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# Anticancer Agents from the Australian Tropical Rainforest: Spiroacetals EBC-23, 24, 25, 72, 73, 75 and 76

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**Abstract:** EBC-23, 24, 25, 72, 73, 75 and 76 were isolated from the fruit of *Cinnamomum laubatii* (family *Lauraceae*) in the Australian tropical rainforests. EBC-23 (**1**) was synthesized stereoselectively, in nine linear steps in 8% overall yield, to confirm the reported relative stereochemistry and determine the absolute stereochemistry. Key to the total synthesis was a series of Tietze–Smith linchpin reactions. The novel spiroacetal structural motif, exemplified by EBC-23 (**1**), was found to inhibit the growth of the androgen-independent prostate tumor cell line DU145 in the mouse model, indicating potential for the treatment of refractory solid tumors in adults.

**Keywords:** anticancer agents · Australian tropical rainforests · natural products · total synthesis

## Introduction

In the course of undertaking a screening program in the north east Australian tropical rainforest to identify biologically active candidates as potential treatments for cancer, a group of novel spiroketals were found in the fruit of *Cinnamomum laubatii* (family *Lauraceae*). Herein, we report the isolation, structure elucidation and biological activity of EBC-23, 24, 25, 72, 73, 75 and 76 (Figure 1) along with the total synthesis of EBC-23 (**1**).[1]

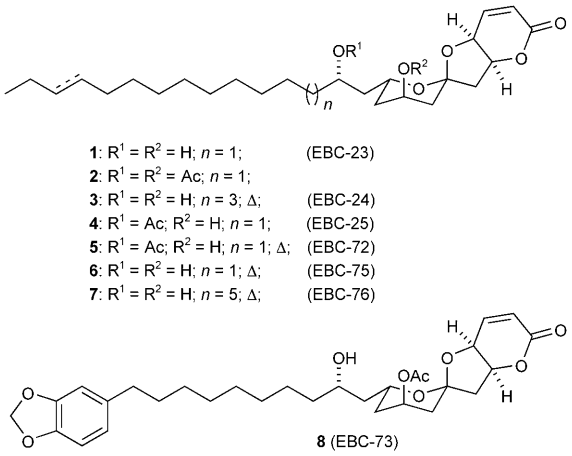


Figure 1. EBC-23 (**1**) and related family members.

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## Results and Discussion

Both the frozen exocarp and seed from the fruit of *Cinnamomum laubatii* were extracted. The exocarp gave EBC-23 (**1**), EBC-24 (**3**), EBC-25 (**4**), EBC-72 (**5**), EBC-73 (**8**), EBC-75 (**6**) and EBC-76 (**7**), whereas EBC-23 (**1**), EBC-24 (**3**) and EBC-25 (**4**) were also obtained from the seed.

LRESIMS analysis of EBC-23 (**1**) proved difficult, however, derivatization with acetic anhydride provided the diacetyl derivative (**2**), which displayed a single signal on LR-ESIMS analysis ($[M+Na]^+$, $m/z$ 559) confirming the LR-ESIMS ($[M+Na]^+$, $m/z$ 475) molecular ion. IR absorption

bands at 3448 and 1729 $cm^{-1}$ indicated hydroxy and lactone carbonyl groups. HRESIMS analysis of **1** ($[M+Na]^+$, *m/z* 475.3024), in conjunction with a remarkably well deconvoluted $^{13}C$ NMR spectrum in the alkyl region, established a molecular formula of $C_{26}H_{44}O_6$. The $^1H$ NMR (Table 1) spectrum displayed characteristic resonances for a saturated long chain ($\delta_H$ 1.2) and associated primary methyl ($\delta_H$ 0.9, $J=7.2$ Hz, t), a one proton coupled AB system ($\delta_H$ 2.4), five oxygenated methines ($\delta_H$ 3.8, 4.1, 4.4, 4.5, and 5.0), and two olefinic protons ($\delta_H$ 6.2 and 6.9). The $^{13}C$ NMR (Table 2) spectra revealed 23 of the 26 carbons, which in combination with DEPT measurements were found to be one methyl, 13 methylenes, 7 methines (2 olefinic and 5 oxygenated), one spiroacetal and one α,β-unsaturated lactone carbonyl carbon. Further evaluation of the α,β-unsaturated lactone moiety with $^1H,^1H$ COSY, HSQC and HMBC experiments suggested a *syn*-disubstituted six-membered α,β-unsaturated lactone of type **9**. Comparison of **9** with the known natural product osumundalactone[2] **10** and the synthetic *syn*-isomer[3] **11** confirmed, along with the NOESY spectrum, the presence of fragment **9** (i.e., two olefinic *dd* patterns for **10**, and only one *dd* and one *d* pattern for **11** matching that of **1**) (Figure 2).

Key $^1H,^1H$ COSY and HMBC correlations, in conjunction with the ACD/labs software,[4] established the position of the AB system (C7) in relation to the lactone ring and the spiroacetal carbon (C8). In turn the spiroacetal carbon (C8) initiated the connectivity and substitution of the tetrahydro-

Table 1. Proton-NMR data for EBC-23, 24, 25, 72, 75, and 76.

| | EBC-23 (750 MHz) | EBC-24 (500 MHz) | EBC-25 (500 MHz) | EBC-72 (500 MHz) | EBC-75 (500 MHz) | EBC-76 (500 MHz) |
|---|---|---|---|---|---|---|
| 3-H | 6.21 (d, 1H, $J=10.0$ Hz) | 6.20 (d, 1H, $J=9.9$ Hz) | 6.17 (dd, 1H, $J=9.9$, 0.4 Hz) | 6.18 (dd, 1H, $J=9.9$, 0.5 Hz) | 6.20 (dd, 1H, $J=9.9$, 0.3 Hz) | 6.23 (d, 1H, $J=9.9$ Hz) |
| 4-H | 6.89 (dd, 1H, $J=10.0$, 5.2 Hz) | 6.88 (dd, 1H, $J=9.9$, 5.2 Hz) | 6.86 (dd, 1H, $J=9.9$, 5.2 Hz) | 6.87 (dd, 1H, $J=9.9$, 5.1 Hz) | 6.88 (dd, 1H, $J=9.9$, 5.2 Hz) | 6.91 (dd, 1H, $J=9.9$, 5.2 Hz) |
| 5-H | 4.51 (dd, 1H, $J=5.2$, 4.5 Hz) | 4.50 (dd, 1H, $J=5.2$, 4.6 Hz) | 4.51 (ddd, 1H, $J=5.2$, 4.6, 0.4 Hz) | 4.52 (ddd, 1H, $J=5.2$, 4.6, 0.4 Hz) | 4.52 (ddd, 1H, $J=5.2$, 4.6, 0.3 Hz) | 4.52 (dd, 1H, $J=5.2$, 4.6 Hz) |
| 6-H | 5.04 (ddd, 1H, $J=6.9$, 4.5, 2.5 Hz) | 5.03 (ddd, 1H, $J=6.9$, 4.6, 2.5 Hz) | 5.00–5.05 (m, 1H) | 5.01–5.05 (m, 1H) | 5.03 (ddd, 1H, $J=6.9$, 4.6, 2.5 Hz) | 5.06 (ddd, 1H, $J=6.9$, 4.6, 2.4 Hz) |
| | 2.54 (α, dd, 1H, $J=14.9$, 6.9 Hz) | 2.53 (α, dd, 1H, $J=14.9$, 6.9 Hz) | 2.49 (α, dd, 1H, $J=14.6$, 6.9 Hz) | 2.50 (α, dd, 1H, $J=14.6$, 7.0 Hz) | 2.54 (α, dd, 1H, $J=14.9$, 6.8 Hz) | 2.56 (α, dd, 1H, $J=14.9$, 6.9 Hz) |
| | 2.30 (β, dd, 1H, $J=14.9$, 2.5 Hz) | 2.28 (β, dd, 1H, $J=14.9$, 2.5 Hz) | 2.22 (β, dd, 1H, $J=14.7$, 2.7 Hz) | 2.22 (β, dd, 1H, $J=14.6$, 2.6 Hz) | 2.22 (β, dd, 1H, $J=14.9$, 2.5 Hz) | 2.31 (β, dd, 1H, $J=14.9$, 2.5 Hz) |
| 10-H | 1.98–2.05 (m, 2H) | 1.99–2.03 (m, 2H) | 1.93–1.98 (m, 2H) | 1.90–1.99 (m, 2H) | 1.99–2.03 (m, 2H) | 2.01–2.05 (m, 2H) |
| 11-H | 4.09–4.13 (m, 1H) | 4.07–4.13 (m, 1H) | 4.04–4.11 (m, 1H) | 4.05–4.11 (m, 1H) | 4.07–4.13 (m, 1H) | 4.09–4.16 (m, 1H) |
| | 1.75–1.80 (m, 1H) | 1.73–1.80 (m, 1H) | 1.70–1.76 (m, 1H) | 1.71–1.77 (m, 1H) | 1.74–1.80 (m, 1H) | 1.79 (dddd, 1H, $J=14.0$, 3.2, 1.8, 1.7 Hz) |
| | 1.47–1.52 (m, 1H) | 1.45–1.53 (m, 1H) | 1.36–1.44 (m, 1H) | 1.37–1.44 (m, 1H) | 1.47–1.52 (m, 1H) | 1.51 (ddd, 1H, $J=14.0$, 11.7, 2.8 Hz) |
| 13-H | 4.35–4.40 (m, 1H) | 4.33–4.40 (m, 1H) | 4.17 (dddd, 1H, $J=11.6$, 9.2, 4.3, 2.2 Hz) | 4.18 (dddd, 1H, $J=11.6$, 9.2, 4.3, 2.2 Hz) | 4.33–4.40 (m, 1H) | 4.39 (dddd, 1H, $J=16.0$, 6.7, 2.2, 2.0 Hz) |
| 15-H | 1.56–1.65 (m, 2H) | 1.54–1.66 (m, 2H) | 1.47–1.55 (m, 2H) | 1.47–1.56 (m, 2H) | 1.54-1.66 (m, 2H) | 1.55–1.66 (m, 2H) |
| 16-H | 3.76–3.82 (m, 1H) | 3.75–3.81 (m, 1H) | 4.95–5.05 (m, 1H) | 4.96–5.05 (m, 1H) | 3.74–3.82 (m, 1H) | 3.78–3.84 (m, 1H) |
| (ω-2)-H, (ω-3)-H | | 5.31–5.45 (m, 2H) | | 5.28–5.45 (m, 2H) | 5.30–5.45 (m, 2H) | 5.32–5.47 (m, 2H) |
| (ω-1)-H, (ω-4)-H | | 1.90–2.00 (m, 4H) | | 1.90–1.99 (m, 4H) | 1.90–1.99 (m, 4H) | 1.93–2.01 (m, 4H) |
| ω-H | 0.86 (t, 3H, $J=7.1$ Hz) | 0.94 (t, 3H, $J=7.4$ Hz) | 0.85 (t, 3H, $J=6.9$ Hz) | 0.94 (t, 3H, $J=7.4$ Hz) | 0.93 (t, 3H, $J=7.4$ Hz) | 0.96 (t, 3H, $J=7.4$ Hz) |
| alkyl-H | 1.42–1.47 (m, 1H) 1.35–1.42 (m, 2H) 1.20–1.33 (m, 21H) | 1.34–1.47 (m, 2H) 1.19–1.34 (m, 18H) | 1.76–1.87 (m, 1H) 1.58 (dt, 1H, $J=14.5$, 4.5 Hz) 1.17–1.31 (m, 22H) | 1.77–1.85 (m, 1H) 1.56–1.63 (m, 1H) 1.17–1.34 (m, 14H) | 1.35–1.40 (m, 1H) 1.40–1.47 (m, 2H) 1.19–1.34 (m, 13H) | 1.36–1.45 (m, 3H) 1.22–1.36 (m, 21H) |
| acetyl-H | | | 2.00 (s, 3H) | 2.00 (s, 3H) | | |
| OH | 3.05 (d, 1H, $J=9.2$ Hz) 2.96 (s, 1H) | 3.06 (d, 1H, $J=9.2$ Hz) 2.96 (s, 1H) | 3.11 (d, 1H, $J=9.2$ Hz) | 3.11 (d, 1H, $J=9.2$ Hz) | 3.07 (br s, 2H) | 3.07 (d, 1H, $J=9.1$ Hz) 2.98 (s, 1H) |

