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PAPER

Synthesis of the macrolactone core of (+)-neopeltolide by transannular cyclization†

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The synthesis of the macrolactone core of (+)-neopeltolide has been achieved. The key synthetic strategy involves the highly diastereoselective synthesis of the 2,6-*cis*-disubstituted tetrahydropyran ring by a transannular cyclization of δ-hydroxy alkene using mercuric trifluoroacetate. Two of the six stereocenters C-5 and C-11 were realized from L-malic acid, while the remaining stereocenters C-3 (Sharpless asymmetric epoxidation), C-7 (transannular cyclization), C-9 (regioselective epoxide opening) and C-13 (chelation controlled reduction) were derived by asymmetric synthesis. The macrolactone ring was synthesized by macrocyclization using a RCM protocol.

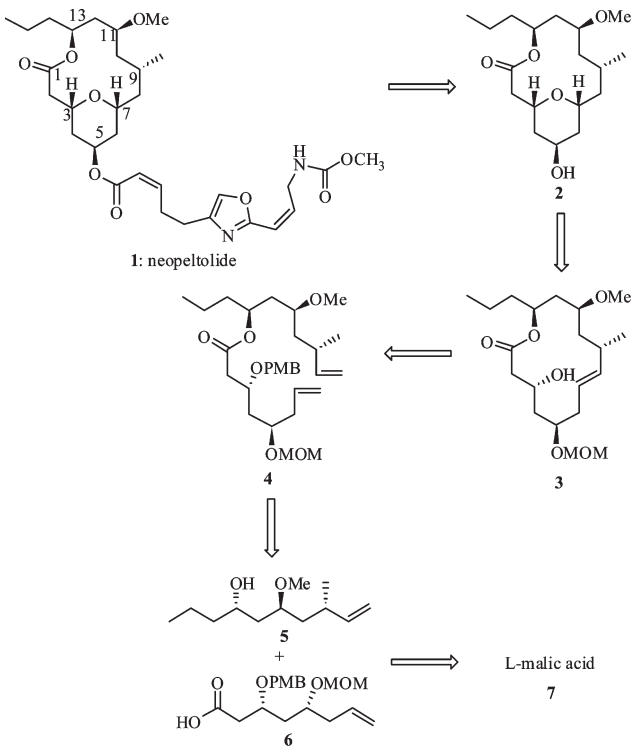
Introduction

(+)-Neopeltolide is a marine macrolide isolated from a deep-water sponge of the family *Neopeltidae* off the north coast of Jamaica in 2007 by Wright *et al.*[1] The structural features of **1** include: a trisubstituted 2,6-*cis* tetrahydropyran moiety, within a 14-membered macrolide and 6-stereocenters (3*R*, 5*R*, 7*R*, 9*S*, 11*S*, 13*S*), besides the presence of an unsaturated oxazole-containing side chain at C5 on the tetrahydropyran ring. Macrolide **1** exhibited significant and highly potent *in vitro* toxicity towards several cancer cell lines, including A549 human lung adenocarcinoma, NCI/ADR-RES ovarian carcinoma and P388 murine leukemia cell lines with an IC_{50} values of 1.2, 5.1 and 0.56 nM, respectively. In addition, **1** has also exhibited potent antifungal activity against pathogenic yeast *Candida albicans* with a MIC of 0.63 μg mL^{-1}, and cytostatic effects in PANC-1 pancreate cell line and the DLD-1 colorectal adenocarcinoma cell line, besides targeting the cytochrome bc_1 complex. Due to the biological activity and structural complexity of (+)-neopeltolide (**1**), several groups have reported the total synthesis[2] and formal synthesis.[3] Herein, we report the formal synthesis of **1** by accomplishing the synthesis of **2**, through a transannular cyclization as the key step in the construction of the 2,6-*cis*-disubstituted tetrahydropyran ring.

Results and discussion

Retrosynthetic analysis

Retrosynthetic analysis (Scheme 1) of **1** showed that the macrolactone **2** is the late stage intermediate, which could be



Scheme 1 The retrosynthetic strategy of neopeltolide **1**.

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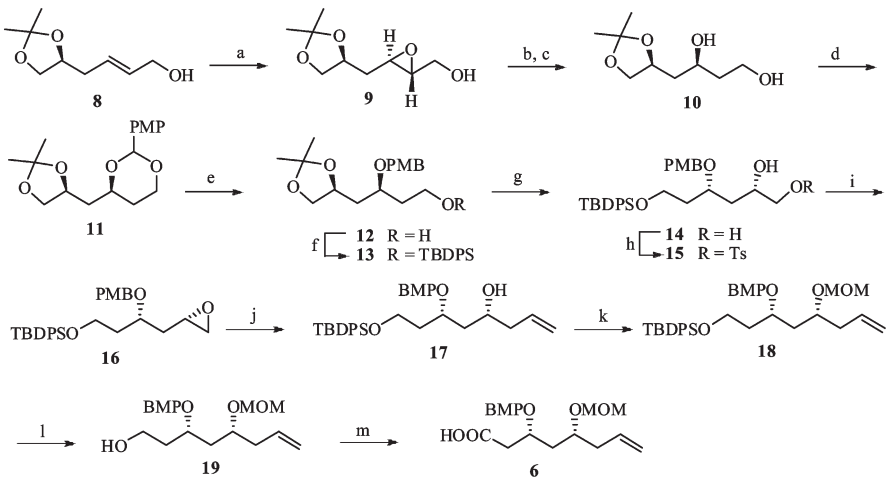


