffer (10 μL), and the luminescence was measured using a plate reader. The results were compared to control wells in which MeOH was used instead of compound **15**.

Cell lines were obtained from the German Collection of Microorganisms and Cell Cultures (DSMZ, Braunschweig, Germany). Primary human fibroblasts isolated from foreskin were a generous gift from Dr. Karl-Heinz Thierauch (Bayer-Schering Pharma AG, Berlin, Germany). Antiproliferative activities were measured in 96-well plates. Serial dilutions of inhibitor (60 μL) were incubated with suspended cells (120 μL, 50000 cells mL^{-1}; two replicates). After five days, the metabolic activity in each well was determined using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.

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Keywords: gephyronic acid · myriaporones · natural products · ribosomes · tedanolide

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