Table 2. Carbon-NMR data for EBC-23, 24, 25, 72, 75, and 76.

| | EBC-23 (125 MHz) | EBC-24 (125 MHz) | EBC-25 (125 MHz) | EBC-72 (125 MHz) | EBC-75 (125 MHz) | EBC-76 (125 MHz) |
|---|---|---|---|---|---|---|
| C-2 | 161.0 | 161.0 | 161.2 | 161.3[a] | 161.1 | 161.0 |
| C-3 | 124.6 | 124.5 | 124.2 | 124.2 | 124.6 | 124.6 |
| C-4 | 138.6 | 138.6 | 139.1 | 139.1 | 138.7 | 138.6 |
| C-5 | 68.9 | 68.8 | 68.6 | 68.7 | 68.9 | 68.9 |
| C-6 | 78.8 | 78.8 | 79.0 | 79.1 | 78.8 | 78.8 |
| C-7 | 47.7 | 47.7 | 47.5 | 47.6 | 47.7 | 47.7 |
| C-8 | 106.6 | 106.5 | 106.4 | 106.5 | 106.6 | 106.6 |
| C-10 | 38.8 | 38.7 | 38.7 | 38.7 | 38.8 | 38.8 |
| C-11 | 64.2 | 64.2 | 64.3 | 64.4 | 64.2 | 64.2 |
| C-12 | 37.7 | 37.7 | 37.5 | 37.6 | 37.7 | 37.8 |
| C-13 | 67.6 | 67.7 | 64.3 | 64.4 | 67.7 | 67.8 |
| C-15 | 42.2 | 42.2 | 34.6 | 34.6 | 42.2 | 42.2 |
| C-16 | 71.8 | 71.8 | 71.7 | 71.7 | 71.8 | 71.9 |
| C-(ω-4) | | 32.5 | | 32.6 | 32.6 | 32.6 |
| C-(ω-3) | | 129.3 | | 129.3 | 129.4 | 129.4 |
| C-(ω-2) | | 131.8 | | 131.9 | 131.9 | 131.9 |
| C-(ω-1) | | 25.6 | | 25.6 | 25.6 | 25.6 |
| C-ω | 14.1 | 14.0 | 14.1 | 14.0 | 14.0 | 14.0 |
| alkyl-C | 37.7, 31.9, 29.67 (2), 29.65 (3), 29.63, 29.61, 29.58, 29.3, 25.4, 22.7 | 37.7, 29.66, 29.63, 29.62, 29.59 (2), 29.56, 29.49, 29.15, 25.4 | 39.8, 31.9, 29.64, 29.62, 29.61 (2), 29.60, 29.54, 29.49, 29.3, 25.1, 22.6 | 39.9, 29.66, 29.53 (3), 29.50, 29.16, 25.1 | 37.7, 29.68, 29.66, 29.61, 29.55, 29.51, 29.2, 25.5 | 37.8, 31.9, 29.70, 9.68 (3), 29.64 (2), 29.62, 29.54, 29.2, 25.5 |
| acetyl-C | | | 170.5, 21.4 | 170.6, 21.4 | | |

[a] Not visible in $^{13}C$ spectrum, chemical shift obtained from HMBC spectrum.

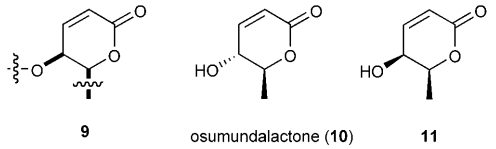



Figure 2. Comparison of suspected *syn*-configuration **9** to that of osumundalactone **10** and *syn*-synthetic isomer **11**.

pyran ring supported by the carbon chemical shift value ($\delta_C$ 106.5) suggesting a [6.5]-[5] anomeric[6] over a [6.6]-[7] spiroketal system. The remaining correlations in the $^1H,^1H$ COSY, HSQC and HMBC spectra ascribed the location of the hydroxyl substituted (C16) long chain alkyl group at position C13 of the tetrahydropyran ring (Figure 3). NOESY and 1D NOE experiments suggested H5 ($\delta_H$ 4.5) correlated with H13 ($\delta_H$ 4.4), which in turn correlated with H16 ($\delta_H$ 3.8). This indicated that the stereochemistry at the spiroacetal carbon (C8) was *EE* and the side chain hydroxyl was α configured. Even though a *syn* correlation was present between H13 ($\delta_H$ 4.4) and H12β ($\delta_H$ 1.8) the corresponding correlation to H11 ($\delta_H$ 4.1) was ambiguous. When NMR measurements were performed on a much more diluted sample a sharp doublet ($\delta_H$ 3.05) and sharp singlet ($\delta_H$ 2.95) appeared for the two hydroxyl groups. Consequently, this development with NOE correlations between H13 ($\delta_H$ 4.4), the C11 hydroxyl hydrogen and H16 ($\delta_H$ 3.8) defined both configurations at C11 and C16 (i.e., H16β).