Scheme 2 *Reagents and conditions*: (a) (−)-DIPT, $Ti(O^iPr)_4$, cumene hydroperoxide, 4 Å molecular sieves, CH_2Cl_2, −20 °C; (b) Red-Al, THF, 0 °C–rt; (c) $NaIO_4$, sat. $NaHCO_3$, CH_2Cl_2, 0 °C–rt; (d) *p*-anisaldehyde dimethyl acetal, PPTS, CH_2Cl_2, 0 °C–rt; (e) DIBALH, CH_2Cl_2, 0 °C–rt; (f) TBDPSCl, imidazole, CH_2Cl_2, 0 °C–rt; (g) $CuCl_2{\cdot}2H_2O$, CH_3CN, 0 °C–rt; (h) *p*-TsCl, Bu_2SnO, Et_3N, CH_2Cl_2; (i) K_2CO_3, MeOH, 0 °C–rt; (j) vinylmagnesium bromide, CuI, THF, −20 °C; (k) MOMCl, DIPEA, DMAP, 0 °C–rt; (l) TBAF, THF, 0 °C–rt; (m) TEMPO, BAIB, $CH_2Cl_2 : H_2O$ (1 : 1).

synthesized from **3**, that in turn could be generated from bis olefin **4**. Ester **4** could be obtained from alcohol fragment **5** and acid fragment **6**. Both the alcohol **5** and acid **6** components could be envisaged from L-malic acid using general chemical transformations.

Thus, the key synthetic strategy is to construct the macrolide ring through macrocyclization using a RCM protocol and finally formation of the tetrahydropyran ring through mercuric trifluoroacetate-mediated cyclization within the macrolide ring.

Synthesis of acid fragment 6

The synthesis of the acid fragment **6** was initiated from L-malic acid-derived allylic alcohol **8**[4b] (Scheme 2). Accordingly, alcohol **8** on Sharpless asymmetric epoxidation with cumene hydroperoxide, (−)-DIPT and $Ti(O^iPr)_4$ gave epoxy alcohol **9** in 85% yield. Regioselective reductive opening of epoxide **9** with Red-Al[5] at 0 °C in THF afforded 1,3-diol **10** (80%) along with the corresponding 1,2-diol. The unwanted 1,2-diol was oxidatively cleaved with $NaIO_4$ and the resultant aldehyde was removed by column chromatography to give the pure 1,3-diol **10**. Treatment of diol **10** with *p*-anisaldehyde dimethyl acetal and PPTs gave **11** (79%), which on subsequent regioselective reductive ring opening with DIBAL-H at 0 °C to room temperature for 4 h afforded alcohol **12** in 86% yield. Reaction of alcohol **12** with TBDPS-Cl and imidazole afforded silyl ether **13** (92%), which on reaction with $CuCl_2{\cdot}2H_2O$ afforded diol[6] **14** (79%). A regioselective tosylation[7] of diol **14** gave **15** in 95% yield, which, on further reaction with K_2CO_3 in methanol furnished epoxide **16** (83%).

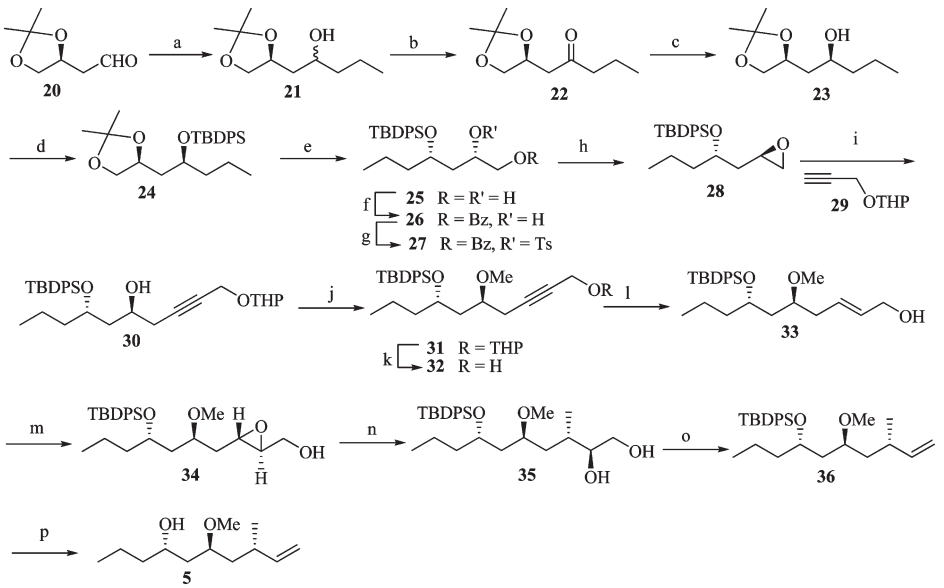
Treatment of epoxide **16** with vinylmagnesium bromide in the presence of CuI[8] in THF at −20 °C gave homoallylic alcohol **17** in 82% yield, which on reaction with MOM-Cl and $^iPr_2NEt$ afforded **18** (92%). Reaction of **18** with TBAF in THF furnished alcohol **19** (85%), which on subsequent oxidation with TEMPO and BAIB[9] furnished acid **6** in 70% yield.