To ascertain the proposed configuration at C8, geometry optimizations at the B3LYP/6-31G* level of theory[8] were undertaken for isomers having the proposed and inverted configuration at C5/6, C11, and C16.[9] To estimate the effect of anomeric stabilization, geometry optimizations were also performed on a set of isomers having the inverted configuration at C8. It became apparent, that the isomer shown in Figure 3 possessed the lowest energy of all studied isomers. Each isomer with the inverted configuration at C8 was predicted to have a higher energy than the corresponding epimer with the proposed configuration, although analysis of the results was complicated by possible hydrogen bonding between the hydroxyl group on C16 to the ketone part of the enlactone moiety and the fact that inverting the six-membered ring would lead to another chair-like conformer, again benefiting from anomeric stabilization. Interestingly, inversion at C11 and/or C16 was predicted to lead to the

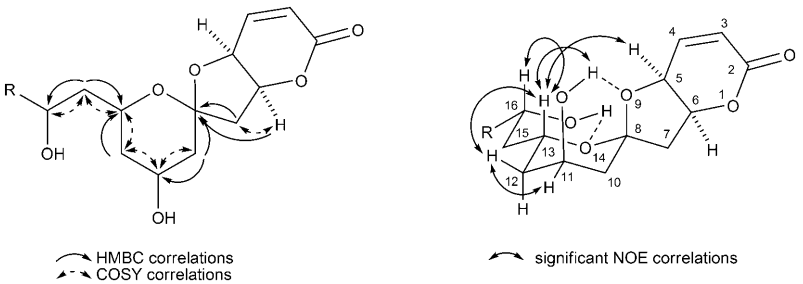



Figure 3. HMBC correlations between the proton (tail) and the carbon (head), COSY correlations and significant NOE correlations.

same increase in relative energy for both possible configurations at C5/6, respectively.

With the elucidation of the parent molecule complete other EBC-23 family members (namely 24, 25, 72, 73, 75 and 76) were easily identified and elucidated. The main differences in structure from that of EBC-23 (**1**) were attributed to side chain length, acetylation and points of unsaturation. Side chain length information could be garnered from LRESIMS (and HRESIMS), whereas acetylation could be deduced from $^1$H NMR chemical shift data and absolute location inferred from the absence of H16 ($\delta_H$ 3.8) seen in EBC-23 (**1**). Unsaturation occurred two carbons from the end of the chain in all cases [that is, EBC-24 (**3**), EBC-72 (**5**), EBC-75 (**6**) and EBC-76 (**7**)] as realized from HMBC correlations. In only one case [that is, EBC-73 (**8**)] was aromatic functionality observed as part of the side chain. This was confirmed as a *meta*-substituted benzodioxole, due to the signature aromatic splitting pattern, and the dioxymethylene NMR chemical shift ($\delta_H$ 5.9; $\delta_C$ 100).

For the purpose of confirming the relative and determining absolute stereochemistry, and reaffirming the biological activity, a synthetic campaign was initiated to concisely construct both enantiomers of EBC-23 (**1**). In this light it was beneficial to postulate a biosynthetic pathway. The EBC-23 (**1**) structural motif could be imagined by extension of that known from the related polyketide lactones already isolated from the *Lauraceae* family.[10] If a precursor such as **12**, which closely resembles passifloricin B albeit missing one hydroxyl group,[11] undergoes regioselective oxidation, followed by elimination, allylic oxidation and cyclization, EBC-23 (**1**) is realized (Figure 4). Starting with the regioselective oxidation, in the aforementioned sequence, would be pivotal so as to prevent Michael addition of hydroxyl groups to the enlactone, as observed in related natural products.[12]

In consideration of the above postulated biosynthetic origin retrosynthetic analysis was best initiated by ring opening of the spiroacetal moiety arriving at a straight chain polyketide **13**. Keto functionality seen in **13** serves as a point of fusion, as shown in **14**, via an acyl equivalent (**15**). A Tietze[13]–Smith[14] linchpin convergence strategy with epoxides **16** and **17** would satisfy this criteria, although subsequent ring-closing metathesis would be required to install the lactone.[15] A slight deviation of this approach could directly utilize the fully constructed, and suitably substituted,

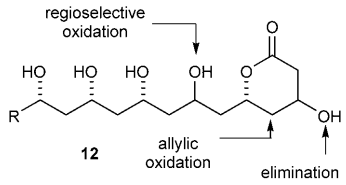
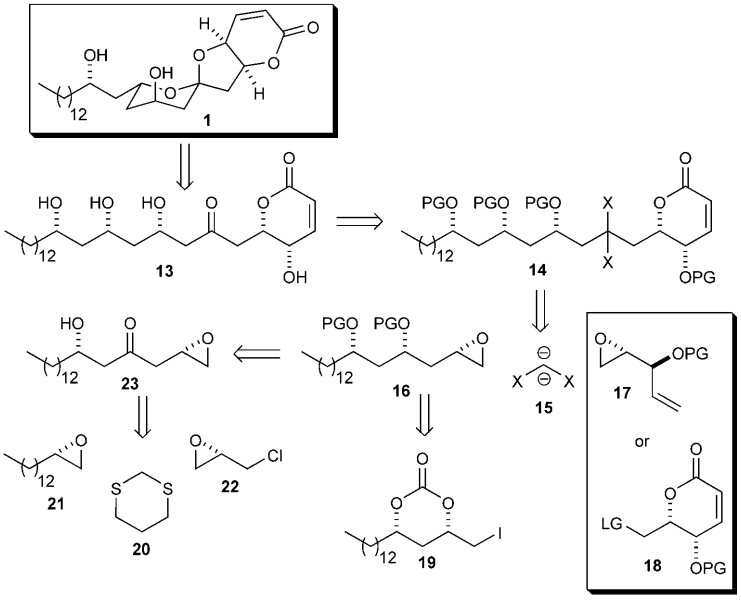


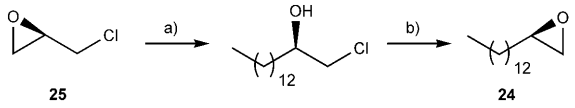

Figure 4. Possible biosynthetic pathway to EBC-23 (**1**).

lactone (**18**) as the right-hand fragment. The synthetic approach to the left-hand fragment **16** must contain sufficient stereochemical flexibility in the event that the relative stereochemical assignment of **1** is incorrect, or structure–activity studies (SAR) are required. For this task multiple options are available, for example, via asymmetric aldol chemistry, reiterative[16] Bartlett iodo carbonate cyclization (i.e., **19**),[17] or again Tietze[13]–Smith[14] linchpin methodology to access ketone **23** from dithiane **20** and epoxides **21** and **22** (Scheme 1).



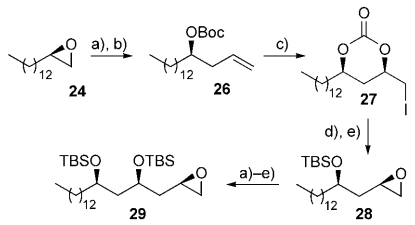

Scheme 1. Retrosynthetic analysis of EBC-23 (**1**).

Synthetic studies began by targeting the all-*R* isomer. To access the left-hand fragment **16** scalable amounts of enantiopure epoxide **24** were required.[18] Initially Jacobsen epoxide resolution methodology[19] was utilized, but this was later superseded by the method of Lepoittevin,[20] which provided **24** in large quantities and in high enantiomeric excess starting from (*R*)-epichlorohydrin (**25**) (Scheme 2).




Scheme 2. a) $CH_3(CH_2)_{11}MgBr$, THF, CuI, −78 to −45 °C, 75 %; b) NaOH, MeOH, THF, $H_2O$, RT, 3 h, 91 %. THF = Tetrahydrofuran, MeOH = Methanol.

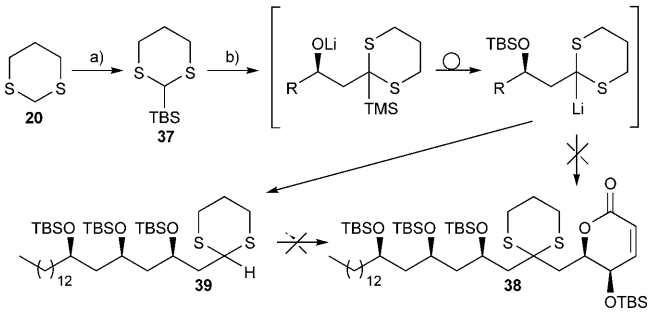
In the first instance the reiterative[16] Bartlett iodo carbonate cyclization[17] approach was applied to the synthesis of the left-hand fragment **29**. Reaction of epoxide **24** with vinyl magnesium bromide followed by treatment with di-*tert*-butyl dicarbonate afforded **26**, which on treatment with iodine bromide gave iodo carbonate **27**. Treatment of carbonate **27** with base followed by *tert*-butyldimethylsilyl chloride produced epoxide **28**. Reiteration of this process facilitated conversion of **28** into the desired material **29** (Scheme 3).



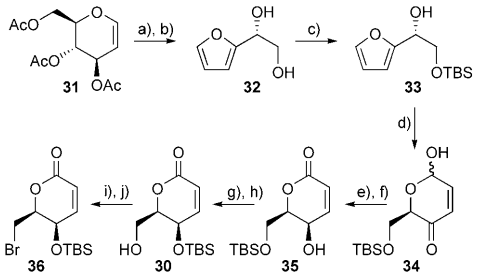

Scheme 3. a) $CH_2CHMgBr$, CuI, THF, −30 °C to RT, 1.5 h, 98 %; b) $Boc_2O$, $NEt_3$, DMAP, $CH_2Cl_2$, RT, 12 h, 99 %; c) IBr, toluene/$CH_2Cl_2$, −78 °C to RT, 1 h, quant.; d) $K_2CO_3$, MeOH, −78 °C to RT, overnight, 64 %; e) TBSCl, $NEt_3$, DMAP, DMF, RT, 8 h, 88 %; TBS = *tert*-butyldimethylsilyl; Boc = *tert*-butyloxycarbonyl; DMAP = 4-*N*,*N*-dimethylaminopyridine; DMF = *N*,*N*-dimethylformamide.

Work by O'Doherty et al.[21] disclosing the synthesis of hydroxylactone **30**, via transformations **31**, **32**,[22] **33**, **34** to **35**, suggested access to a derivative that resembled the right hand fragment lactone **18**, that is bromide **36**, might be achievable (Scheme 4). Repetition of the O'Doherty sequence proceeded smoothly except in the case of hemiacetal **34**, which required the use of Celite as an additive in the Jones oxidation. Conversion of **30**, via a Finkelstein reaction of the corresponding mesylate with lithium bromide, afforded the target right hand fragment **36** in excellent yield (90 %) (Scheme 4). Treatment of **30** with carbon tetrabromide/triphenylphosphine was less efficient.

Investigation into the convergence of the two halves (i.e., **29** and **36**) concentrated on the use of dithiane (**20**) as the one carbon unit linker. Epoxide **29** was reacted with the anion of TBS-dithiane **37**, which underwent the first addition step of the linchpin reaction followed by the Brook rearrangement.[23] Albeit through much effort the second step of the linchpin reaction, that is, addition of lactone **36**, failed to afford the advanced intermediate **38** with no recovery of starting material. If the reaction was quenched after the initial step substituted dithiane **39** could be obtained in high yield, however, deprotonation with any number of strong bases and subsequent addition of lactone **36** also failed to deliver the advanced intermediate **38**, again with no recovery of starting material (Scheme 5). Although dithianes have been used extensively in natural product total synthesis[24] it was suspected that the failed reactions above were the result of dithiane *S*-alkylation of lactone **36** as opposed to *C*-alkylation. However, spectroscopic evidence to support these suspicions were unable to be obtained due to complete decomposition.




Scheme 5. a) *n*BuLi, TBSCl, THF, −60 °C to RT, 6 h, (90 %); b) **37**, *n*BuLi, THF, RT, 20 min; then **29**, $Et_2O$, −30 °C to RT, overnight; TBS = *tert*-butyldimethylsilyl.

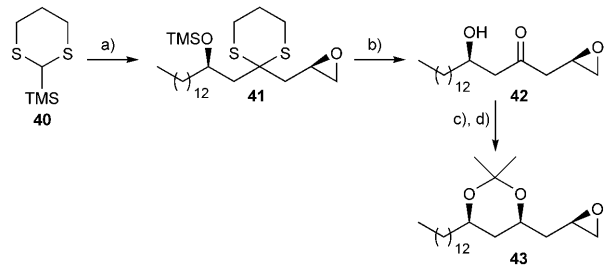



Scheme 4. a) NaOMe, MeOH, RT, 4 h, quant.; b) $FeCl_3 \cdot 6H_2O$, MeCN, RT, 1 h, 82 %; c) TBSCl, imidazole, $CH_2Cl_2$, 0 °C to RT, 45 min, 87 %; d) NBS, NaOAc, $NaHCO_3$, THF, 0 °C, 1 h, 89 %; e) Jones reagent, Celite, acetone, RT, 1 h, quant.; f) $NaBH_4$, $CeCl_3$, $CH_2Cl_2$/MeOH, −78 °C to RT, 1.5 h, 90 %; g) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, RT, 17 h, 75 %; h) HF, $H_2O$/MeCN, 0 °C, 1 h, 76 %; i) MsCl, $CH_2Cl_2$, 0 °C, 15 min, 98 %; j) LiBr, acetone, reflux, 96 hr, 92 %; TBS = *tert*-butyldimethylsilyl; NBS = *N*-bromosuccinimide; Tf = trifluoromethanesulfonyl; Ms = methansulfonyl.

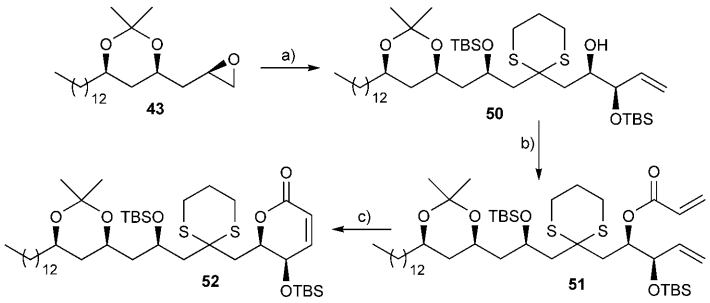
Since the initial step in the linchpin reaction (Scheme 5) with epoxide **29** was working well but the coupling to lactone **36** was not, the alternative retrosynthetic strategy based on ring-closing metathesis was investigated. To test this approach allyl epoxide **17** (Scheme 1) was required, but at the same time it was clear that the 10-step sequence leading to epoxide **29** was long-winded and tedious for scale-up. At this juncture a further application of the Tietze–Smith linchpin reaction, applied to the synthesis of the left-hand fragment (i.e., epoxide **16**), was deployed.

The one-pot linchpin reaction of TMS-dithiane (**40**) with epoxide **24**, and then (*R*)-epichlorohydrin (**25**), afforded the disubstituted dithiane **41** in 61 % yield. TBS-dithiane (**37**) normally outperforms **40** in linchpin reactions (i.e., affording higher yields),[25] but in this study *O*-TMS protection fortuitously underwent simultaneous deprotection when the keto group was unmasked [$Hg(ClO_4)_2$], giving hydroxyketone **42** in high yield. *syn*-Selective reduction,[26] followed by ketal protection,[27] proceeded smoothly in 74 % yield (over 2 steps) affording the desired left-hand fragment **43** [namely (*R*,*R*,*R*)-enantiomer of **16**] (Scheme 6).

For the second linchpin coupling enantiopure allyl epoxide **17** (Scheme 1) was required (i.e., **44**) (Scheme 7).

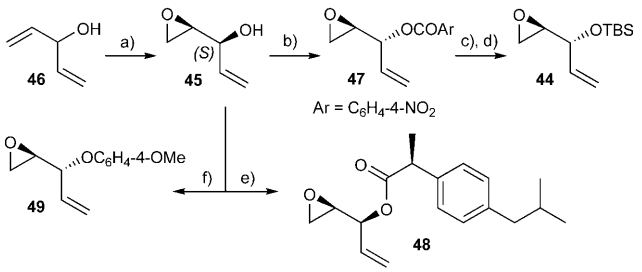



Scheme 6. a) **40**, *n*BuLi, THF, RT, 20 min; then **24**, $Et_2O$, −30 °C, 1 h; then HMPA, (*R*)-epichlorohydrin (**25**), −50 °C to RT, overnight, 61 %; b) $Hg(ClO_4)_2{\cdot}H_2O$, $CaCO_3$, THF, $H_2O$, RT, 6 min, 79 %; c) $Et_2BOMe$, $NaBH_4$, MeOH, THF, −78 °C, 4 h; d) $Me_2C(OMe)_2$, PPTS, $CH_2Cl_2$, RT, 5 h, 74 % over 2 steps (de > 95:5, *ee* 92 %); HMPA = hexamethylphosphorous triamide, PPTS = *p*-toluenesulfonic acid.




Scheme 8. a) **37**, *n*BuLi, THF, RT, 30 min; then **43**, $Et_2O$, −30 °C, 1 h; then HMPA, **44**, −50 °C to RT, overnight, 78 %; b) $CH_2CHCOCl$, $CH_2Cl_2$, $NEt_3$, 0 °C, 2 h, 82 %; h) **56**, MW, 150 °C, 150 W, toluene, 3 h, 65 %. MW = microwave irradiation.

Acquisition of this material was achieved through direct transformation of the known epoxide **45** (derived from divinyl carbinol **46**),[28] via Mitsunobu inversion (**47**),[29] subsequent hydrolysis and protection (Scheme 7). Unfortunately,




Scheme 7. a) (+)-DIPT, Ti(O*i*Pr)$_4$, *t*BuOOH, $CH_2Cl_2$, −20 °C, 9 days, 70–80 %; b) DIAD, $PPh_3$, *p*-$NO_2PhCO_2H$, THF, RT, 3 h, > 95 %; c) $K_2CO_3$, MeOH, $H_2O$, RT, 2 h, 98 %; d) TBSCl, Imidazole, $CH_2Cl_2$, 0 °C to RT, 1.5 h, 66 %, *ee* 90 %; e) (*S*)-ibuprofen (> 99 % *ee*), DCC, $CH_2Cl_2$, RT, 2 h, 59 %; f) see ref. [31]. DIPT = diisopropyl tartrate, DIAD = diisopropylazodicarboxylate, DCC = dicyclohexylcarbodiimide.

however, the Mitsunobu reaction proceeded with slight (≈10 %) epimerization[30] as determined from the (*S*)-ibuprofen derivative **48** (Scheme 7). This stereochemical issue could be avoided by substituting *p*-nitrobenzoic acid with *p*-methoxyphenol in the Mitsunobu reaction, but it was discovered that the change from a silyl protecting group (i.e., **44**) to an aromatic ether (i.e., **49**[31]) completely prevented the linchpin coupling shown in Scheme 8.