Synthesis of alcohol fragment 5

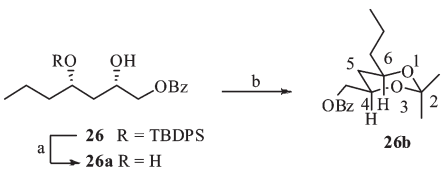
Alcohol fragment **5** was synthesized from L-malic acid-derived aldehyde **20**[4a] (Scheme 3). Accordingly, reaction of **20** with *n*-propylmagnesium bromide in THF gave a diastereomeric mixture of carbinols **21** (1.5 : 1) in 70% yield, which was subjected to oxidation under Swern reaction conditions to give ketone **22**. Chelation controlled reduction of **22** with $LiAlH_4$ and LiI afforded the *syn* alcohol **23** in 81% yield (95% de),[10] which on reaction with TBDPS-Cl and imidazole afforded ether **24** (82%). Acetonide deprotection in **24** with $CuCl_2{\cdot}2H_2O$ afforded diol[6] **25** in 75% yield. Regioselective protection of primary alcohol in **25** with benzoyl chloride[7] furnished **26** in 94% yield, which on further reaction with Et_3N and *p*-TsCl afforded **27**.

Base (K_2CO_3) mediated reaction of **27** in methanol led to the deprotection of the benzoyl ester in **27**, which on concomitant ring closure furnished epoxide **28** in 83% yield (for two steps). Opening of the epoxide **28** with alkynyl borane reagent, generated *in situ* from **29**, by the reaction with *n*-BuLi and $BF_3{\cdot}OEt_2$[11] in THF at −78 °C, afforded the alcohol **30** in 67% yield. Treatment of **30** with NaH and MeI gave ether **31** in 82% yield, which on treatment with PPTS in methanol furnished **32** in 75% yield. Stereospecific reduction of propargylic alcohol **32** with Red-Al[12] gave (*E*)-allylic alcohol **33** (94%), which on Sharpless asymmetric epoxidation afforded the desired epoxy alcohol **34** in 75% yield. Regioselective opening of **34** with Me_3Al[13] in hexane at 0 °C furnished 1,2-diol **35** in 85% yield, which on subsequent reaction with Ph_3P, imidazole and I_2 gave olefin[14] **36** in 70% yield. Finally, treatment of TBDPS ether **36** with TBAF afforded alcohol **5** in 84% yield.

To establish the relative configuration in **26**, it was treated with TBAF to give **26a** (Scheme 4), which on reaction with 2,2-dimethoxy propane and *p*-TsOH (cat.) in CH_2Cl_2 furnished acetonide **26b**. The ^{13}C NMR of **26b** revealed the presence of two peaks corresponding to the two methyl groups of the acetonide: at 19.7 ppm and 30.1 ppm, characteristic of a *syn*-1,3-diol derivative.[15]



Scheme 3 *Reagents and conditions*: (a) *n*-propyl bromide, Mg, THF, 0 °C–rt; (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (c) $LiAlH_4$, LiI, −40 to −100 °C; (d) TBDPSCl, imidazole, CH_2Cl_2, 0 °C–rt; (e) $CuCl_2{\cdot}2H_2O$, CH_3CN, 0 °C–rt; (f) BzCl, Bu_2SnO, Et_3N, CH_2Cl_2; (g) *p*-TsCl, DMAP, Et_3N, CH_2Cl_2, 0 °C–rt; (h) K_2CO_3, MeOH, 0 °C–rt; (i) n-BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C; (j) MeI, NaH, THF, 0 °C–rt; (k) PPTs, MeOH, 0 °C–rt; (l) Red-Al, diethyl ether, −20 °C; (m) (−)-DIPT, $Ti(O^iPr)_4$, cumene hydroperoxide, 4 Å molecular sieves, CH_2Cl_2, −20 °C; (n) Me_3Al, hexane, 0 °C–rt; (o) Ph_3P, I_2, imidazole, CH_2Cl_2, 0 °C–rt; (p) TBAF, THF, 0 °C–rt.



Scheme 4 *Reagents and conditions*: (a) TBAF, THF, 0 °C–rt; (b) $Me_2C(OMe)_2$, *p*-TsOH, CH_2Cl_2, 0 °C–rt.

Synthesis of macrolactone 2

In a further study on the synthesis of **2** from segments **5** and **6**, alcohol **5** was subjected to esterification with acid **6** (Scheme 5) using DCC and DMAP to give ester **4** in 67% yield. Ring closing metathesis (RCM) of ester **4** under high dilution conditions with 10 mol% of Grubb's second generation catalyst afforded the 14-membered macrolactone **37** in 65% yield,[16] which on oxidative deprotection of PMB ether with DDQ gave δ-hydroxy alkene **3** in 90% yield.