Gratifyingly, the long awaited key linchpin reaction of **43** and **44**, with the anion of dithiane **37**, gave the desired coupled product **50** in high yield (78 %). Reaction of **50** with acryloyl chloride proceeded smoothly affording acrylate **51** in 82 % yield (Scheme 8).

Much to our surprise, and contrary to literature precedent, ring-closing metathesis (RCM) required substantial investigation to facilitate the formation of the desired lactone ring system (**52**). Although Grubbs first-generation catalyst **53** has been reported to form lactones of this type with hydroxy substitution in the γ-position,[32] all attempts with this catalyst failed. Grubbs second-generation (**54**), first-generation Hoveyda–Grubbs (**55**) and second-generation Hoveyda–Grubbs (**56**) (Figure 5) have also been reported to effect the desired ring-closure,[33] but these too failed under normal conditions. When microwave irradiation[34] was applied to the system, however, lactone **52** was obtained in 65 % yield, but only using the Hoveyda–Grubbs second-generation catalyst (**56**) (Scheme 8). Even though RCM reactions are routinely performed in the presence of dithiane ring systems,[35] it is believed the difficulties encountered with the present RCM reactions are most likely attributed to the close proximity of sulfur atoms to the reaction centre allowing sulfur atom co-ordination to ruthenium thus preventing catalyst turnover.[36]

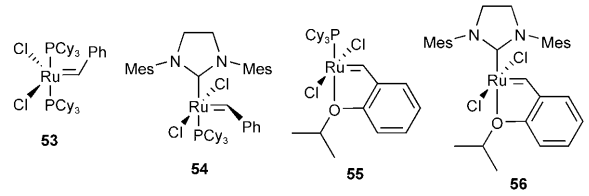
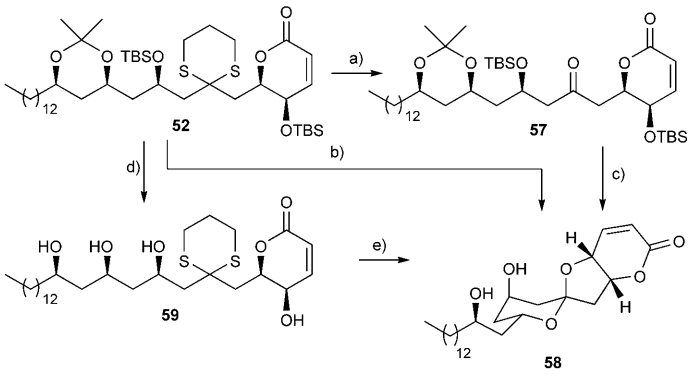



Figure 5. Ring-closing metathesis reaction catalysts.

Having established the carbon backbone in lactone **52**, deprotection cyclisation strategies could now be probed. The dithiane deprotection approach, investigated first, proceeded without incident giving ketone **57** in 95 % yield. Concomitant deprotection–cyclisation of ketone **57** with a variety of acids (e.g. aq HF,[37] CSA[37]) only afforded trace amounts of the target **58** (Scheme 9). On recommendation from a wonderful review by Pihko et al.,[38] direct methods for conversion of **52** to **58** (i.e., treatment with HF·py,[39] aq HF[40] or HCl[41,42]) were then investigated, which unfortunately provided little improvement. Following the work of Nakata,[43] however, TBS and acetonide deprotection performed with hydrogen fluoride pyridine complex afforded the polyol **59**, which on treatment with CAN[44] revealed the target in 54 % yield over two steps (substituting CAN for PIFA[45] failed). Considering the effort required to drive cyclisation with acid promoters, and the fact that CAN performed this task extremely well, suggests that formation of the spiroacetal was




Scheme 9. a) $Hg(ClO_4)_2 \cdot H_2O$, $CaCO_3$, THF, $H_2O$, RT, 20 min, 95%; b) aq HF (50%), $CH_3CN$, $CH_2Cl_2$, RT, 4 h, <5%; c) CSA, $CH_2Cl_2$, MeOH, 14 h, 0°C to RT, <5%; d) aq HF, $CH_3CN$, $CH_2Cl_2$, RT, 16 h; e) CAN, $CH_3CN$, $H_2O$, RT, 0.5 h, 54% (over 2 steps). CSA = camphorsulfonic acid, CAN = cerium ammonium nitrate.

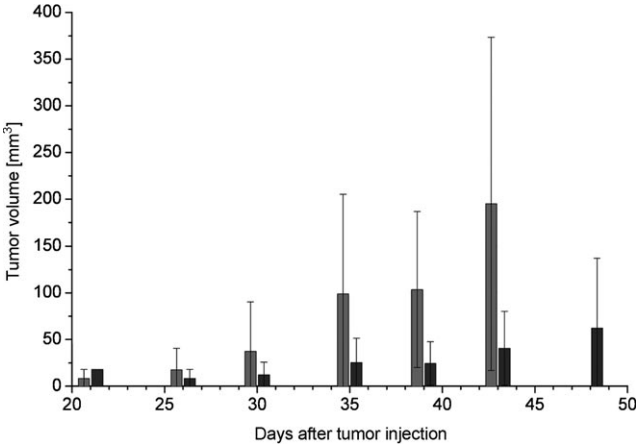
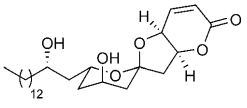



Figure 6. Inhibition of the growth of DU145 prostate tumors in nu-/nu-mice treated with EBC-23 (**1**: black, controls in grey) i.p. daily from day 6 to day 33 (100 μg/mouse days 6–9, then 200 μg/mouse). Significance in a permutation test including all time points $p = 0.005$ ($n = 12$ tumors per group).

mediated by metal (namely cerium) templated preorganisation as precedented by Smith[41] and Evans.[37,46]

Direct comparison of the optical rotation of both the synthetic material **58** (−16.6) and the natural material **1** (+16.3) revealed that the wrong enantiomer had been synthesized. Repeating the synthesis with *ent*-**43** and *ent*-**44**, however, afforded synthetic material **60** (+15.9), matching both the relative and absolute stereoconfiguration of the natural material EBC-23 (**1**).




**60**

Inhibition of cell growth by EBC-23 family members was quantitated after six days of treatment in culture. The results (Table 3) showed significant inhibitory activity against a range of tumor cell types, with normal cells (NFF) being less susceptible. EBC-23 (**1**) was selected for further evaluation in a mouse model.

Xenografts of the human prostate tumor cell line DU-145 in immunodeficient mice were treated daily with EBC-23 (**1**) (Figure 6). Tumor growth in the treated mice was inhibited compared with the solvent-only controls, and no side effects were observed. Considerable variation in tumor size occurred within each group but comparison with an iterative method (D statistic) which included measurements at all time points showed that growth was significantly inhibited in the group treated with EBC23 (**1**). Synthetic EBC-23 (**1**) displayed the same biological profile as that of the natural material. Interestingly, however, the opposite enantiomer also displayed strong activity, but less than the natural (and matching synthetic) material.

EBC-23 (**1**) has the ability to inhibit the growth of the androgen-independent prostate tumor cell line DU145 in the mouse model indicating that it has potential for the treatment of refractory solid tumors in adults. Both spiroacetals[47] and γ-oxygen-δ-lactones[48] of type **9** have independently demonstrated potent cancer related pharmacological activities. It is therefore no surprise that these surfactant-like molecules combining both spiroacetal and enlactone moieties deliver potent efficacy, further optimized by a convenient lipophilic side chain to potentially control metabolism and enable cell membrane permeability. This is the wonder of mother nature (biodiversity) in that she not only oversees and orchestrates plant evolution, but also plays medicinal chemist for mankind.[49]

## Conclusions

In conclusion, two linchpin reactions were key to the concise total synthesis of EBC-23, in both enantiopodes (**58** and **60**), achieved in nine linear steps in 8% overall yield. The total syntheses unequivocally proved the proposed relative and absolute stereoconfiguration. Suitable flexibility built into the synthesis allows multiple stereochemical arrangements poised for further biological evaluation of this unique structure class, reports of which will appear in due course.