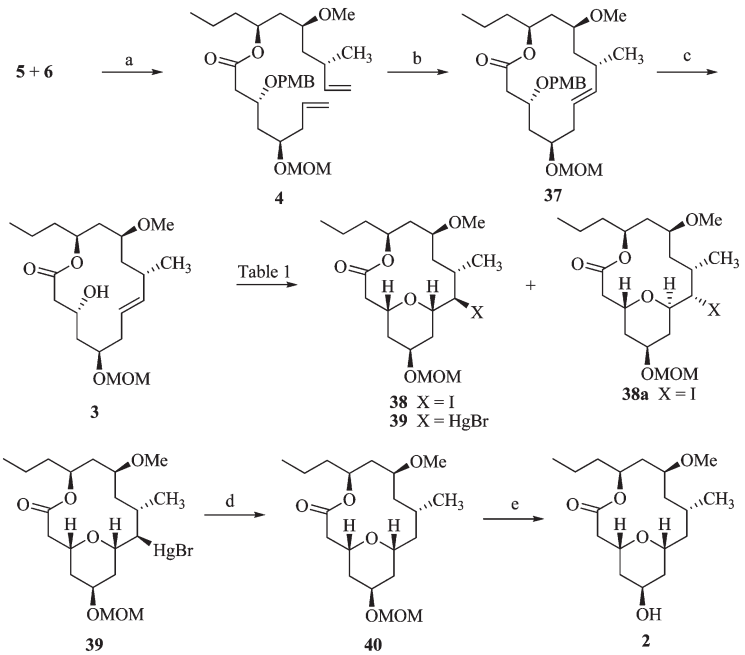
With the macrolactone **3** in hand, attention was directed towards the construction of the 2,6-*cis*-tetrahydropyran ring[17] by transannular cyclization.[18] In such a cyclization on δ-hydroxy alkene **3**, the presence of the C-9 methyl in the α-face adjacent to the alkene was assumed to play a role in the attack of the incoming electrophile from the less hindered β-face. Accordingly, in order to construct the 2,6-*cis*-tetrahydropyran unit of **1**, initially we employed the iodocyclization[19] reaction of **3** (Table 1), with iodine in acetonitrile[19c] (entry 1, Table 1) to give a mixture of isomers **38** and **38a** (60%) in a 15 : 85 ratio respectively. In a further study, the attempted cyclization with NIS in CH_2Cl_2 at 0 °C resulted in **38** and **38a** (78%) with a slightly increased isomeric ratio (30 : 70; entry 2, Table 1). Thus, the desired 2,6-*cis*-tetrahydropyran **38** was obtained as the minor product, along with the major 2,6-*trans* isomer **38a**. However, alcohol **3** on oxymercuration[20] with $Hg(CF_3OO)_2$ in dry CH_2Cl_2 at 0 °C (entry 3, Table 1) and treatment of the resultant organomercurial acetate with saturated aqueous KBr solution gave the 2,6-*cis*-tetrahydropyran **39** as a single product in 84% yield. The above results on the formation of a mixture of **38/38a** on iodoetherification and exclusive formation of **39** on oxymercuration can be rationalized based on the conformational transition state and steric factors, respectively, as evidenced from the literature.[21]

The structures of **38**, **38a** and **39** were established by ^1H NMR (500 MHz, $CDCl_3$) data and assignments were made with the aid of TOCSY and NOESY experiments. The characteristic NOE between C_3H/C_7H in **39** (Fig. 1) suggested that both the protons are on the same face of the structure. This was further supported by NOE correlation between C_7H/C_9H and $C_8H/C_{11}H$, confirming the structure of **39** (Fig. 1(a)). The energy minimized structure as shown in Fig. 1(b) is also in agreement with the assigned structure from NMR data.

Treatment of **39** with Bu_3SnH and AIBN in toluene under reflux conditions afforded **40** (Scheme 5) in 93% yield, which on final deprotection of the MOM ether in **40** using conc. HCl in MeOH gave **2** in 86% yield; the spectral and analytical data of **2** is in accordance with the data reported earlier.[3e]

Conclusion

In summary, an efficient synthesis of the 14-membered macrolactone core of biologically potent neopeltolide was achieved by RCM mediated macrocyclization and transannular cyclization with $Hg(CF_3OO)_2$ to construct the 2,6-*cis*-disubstituted tetrahydropyran ring of neopeltolide.



Scheme 5 *Reagents and conditions*: (a) DCC, DMAP, CH_2Cl_2, 0 °C–rt; (b) Grubb's 2nd generation catalyst, CH_2Cl_2, rt; (c) DDQ, $CH_2Cl_2 : H_2O$ (19 : 1); (d) *n*-Bu_3SnH, AIBN, toluene, reflux; (e) conc. HCl, MeOH, 0 °C–rt.

Table 1 Formation of *cis*-2,6-disubstituted tetrahydropyran unit of **1** from **3**

Entry	Conditions	*Syn*/*anti*[a]	Yield[b] (%)
1	I_2, CH_3CN, −40 °C–0 °C	15 : 85	60
2	NIS, CH_2Cl_2, 0 °C–rt	30 : 70	78
3	$Hg(CF_3COO)_2$, CH_2Cl_2, 0 °C, sat. KBr, rt	100 : 0	84

[a] Product ratio was determined by ^{1}H NMR spectral analysis (500 MHz). [b] Isolated yield.

Experimental

General

Solvents were dried over standard drying agents prior to use. Chemicals were purchased and used without further purification. All column chromatographic separations were performed using silica gel (Acme's 60–120 mesh). Organic solutions were dried over anhydrous Na_2SO_4 and concentrated below 40 °C *in vacuo*. ^{1}H NMR (300 MHz, 500 MHz and 600 MHz) and, ^{13}C NMR (75 MHz and 125 MHz) spectra were measured with a Bruker Avance 300 MHz, Inova-500 MHz and Bruker-600 MHz with TMS as internal standard for solutions in deutero chloroform. *J* values were given in Hz. IR-spectra were recorded on Perkin-Elmer IR-683 spectrophotometer with NaCl optics. Optical rotations were measured with JASCO DIP 300 digital polarimeter at 25 °C. Mass spectra were recorded on direct inlet system or LC by MSD trap SL (Agilent Technologies).

(4*R*,6*S*)-8-(*tert*-Butyldiphenylsilyloxy)-6-(4-methoxybenzyloxy)-oct-1-en-4-ol (17). To a suspension of CuI (1.75 g, 9.18 mmol) in THF (15 mL) at −20 °C, vinylmagnesium bromide (27.55 mL, 27.55 mmol, 1 M in THF) was added and stirred for 15 min. A solution of epoxide **16** (4.50 g, 9.18 mmol) in THF (30 mL) was added and stirred at −40 °C for 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl solution (10 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with water (50 mL), brine (50 mL) and dried (Na_2SO_4). Solvent was evaporated and the crude residue purified by column chromatography (60–120 mesh silica gel, 12% ethyl acetate in pet. ether) to afford **17** (3.90 g, 82%) as a colourless oil; $[\alpha]_D^{25}$ +57.3 (*c* 0.6, $CHCl_3$); IR (neat): 3069, 2932, 2857, 1715, 1612, 1514, 1427, 1250, 1109, 821, 734, 704 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63–7.61 (m, 4H), 7.41–7.33 (m, 6H), 7.12 (d, 2H, J = 8.8 Hz), 6.79 (d, 2H, J = 8.8 Hz), 5.82–5.71 (m, 1H), 5.05–5.02 (m, 2H), 4.45 (d, 1H, J = 11.0 Hz), 4.29 (d, 1H, J = 11.0 Hz), 3.82–3.67 (m, 4H), 3.77 (s, 3H), 2.18–2.07 (m, 2H), 1.96–1.86 (m, 1H), 1.74–1.68 (m, 1H), 1.60–1.52 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.2, 135.5, 134.9, 133.6, 129.9, 129.7, 129.5, 127.6, 117.3, 113.8, 77.0, 70.8, 70.4, 60.2, 55.2, 42.1, 40.6, 36.5, 26.8, 19.1; HRMS (ESI): *m*/*z* calculated for $C_{32}H_{42}O_4Si$ $(M + Na)^+$ 541.2746, found 541.2750.

(3*R*,5*R*)-3-(4-Methoxybenzyloxy)-5-(methoxymethoxy)oct-7-enoicacid (6). To a stirred solution of **19** (1.50 g, 4.63 mmol) in 1 : 1 solution of CH_2Cl_2–water (20 mL), BAIB (4.47 g, 13.89 mmol) and TEMPO (0.22 g, 1.39 mmol) were added and stirred at room temperature for 1.5 h. The reaction mixture was diluted with $CHCl_3$ (20 mL) and washed with sat. $Na_2S_2O_3$ (10 mL), brine (10 mL) and dried (Na_2SO_4). Solvent was evaporated and the residue purified by column chromatography (60–120 mesh silica gel, 20% ethyl acetate in pet. ether) to afford **6** (1.1 g, 70%) as a colourless oil; $[\alpha]_D^{25}$ −40.5 (*c* 0.7, $CHCl_3$); IR (neat): 2932, 1714, 1612, 1514, 1456, 1250, 1171,

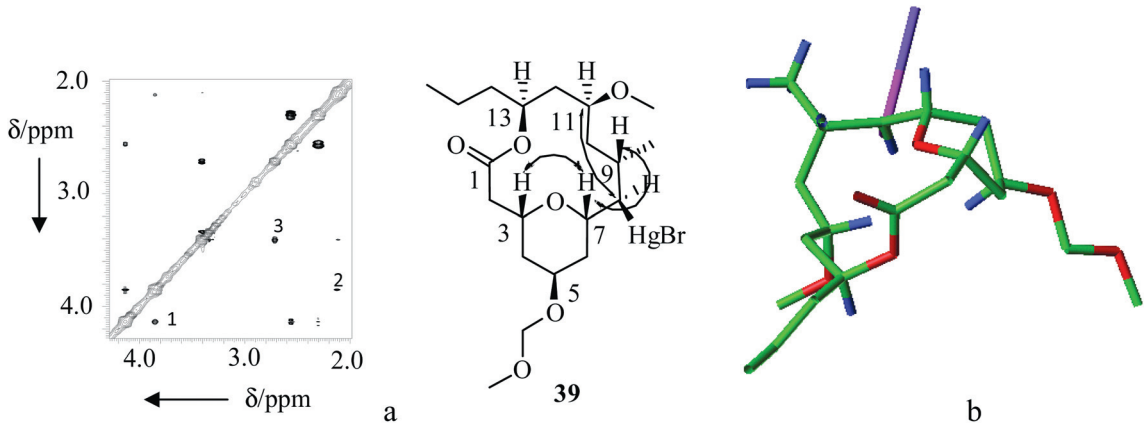


Fig. 1 (a) NOESY spectrum (in $CDCl_3$) of **39** (the NOEs C_3H/C_7H, C_7H/C_9H and $C_8H/C_{11}H$ are marked as 1, 2 and 3 respectively), (b) energy minimized structure of **39**.