Table 3. Inhibition $IC_{50}$ [$\mu g\,mL^{-1}$]* of human cell growth by EBC compounds.

| | EBC-23 | EBC-24 | EBC-25 | EBC-72 | EBC-73 | EBC-75 | EBC-76 |
|---|---|---|---|---|---|---|---|
| NFF | 1.8 | 0.8 | 0.75 | 0.8 | 0.75 | 0.85 | 1.0 |
| MM96L | 0.2 | 0.4 | 0.48 | 1.8 | 1.5 | 1.3 | 1.3 |
| MCF7 | 0.45 | 0.4 | 1.1 | >2 | 1.5 | 1.3 | >2 |
| DU145 | 0.48 | 0.3 | 0.4 | 1.6 | 1.8 | 1.7 | 0.98 |

[*] Dose required to inhibit growth to 50% of the untreated cells. NFF = normal fibroblasts; MM96L = melanoma; MCF7 = breast carcinoma; DU145 = prostate cancer.

## Experimental Section

**General**: $^1$H and $^{13}$C NMR spectra were recorded on Bruker AV300 (300.13 MHz; 75.47 MHz), AV400 (400.13 MHz; 100.62 MHz), DRX500 (500.13 MHz; 125.76 MHz) and AV750 (749.41 MHz) instruments in deuteriochloroform ($CDCl_3$) or hexadeuteriobenzene ($C_6D_6$) unless otherwise stated. GC/MS data were recorded on a Shimadzu GC-17 A Ver.3, mass-spectrometer: MS QP5050 A, ionisation at 70 eV, column: DB-5 ms 30 m × 0.25 mm, carrier-gas: He, total flow 32.2 mL min$^{-1}$, column flow 1.3 mL min$^{-1}$, injector temperature: 250 °C, standard program: 2 min at 100 °C, followed by a temperature increase of 16 °C min$^{-1}$ and held at 250 °C for 10 min. Low-resolution electrospray ionization mass spectrometry measurements (LRESIMS) were recorded in positive ionization mode on a Bruker Esquire HCT (High Capacity 3D ion trap) instrument with a Bruker ESI source. High resolution electrospray ionization (HRESIMS) accurate mass measurements were recorded in positive mode on a Bruker MicrOTOF-Q (quadrupole-Time of Flight) instrument with a Bruker ESI source. Accurate mass measurements were carried out with external calibration using sodium formate as a reference calibrant. Microanalyses were performed by the University of Queensland Microanalytical Service. High- and low-resolution EI mass spectral data were obtained on a Finnigan MAT900. Microwave irradiation was conducted with a CEM Discover microwave in 10 or 80 mL pressurized vials. IR spectra were measured on a Perkin–Elmer FT-IR spectrometer (Spectrum 2000) with Smiths detection (DuraSamplerIR II). Optical rotations were measured at the sodium D line (589 nm) using a 1 dm quartz cell on a Perkin–Elmer 241MC polarimeter. Tetrahydrofuran (THF) and diethyl ether ($Et_2O$) were dried with sodium/benzophenone. Dichloromethane ($CH_2Cl_2$) was dried with calcium hydride ($CaH_2$). Diethyl ether, petroleum ether (PE) and ethyl acetate (EA) for column chromatography were distilled before use. Flash chromatography was undertaken on silica gel (Flash Silica gel 230–400 mesh).

**Isolation**: The fruit of *Cinnamomum laubatii* (1.0 kg) was homogenized in methanol, and the concentrated extract partitioned between water and ethyl acetate. The ethyl acetate extract was chromatographed on silica gel with petroleum spirit (b.p. 40–60 °C), ethyl acetate and methanol. Fractions that inhibited the growth of the human melanoma cell line MM96L were further fractionated by HPLC on an Agilent Series 1100 HPLC Prep system using a reverse phase Agilent C18 column (30 mm × 250 mm × 10 μm). Isolates were eluted with a 70–100 % methanol/water gradient in the order EBC73 (**8**) (10.7 mg, 0.0011 %), EBC75 (**6**) (55 mg, 0.0055 %), EBC72 (**5**) (10 mg, 0.0010 %), EBC23 (**1**) (196 mg, 0.020 %), EBC24 (**3**) (43.5 mg, 0.0044 %), EBC25 (**4**) (44.6 mg, 0.0045 %) and EBC76 (**7**) (20 mg, 0.0020 %).

**(*S*)-1-Chloro-pentadecan-2-ol**: 1-Bromododecane (4.80 mL, 20.0 mmol) and iodine (one crystal) were added to a stirred suspension of magnesium turnings (0.673 g, 27.7 mmol) in anhydrous THF (80 mL) under an argon atmosphere. The mixture was refluxed for 5 h and then cooled to room temperature. This solution of dodecylmagnesium bromide was cannulated into a stirred suspension of (*S*)-epichlorohydrin (1.30 mL, 16.6 mmol) and copper (I) iodide (0.363 g, 1.91 mmol) in anhydrous THF (35 mL) at −78 °C. The mixture was stirred for 90 min., during which time the temperature increased to −45 °C. The reaction was quenched with sat. $NH_4Cl$ solution (100 mL) and the layers were separated. Additional product was extracted into $Et_2O$ (2 × 75 mL) and the combined organic phase was washed with sat. $NH_4Cl$ solution (100 mL) and brine (100 mL). Drying ($MgSO_4$) followed by concentration in vacuo provided a crude oil, which after flash chromatography (PE/EA 10:1) furnished the title compound as a white solid (3.28 g, 75 %). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 0.86 (t, $J$ = 7.0 Hz, 3H), 1.24 (s, 21H), 1.38–1.56 (m, 3H), 2.10 (brs, 1H), 3.45 (dd, $J$ = 11.0, 7.1 Hz, 1H), 3.61 (dd, $J$ = 11.0, 3.3 Hz, 1H), 3.73–3.83 ppm (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 14.1, 22.7, 25.5, 29.3, 29.5, 29.55, 29.64, 29.7, 31.9, 34.2, 50.6, 71.5 ppm; MS (EI): *m*/*z* (%): 227 (3) [$M^+$−Cl], 213 (28), 168 (4), 125 (7), 111 (14), 97 (27), 83 (28), 69 (30), 57 (41), 43 (100).

**(*R*)-1-Chloro-pentadecan-2-ol**: The title compound was prepared via the above procedure except using (*R*)-epichlorohydrin (**25**). All spectral data were identical to those for (*S*)-1-chloro-pentadecan-2-ol.

**(*S*)-2-Tridecyloxirane (*ent*-24)**:[20] To a solution of (*S*)-1-chloro-pentadecan-2-ol (10.8 g, 41.3 mmol) in THF (55 mL) and MeOH (152 mL) was added a solution of sodium hydroxide (2.09 g, 52.2 mmol) in $H_2O$ (35 mL). The mixture was stirred at room temperature for 3 h. The THF and MeOH were then removed in vacuo and additional $H_2O$ (150 mL) was added. The crude product was extracted into $Et_2O$ (3 × 100 mL) and the combined organic phase was washed with brine (200 mL), dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (PE/EA 20:1) afforded the title compound as a colorless oil (8.44 g, 91 %). $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 0.86 (t, $J$ = 6.9 Hz, 3H), 1.18–1.36 (m, 20H), 1.36–1.47 (m, 2H), 1.47–1.54 (m, 2H), 2.43 (dd, $J$ = 5.2, 2.8 Hz, 1H), 2.72 (dd, $J$ = 5.2, 4.0 Hz, 1H), 2.88 ppm (tdd, $J$ = 5.2, 4.0, 2.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ = 14.1, 22.7, 26.0, 29.3, 29.4, 29.5, 29.62, 29.63, 29.64, 29.7, 31.9, 32.5, 47.1, 52.4 ppm; MS (EI): *m*/*z* (%): 226 (2) [$M^+$], 213 (3), 111 (8), 96 (26), 82 (38), 71 (48), 55 (56), 43 (100).

**(*R*)-2-Tridecyloxirane (24)**: The title compound was prepared via the above procedure. $^1$H and $^{13}$C NMR were identical to that above.

**Epoxide 41**: Under an argon atmosphere *n*BuLi (7.60 mL, 1.39 M solution in hexanes, 10.6 mmol) was added to a solution of 2-trimethylsilyl-1,3-dithiane (**40**) (2.13 g, 11.1 mmol) in anhydrous THF (20 mL) and the solution was stirred at room temperature for 20 min. The solution was then transferred via cannula to a suspension of (*R*)-2-tridecyloxirane (**24**) (2.01 g, 8.88 mmol) in anhydrous $Et_2O$ (80 mL) at −30 °C. The mixture was stirred at −30 °C for one hour and then cooled to −50 °C. Anhydrous HMPA (2.00 mL, 11.5 mmol) and (*R*)-epichlorohydrin (**25**) (1.80 mL, 23.0 mmol) were added in quick succession and the mixture was slowly warmed to RT overnight. The reaction was quenched with sat. $NH_4Cl$ solution (40 mL) and was extracted with $Et_2O$ (2 × 60 mL). The combined organic phase was washed with 10 % LiCl solution (2 × 40 mL), sat. $NH_4Cl$ solution (40 mL), $H_2O$ (40 mL) and brine (40 mL), dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (PE/EA/TEA 30:1:0.6) yielded the title compound as a colorless oil (2.57 g, 61 %). $[\alpha]_D^{20}$ = +15.9 ($c$ = 0.012, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 0.12 (s, 9H), 0.80 (t, $J$ = 6.8 Hz, 3H), 1.24 (s, 22H), 1.47 (m, 2H), 1.91–1.95 (m, 2H), 2.11–2.18 (m, 3H), 2.24 (dd, $J$ = 14.7, 4.4 Hz, 1H), 2.51–2.54 (dd, $J$ = 5.2, 2.7 Hz, 1H), 2.74–2.84 (m, 5H), 3.17–3.23 (m, 1H), 4.05–4.10 ppm (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 0.7, 14.0, 22.6, 24.6, 24.9, 26.1, 26.2, 29.3, 29.6, 29.8, 31.8, 38.9, 41.9, 45.4, 45.6, 46.6, 49.0, 51.5, 69.7 ppm; MS (ESI): *m*/*z*: 497 [$M$+Na]$^+$; HRMS: *m*/*z*: calcd for $C_{25}H_{50}NaO_2S_2Si$: 497.2914, found: 497.2902.