1099, 1033, 918, 821 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, 2H, J = 8.4 Hz), 6.80 (d, 2H, J = 8.4 Hz), 5.78–5.70 (m, 1H), 5.05–5.02 (m, 2H), 4.62 (d, 1H, J = 6.7 Hz), 4.56 (d, 1H, J = 6.7 Hz), 4.46 (d, 1H, J = 10.9 Hz), 4.45 (d, 1H, J = 10.9 Hz), 3.99 (m, 1H), 3.76 (s, 3H), 3.71–3.66 (m, 1H), 3.33 (s, 3H), 2.60–2.58 (m, 2H), 2.27–2.24 (m, 2H), 1.93–1.87 (m, 1H), 1.70–1.65 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 159.2, 134.0, 130.0, 129.4, 117.6, 113.7, 95.3, 73.7, 72.4, 70.9, 55.7, 55.2, 39.3, 38.8, 38.4; HRMS (ESI): m/z calculated for $C_{18}H_{26}O_6$ $(M + Na)^+$ 361.1614, found 361.1627.

(5*S*,7*S*)-7-(*tert*-Butyldiphenylsilyloxy)-1-(tetrahydro-2*H*-pyran-2-yloxy)dec-2-yn-5-ol (30). To a stirred solution of **29** (1.83 g, 13.04 mmol) in dry THF (20 mL), *n*-BuLi (5.22 mL, 13.04 mmol, 2.5 M in hexane) was added at −78 °C and stirred for 30 min. $BF_3{\cdot}Et_2O$ (1.50 mL, 11.96 mmol) was added slowly and stirred for 10 min followed by the addition of epoxide **28** (4.0 g, 10.86 mmol) in THF (20 mL). After 2 h at −78 °C, it was quenched with sat. aq. NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL) and dried (Na_2SO_4). Solvent was evaporated and the residue purified by column chromatography (60–120 mesh silica gel, 7% ethyl acetate in pet. ether) to furnish **30** (3.70 g, 67%) as a colourless oil; $[\alpha]_D^{25}$ +18.33 (*c* 0.65, $CHCl_3$); IR (neat): 3447, 2986, 2934, 1794, 1745, 1645, 1454, 1373, 1217, 1159, 1059, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.68–7.64 (m, 4H), 7.43–7.34 (m, 6H), 4.75 (t, 1H, J = 3.0 Hz), 4.26–4.11 (m, 1H), 4.0–3.96 (m, 2H), 3.82–3.74 (m, 1H), 3.50–3.45 (m, 1H), 3.08–3.07 (s, 1H), 2.42–2.22 (m, 2H), 1.86–1.21 (m, 10H), 1.06 (s, 9H), 0.66 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 134.7, 129.8, 127.6, 96.6, 82.9, 72.2, 67.1, 61.9, 54.5, 40.1, 37.9, 30.2, 22.8, 26.9, 25.3, 19.0, 18.4, 13.7; HRMS (ESI): m/z calculated for $C_{31}H_{44}O_4Si$ $(M + Na)^+$ 531.2906, found 531.2931.

(5*S*,7*S*,*E*)-7-(*tert*-Butyldiphenylsilyloxy)-5-methoxydec-2-en-1-ol (33). To a solution of **32** (1.80 g, 4.11 mmol) in dry ether (20 mL), Red-Al (3.56 mL, 12.33 mmol, 70% w/w in toluene) was added dropwise at 0 °C and allowed to stir for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution (2 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (25 mL), dried (Na_2SO_4), evaporated and the residue purified by column chromatography (60–120 mesh silica gel, 12% ethyl acetate in pet. ether) to furnish **33** (1.70 g, 94%) as a colourless oil; $[\alpha]_D^{25}$ +29.20 (*c* 0.25, $CHCl_3$); IR (neat): 3401, 3073, 2957, 2932, 2859, 1589, 1462, 1427, 1381, 1186, 1109, 821, 704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.71–7.63 (m, 4H), 7.44–7.31 (m, 6H), 5.64–5.45 (m, 2H), 4.02–4.0 (m, 2H), 3.94–3.87 (m, 1H), 3.28–3.2 (m, 1H), 3.04 (s, 3H), 2.11–2.07 (m, 2H), 1.54–1.50 (m, 2H), 1.41–1.17 (m, 4H), 1.03 (s, 9H), 0.72 (t, 3H, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 134.6, 131.7, 129.4, 128.2, 127.4, 76.9, 70.5, 63.6, 55.9, 41.5, 39.8, 35.8, 27.0, 19.4, 17.7, 14.0; HRMS (ESI): m/z calculated for $C_{27}H_{40}O_3Si$ $(M + Na)^+$ 463.2644, found 463.2638.

(2*S*,3*S*,5*S*,7*S*)-7-(*tert*-Butyldiphenylsilyloxy)-5-methoxy-3-methyldecane-1,2-diol (35). To a stirred solution of **34** (1.20 g, 2.63 mmol) in dry hexane (6 mL), Me_3Al (3.94 mL, 7.89 mmol, 2 M in toluene) was added at 0 °C and allowed to stir for 10 min. Reaction mixture was quenched with sat. aq. NH_4Cl solution (1 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (3 mL), dried (Na_2SO_4), evaporated and the residue purified by column chromatography (60–120 mesh silica gel, 25% ethyl acetate in pet. ether) to afford **35** (1.05 g, 85%) as a colourless oil; $[\alpha]_D^{25}$ −37.0 (*c* 0.2, $CHCl_3$); IR (neat): 3401, 3063, 2932, 2866, 1686, 1593, 1464, 1427, 1362, 1109, 823, 741, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.72–7.67 (m, 4H), 7.46–7.39 (m, 6H), 3.83–3.79 (m, 1H), 3.72–3.55 (m, 1H), 3.46 (dd, 1H, J = 7.5, 11.0 Hz), 3.34–3.29 (m, 1H), 3.27–3.21 (m, 1H), 3.16 (s, 3H), 2.0 (br. s, 2H), 1.82 (td, 1H, J = 6.0, 12.5 Hz), 1.66–1.57 (m, 1H), 1.55–1.16 (m, 7H), 1.05 (s, 9H), 0.83 (d, 3H, J = 6.5 Hz), 0.78 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.9, 134.4, 129.5, 127.4, 77.1, 76.4, 70.7, 64.6, 56.0, 41.6, 39.3, 38.8, 33.6, 27.0, 17.8, 17.1, 14.0; HRMS (ESI): m/z calculated for $C_{28}H_{44}O_4Si$ $(M + Na)^+$ 495.2906, found 495.2926.