**Epoxide *ent*-41**: The title compound was prepared via the above procedure. $[\alpha]_D^{20}$ = +14.7 ($c$ = 0.0097, $CHCl_3$); $^1$H and $^{13}$C NMR were identical to that above; MS (ESI): *m*/*z*: 497 [$M$+Na]$^+$; HRMS: *m*/*z*: calcd for $C_{25}H_{50}NaO_2S_2Si$: 497.2914, found: 497.2916.

**(2*R*,6*R*)-6-Hydroxy-1-oxiranyl-4-nonadecanone (42)**: Calcium carbonate (1.06 g, 10.6 mmol) followed by mercury (II) perchlorate hydrate (1.06 g, 2.66 mmol) were added to a solution of epoxide **41** (0.497 g, 1.05 mmol) in THF/$H_2O$ 4:1. The suspension was stirred for 6 min at room temperature. Sat. $NaHCO_3$ solution (45 mL) was then added and the mixture was filtered through a pad of Celite. After the Celite had been washed thoroughly with $E_2O$ the layers of the filtrate were separated and the organic layer was washed with sat. $NaHCO_3$ solution (45 mL), $H_2O$ (45 mL) and brine (45 mL). Drying ($MgSO_4$) followed by concentration in vacuo provided the title compound in sufficient purity for use in the next step as a white solid (246 mg, 79 %). [Note: this material was found to be unstable to silica gel.] $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 0.85 (t, $J$ = 6.7 Hz, 3H), 1.23 (brs, 21H), 1.37–1.46 (m, 3H), 2.48 (dd, $J$ = 4.9, 2.6 Hz, 1H), 2.56–2.70 (m, 4H), 2.81(t, $J$=6.9 Hz, 1H), 3.24 (dddd, $J$ = 6.4, 4.9, 4.0, 2.6 Hz, 1H), 3.99–4.07 ppm (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 14.1, 22.6, 25.4, 29.3, 29.48, 29.53, 29.6, 31.9, 36.5, 46.5, 46.7, 47.5, 49.8, 67.5, 209.0 ppm; MS (ESI) 335 [$M$+Na]$^+$; HRMS: *m*/*z*: calcd for $C_{19}H_{36}O_3$: 663.4955, found: 663.4758.

**(2*S*,6*S*)-6-Hydroxy-1-oxiranyl-4-nonadecanone (*ent*-42)**: The title compound was prepared via the above procedure. $^1$H and $^{13}$C NMR were identical to that above; MS (ESI) 335 [$M$+Na]$^+$; HRMS: *m*/*z*: calcd for $C_{19}H_{36}NaO_3$: 335.2557, found: 335.2544.

**Epoxide 43**: To a solution of hydroxyketone **42** (31.2 mg, 0.1 mmol) in anhydrous THF (0.8 mL) and anhydrous MeOH (0.2 mL) at −70 °C

under argon, was added dropwise diethylmethoxyborane (0.11 mL, 0.11 mmol, 1 M), and the resulting mixture was stirred for 15 min. Then sodium borohydride (4.2 mg, 0.11 mmol) was added, the mixture was stirred for 4 h, followed by the addition of acetic acid (0.1 mL). The reaction mixture was diluted with EtOAc, washed with aqueous $NaHCO_3$, and brine (3 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The residue thus obtained was azeotroped several times with MeOH until the hydrolysis of the boronate was complete. The crude product was used without purification. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 0.82 (t, $J$=6.9 Hz, 3H), 1.22 (s, 22H), 1.74 (m, 1H), 1.42–1.64 (m, 5H), 2.47 (m, 1H), 2.74 (m, 1H), 3.06 (m, 1H), 3.84 (m, 1H), 4.10 ppm (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 14.1, 22.7, 25.3, 29.3, 29.58, 29.63, 31.9, 38.2, 40.2, 42.8, 46.6, 50.0, 71.3, 73.0 ppm.

To the above diol (37 mg, 0.12 mmol) dissolved in anhydrous $CH_2Cl_2$ (1 mL) under an argon atmosphere, was added pyridium *p*-toluenesulfonate (one crystal) and dimethoxypropane (60 μL, 0.5 mmol). The mixture was then stirred for 4 h at room temperature. The filtrate was washed with $NaHCO_3$ solution (3 mL, 5%), and brine (3 mL), dried over $Na_2SO_4$ and concentrated in vacuo. Flash chromatography on silica gel (PE/EA 20:1) afforded the title compound [30 mg, 80% (two steps)] as a white solid (dr 93:7).[50] $[\alpha]_D^{20}$ = +5.0 ($c$=0.012, $CHCl_3$); $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 0.86 (t, $J$=12.93 Hz, 3H), 1.21–1.29 (m, 22H), 1.32–1.36 (m, 1H), 1.36 (s, 3H), 1.41 (s, 3H), 1.47–1.50 (m, 1H), 1.52 (t, $J$=2.4 Hz, 1H), 1.54 (t, $J$=2.5 Hz, 1H), 1.64–1.77 (m, 2H), 2.49 (dd, $J$=5.1, 2.6 Hz, 1H), 2.74 (dd, $J$=5.1, 4.1 Hz, 1H), 3.02 (td, $J$=2.9, 1.9 Hz, 1H), 3.74–3.83 (m, 1H), 3.99 (dtt, $J$=11.7, 5.9, 2.5 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 14.1, 19.8, 22.7, 24.9, 29.3, 29.57, 29.64, 29.7, 30.2, 31.9, 36.4, 36.6, 38.8, 46.8, 48.9, 66.4, 68.9, 98.4; MS (ESI): $m/z$: 377 [$M$+Na]$^+$; HRMS: $m/z$: calcd for $C_{22}H_{42}NaO_3$: 377.3026, found: 377.3020.

**Epoxide *ent*-43**: The title compound was prepared via the above procedure. $[\alpha]_D^{20}$ = −5.1 ($c$=0.011, $CHCl_3$); $^1$H and $^{13}$C NMR were identical to that above; MS (ESI): $m/z$: 377 [M+Na]$^+$; HRMS: $m/z$: calcd for $C_{22}H_{42}NaO_3$: 377.3026, found: 377.3020.

**(*R*)-1-[(*S*)-Oxiran-2-yl]prop-2-enol (45)**: Freshly activated, powdered molecular sieves (3 Å, 2.50 g) were suspended in anhydrous $CH_2Cl_2$ (55 mL) in a 100 mL two-necked flask under an argon atmosphere. The suspension was then cooled to −20 °C, and D-DIPT (0.78 mL, 873 mg, 3.73 mmol), Ti(O*i*Pr)$_4$ (1.18 mL, 1.13 g, 3.96 mmol), and *t*BuOOH (~5.5 M in decane, 7.20 mL, 39.6 mmol) were added consecutively. The mixture was stirred at the same temperature for 15 min before adding freshly distilled [Kugelrohr, 100 °C, discontinuous (tap on/off) vacuum] 1,4-pentadien-3-ol (**46**) (2.35 g, 27.9 mmol, rinse with ~3 mL of $CH_2Cl_2$). The flask was sealed and placed in the freezer (−20 °C) for 9 d with occasional shaking. The reaction was quenched by adding triethylphosphite (2.50 mL, 2.39 g, 14.4 mmol) to the cold flask. After stirring for ca. 20–30 min without a cold bath, saturated $Na_2SO_4$-solution (1.5 mL) was added and the resulting mixture was stirred for 3 h at room temperature open to the atmosphere. Celite (15 g) was added to the reaction. After stirring for another 30 min the resulting slurry was filtered through a pad of Celite which was washed thoroughly with $CH_2Cl_2$. The combined filtrate was dried over $MgSO_4$, filtered and concentrated (rotavap, 200 Torr, 50 °C, ca. 10 min). The title compound was isolated by flash chromatography [50 g $SiO_2$, 5×5 cm, pentane → pentane/ether 1:1; $R_f$ (*t*BuOOH/*t*BuOH)=0.69, $R_f$ (starting material)=0.60, $R_f$ (DIPT)=0.48, $R_f$ (product)=0.31; all in PE/EA 1:1] to give the title compound (60–70%, contaminated with 5–15% of tartrate and ca. 6% of another diastereomer) which was used without further purification in the Mitsunobu reaction. If necessary, the epoxyalcohol can be further purified by distillation (Kugelrohr distillation using a vacuum controller; 80 °C at 100 Torr to remove volatiles, then cooling the receiver flask with dry ice and reduce pressure (to 30 Torr) and increasing the temperature (to 130 °C) to obtain the title compound as a colorless oil (1.57 g, 56%). $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ = 2.74 (dd, $J$=5.0, 4.0 Hz, 1H), 2.79 (ddd, $J$=5.0, 3.0, 0.44 Hz, 1H), 3.08 (d, $J$=4.0, 3.0 Hz, 1H), 4.29–4.36 (m, 1H), 5.38 (dt, $J$=17.3, 1.4 Hz, 1H), 5.45 (dt, $J$=10.5, 1.4 Hz, 1H), 5.83 ppm (ddd, $J$=17.3, 10.5, 6.3 Hz, 1H); The $^{13}$C NMR spectrum was in agreement with that reported previously.[28]