***tert*-Butyl((4*S*,6*S*,8*S*)-6-methoxy-8-methyldec-9-en-4-yloxy)diphenylsilane (36).** To a stirred solution of **35** (1.0 g, 2.11 mmol) in dry CH_2Cl_2 (10 mL), Ph_3P (2.21 g, 8.44 mmol), imidazole

(0.57 g, 8.44 mmol) and I_2 (1.60 g, 6.36 mmol) were added at 0 °C and allowed to stir for 30 min. The reaction mixture was quenched with sat. aq. NaOH (1 mL) and extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine (3 mL), dried (Na_2SO_4), evaporated and the residue purified by column chromatography (60–120 mesh silica gel, 5% ethyl acetate in pet. ether) to furnish **36** (0.65 g, 70%) as a colourless oil; $[\alpha]_D^{25}$ +23.27 (*c* 0.3, $CHCl_3$); IR (neat): 3468, 3072, 2959, 2932, 2858, 1641, 1585, 1462, 1427, 1379, 1259, 1184, 1109, 1041, 912, 821, 730, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.67–7.60 (m, 4H), 7.39–7.30 (m, 6H), 5.66–5.56 (m, 1H), 4.93–4.83 (m, 2H), 3.92–3.86 (m, 1H), 3.34–3.24 (m, 1H), 3.06 (s, 3H), 2.16–2.08 (m, 1H), 1.56–1.43 (m, 2H), 1.40–1.11 (m, 6H), 1.03 (s, 9H), 0.93 (d, 3H, *J* = 6.8 Hz), 0.68 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 144.4, 135.9, 134.8, 129.4, 127.3, 112.5, 75.7, 70.4, 55.6, 42.0, 40.7, 39.6, 34.2, 27.0, 20.5, 19.4, 17.7, 14.0; HRMS (ESI): *m*/*z* calculated for $C_{28}H_{42}O_2Si$ $(M + Na)^+$ 461.2851, found 461.2860.

(4*S*,6*S*,8*S*)-6-Methoxy-8-methyldec-9-en-4-ol (5). To a stirred and cooled (0 °C) solution of **36** (0.60 g, 1.37 mmol) in dry THF (0.5 mL) TBAF (2.05 mL, 2.05 mmol, 1 M in THF) was added and stirred for 3 h. The reaction mixture was diluted with water (2 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (2 mL), dried (Na_2SO_4), evaporated and the residue purified by column chromatography (60–120 mesh silica gel, 7% ethyl acetate in pet. ether) to furnish **5** (0.23 g, 84%) as a colourless oil; $[\alpha]_D^{25}$ +91.9 (*c* 0.2, $CHCl_3$); IR (neat): 3450, 2927, 2857, 1725, 1631, 1461, 1379, 1255, 1112, 1031, 763, 702, 607, 502, 408 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.71–5.59 (m, 1H), 4.99–4.89 (m, 2H), 3.88–3.80 (m, 1H), 3.52–3.41 (m, 1H), 3.33 (s, 3H), 2.30–2.33 (m, 1H), 2.23–2.04 (m, 1H), 1.78–1.63 (m, 2H), 1.54–1.23 (m, 6H), 1.02 (d, 3H, *J* = 6.6 Hz), 0.93 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (300 MHz, $CDCl_3$): δ 144.0, 112.9, 77.8, 68.5, 56.4, 39.9, 39.7, 38.6, 34.8, 20.8, 18.9, 14.1; HRMS (ESI): *m*/*z* calculated for $C_{12}H_{24}O_2$ $(M + Na)^+$ 223.1673, found 223.1685.

((1*R*,5*S*,7*S*,9*S*,10*R*,11*S*,13*S*)-7-Methoxy-13-(methoxymethoxy)-9-methyl-3-oxo-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecan-10-yl)mercury(II) bromide (39). To a stirred solution of **3** (15 mg, 0.04 mmol) in CH_2Cl_2 (0.6 mL), mercury trifluoroacetate (34 mg, 0.08 mmol) was added at 0 °C and allowed the reaction mixture to stir at room temperature for 1 h. The reaction mixture was treated with KBr solution (1 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with water (2 × 3 mL), brine (2 × 3 mL) and dried (Na_2SO_4). Solvent was evaporated and the residue purified by column chromatography (60–120 mesh silica gel, 12% ethyl acetate in pet. ether) to furnish **39** (22 mg, 84%) as a colourless oil; $[\alpha]_D^{25}$ +44.6 (*c* 0.21, $CHCl_3$); IR (neat): 3452, 2923, 2854, 1725, 1642, 1459, 1382, 1269, 1148, 1037, 761 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.83–4.74 (m, 1H), 4.69 (d, 1H, *J* = 6.5 Hz), 4.67 (d, 1H, *J* = 6.5 Hz), 4.19–4.10 (m, 1H), 4.08–4.05 (m, 1H), 3.91–3.79 (m, 1H), 3.43–3.35 (m, 1H), 3.39 (s, 3H), 3.33 (s, 3H), 2.71 (dd, 1H, *J* = 2.5, 10.0 Hz), 2.55 (dd, 1H, *J* = 5.0, 13.0 Hz), 2.29 (dd, 1H, *J* = 10.0, 13.0 Hz), 2.18–2.03 (m, 2H), 1.96–1.82 (m, 2H), 1.67–1.41 (m, 4H), 1.38–1.22 (m, 4H), 1.16 (d, 3H, *J* = 6.5 Hz), 0.92 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 95.2, 77.2, 76.1, 75.6, 70.1, 69.7, 56.3, 55.6, 42.5, 40.8, 40.0, 39.2, 36.6, 35.7, 34.1, 29.7, 21.7, 19.2, 13.8; HRMS (ESI): *m*/*z* calculated for $C_{20}H_{35}O_6BrHg$ $(M + Na)^+$ 675.1220, found 675.1221.

(1*R*,5*S*,7*S*,9*S*,11*R*,13*R*)-7-Methoxy-13-(methoxymethoxy)-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1]pentadecan-3-one (40). To a stirred solution of **39** (15 mg, 0.02 mmol) in dry toluene (3 mL), AIBN (5 mg) was added and the resulting mixture was heated at reflux under a nitrogen atmosphere. Bu_3SnH (14 μL, 0.05 mmol) was added to the reaction mixture and continued stirring for 3 h. Toluene was evaporated and the residue purified by column chromatography (60–120 mesh silica gel, 15% ethyl acetate in pet. ether) to afford **40** (8.0 mg, 93%) as a colourless oil; $[\alpha]_D^{25}$ +7.0 (*c* = 0.20, $CHCl_3$); IR (neat): 2924, 2854, 1743, 1463, 1436, 1378, 1259, 1195, 1071 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.22–5.15 (m, 1H), 4.68 (s, 2H), 4.17–4.09 (m, 1H), 4.05–4.0 (m, 1H), 3.65–3.56 (m, 2H), 3.38 (s, 3H), 3.31 (s, 3H), 2.58 (dd, 1H, *J* = 4.0, 14.6 Hz), 2.38–2.28 (m, 3H), 1.90–1.75 (m, 1H), 1.73–1.47 (m, 6H), 1.45–1.32 (m, 4H), 1.19–1.03 (m, 2H), 0.98 (d, 3H, *J* = 6.8 Hz), 0.88 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 94.9, 75.7, 75.4, 72.9, 70.1, 69.6, 56.2, 55.4, 44.3, 42.6, 42.3, 40.2, 37.2, 37.0, 31.9, 29.4, 22.7, 18.9, 14.1; HRMS (ESI): *m*/*z* calculated for $C_{20}H_{36}O_6$ $(M + Na)^+$ 395.24046, found 395.24041.

(1*R*,5*S*,7*S*,9*S*,11*R*,13*R*)-13-Hydroxy-7-methoxy-9-methyl-5-propyl-4,15-dioxabicyclo[9.3.1] pentadecan-3-one (2). To a stirred solution of **40** (8.0 mg, 0.02 mmol) in MeOH (0.50 mL), conc. HCl (20 μL) was added at 0 °C. After stirring at 0 °C for 0.5 h and for 24 h at room temperature, the reaction mixture was quenched with saturated aq. $NaHCO_3$ solution (2 mL) and extracted with EtOAc (4 × 5 mL). The organic layers were washed with brine (5 mL), dried (Na_2SO_4), evaporated and the residue purified by column chromatography (60–120 mesh silica gel, 20% ethyl acetate in pet. ether) to furnish **2** (6.0 mg, 86%) as a colorless oil; $[\alpha]_D^{25}$ +27.3 (*c* 0.1, $CHCl_3$); Lit.[3e] $[\alpha]_D^{25}$ +24.5 (*c* 0.1, $CHCl_3$); IR (neat): 3448, 2922, 2853, 1728, 1645, 1462, 1379, 1219, 1082, 771 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.12 (dt, 1H, *J* = 4.5, 9.5 Hz), 4.18 (t, 1H, *J* = 2.5 Hz), 4.12 (qt, 1H, *J* = 2.0, 10.5 Hz), 3.61 (td, 1H, *J* = 2.1, 11.0 Hz), 3.53 (t, 1H, *J* = 10.0 Hz), 3.24 (s, 3H), 2.52 (dd, 1H, *J* = 4.0, 14.5 Hz), 2.28 (dd, 1H, *J* = 11.0, 14.5 Hz), 1.79 (dd, 1H, *J* = 11.0, 13.5 Hz), 1.65–1.58 (m, 2H), 1.54–1.40 (m, 5H), 1.38–1.33 (m, 5H), 1.08 (dt, 1H, *J* = 2.0, 10.5 Hz), 0.91 (d, 3H, *J* = 7.0 Hz), 0.84 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 75.9, 75.1, 73.1, 69.3, 65.2, 56.4, 44.4, 42.5, 40.4, 39.6, 38.5, 37.2, 31.6, 29.9, 25.9, 19.1, 14.1; HRMS (ESI): *m*/*z* calculated for $C_{18}H_{32}O_5$ $(M + Na)^+$ 351.2147, found 351.2133.

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