**Nitroester 47**: To (*R*)-1-[(*S*)-oxiran-2-yl]prop-2-enol (**45**) (460 mg, 4.6 mmol), triphenylphosphine (2.41 g, 9.2 mmol) and *p*-nitrobenzoic acid (1.54 g, 9.2 mmol) in anhydrous THF (35 mL) at 0 °C under an argon atmosphere, was slowly added diisopropylazodicarboxylate (1.3 mL, 9.2 mmol) at 0 °C. The reaction was stirred for 15 min. while warming up to room temperature, then stirred for 3 h at RT. The reaction mixture was diluted with $Et_2O$ (30 mL), washed with aqueous $NaHCO_3$ (2× 30 mL), and brine (30 mL), dried over $Na_2SO_4$ and concentrated in vacuo. After flash chromatography on silica gel (PE/EA 3:1) the nitroester (1.12 g, 98%) was obtained as a yellow oil. $[\alpha]_D^{20}$ = −24.2 ($c$=0.074, $CHCl_3$); $^1$HNMR ($CDCl_3$, 300 MHz): $\delta$ = 2.71–2.74 (dd, $J$=4.8, 2.6 Hz, 1H), 2.88 (dd, $J$=4.8, 4.0 Hz, 1H), 3.27 (ddd, $J$=6.3, 4.0, 2.6 Hz, 1H), 5.24–5.51 (m, 3H), 5.91 (dd, $J$=10.6, 6.3 Hz, 1H), 8.11–8.38 ppm (m, 4H); MS (ESI): $m/z$: 272 [M+Na]$^+$; HRMS: $m/z$: calcd for $C_{12}H_{11}NNaO_5$: 272.0529, found: 272.0525.

**Nitroester *ent*-47**: The title compound was prepared via the above procedure. $^1$H and $^{13}$C NMR were identical to that above; HRMS: $m/z$: calcd for $C_{12}H_{11}NNaO_5$: 272.0529, found: 272.0525.

***tert*-Butyldimethyl{(*S*)-1-[(*S*)-oxiran-2-yl]allyloxy}silane (*ent*-44)**

**(*S*)-1-[(*S*)-oxiran-2-yl]prop-2-enol**: Nitroester *ent*-**47** (794 mg, 3.19 mmol) and potassium carbonate (484 mg, 3.5 mmol) were suspended in MeOH (30 mL) and $H_2O$ (2.0 mL) at RT. After stirring for 2 h the reaction flask was placed in a Kugelrohr distillation apparatus to remove excess MeOH [vacuum controlled (55 °C/80 Torr), cooling the outer collection flask with dry ice]. The residue was washed with $Et_2O$/*n*-pentane 1:1, then concentrated on a rotary evaporator (40 °C/540 Torr) to afford the title compound (312 mg, 98%) as colorless oil. $[\alpha]_D^{20}$ = −5.1 ($c$=0.027, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 2.41 (brs, 1H), 2.72 (dd, $J$=4.9, 2.7 Hz, 1H), 2.80 (t, $J$=4.4 Hz, 1H), 3.03 (ddd, $J$=5.0, 4.1, 2.7 Hz, 1H), 3.97 (t, $J$=5.2 Hz, 1H), 5.18–5.41 (m, 2H), 5.90 ppm (ddd, $J$=17.3, 10.5, 5.5 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = 44.7, 54.7, 72.5, 116.8, 136.2 ppm.

**(*R*)-1-[(*R*)-oxiran-2-yl]prop-2-enol**: All spectral data were identical to those above.

(*S*)-1-[(*S*)-Oxiran-2-yl]prop-2-enol (400 mg, 4 mmol) and imidazole (656 mg, 9.63 mmol) were dissolved in anhydrous $CH_2Cl_2$ (10 mL) under an argon atmosphere. *tert*-Butyldimethylsilyl chloride (1.12 g, 7.43 mmol) was added in one portion at 0 °C (using 6 mL of anhydrous $CH_2Cl_2$ to rinse). The reaction was stirred for 90 min. while slowly warming up to RT, at which time TLC showed complete consumption of starting material. The reaction was quenched by adding $NaHCO_3$ solution (10 mL) and the product was extracted into $Et_2O$ (2×10 mL). The combined organic phase was washed with $NaHCO_3$ solution (10 mL) and $NH_4Cl$ solution (10 mL), dried over $Na_2SO_4$, and concentrated (rotavap, 50 °C/200 Torr). After flash chromatography on silica gel (pentane/$Et_2O$ 30:1) the title compound (ent-**44**) (565 mg, 66%) was obtained as a colorless oil. $[\alpha]_D^{20}$ = −25.7 ($c$=0.055, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 0.04 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 2.57–2.59 (dd, $J$=4.9, 2.7 Hz, 1H), 2.74–2.77 (dd, $J$=4.9, 4.0 Hz, 1H), 2.91–2.95 (m, 1H), 3.85 (td, $J$=6.3, 1.6 Hz, 1H), 5.13 (td, $J$=10.5, 1.6 Hz, 1H), 5.31 (td, $J$=17.2, 1.6 Hz, 1H), 5.81 ppm (m, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = −5.0, −4.9, 25.7, 44.2, 55.2, 75.0, 115.8, 136.4 ppm.

***tert*-Butyldimethyl{(*R*)-1-[(*R*)-oxiran-2-yl]allyloxy}silane (44)**: The title compound was prepared via the above procedure. $[\alpha]_D^{20}$ = +24.2 ($c$= 0.022, $CHCl_3$); $^1$H and $^{13}$C NMR were identical to that above; MS (ESI): $m/z$: 237 [$M$+ Na]$^+$; HRMS: $m/z$: calcd for $C_{11}H_{22}NaO_2Si$: 237.1281, found: 237.1283.

**Second linchpin reaction (*ent*-50)**: A solution of TBS-dithiane (**37**) (777 mg, 3.32 mmol) in anhydrous THF (10 mL), under an argon atmosphere, was treated with *n*BuLi (2.4 mL, 3.32 mmol, 1.39 M) at 0 °C and stirred at room temperature for 20 min. This solution was transferred via cannula to a pre-cooled solution of epoxide (*ent*-**43**) (966 mg, 2.72 mmol) in anhydrous $Et_2O$ (20 mL) under an argon atmosphere at −30 °C. The reaction mixture was then stirred at −30 °C for 1 h and cooled to −50 °C before anhydrous HMPA (1.17 mL, 5.2 mmol) and a solution of vinylepoxide (*ent*-**44**) (700 mg, 3.26 mmol) in $Et_2O$ (20 mL) were added successively. The reaction was then allowed to warm up to room temperature with stirring overnight. The reaction was quenched by adding $NH_4Cl$ so-

lution (20 mL) at RT. The aqueous phase was extracted with $Et_2O$ (20 mL×3) and the combined organic extracts were washed with LiCl solution (20 mL×2, 10%), $NH_4Cl$ solution (20 mL), brine, dried over $Na_2SO_4$ and concentrated in vacuo. Subjecting the residue to flash chromatography on silica gel (PE/EA 60:1) afforded the first generation dithiane addition by-product (320 mg, 20%) as a colorless oil. Changing the solvent system (PE/EA 30:1) afforded the desired product (*ent*-**50**) (1.7 g, 78%) as a colorless oil. $[\alpha]_D^{20}=-13.4$ ($c=0.025$, $CHCl_3$); $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 0.03 (s, 3H), 0.06 (s, 6H), 0.10 (s, 3H), 0.85–0.88 (m, 12H), 0.88 (s, 9H), 1.08–1.15 (m, 1H), 1.23 (s, 23H), 1.35 (s, 3H), 1.40 (s, 3H), 1.42–1.49 (m, 2H), 1.62–1.67 (m, 1H), 1.74–1.79 (m, 1H), 1.89–1.95 (m, 2H), 1.98 (dd, $J$=15.1, 5.7 Hz, 1H), 2.07 (d, $J$=5.0 Hz, 2H), 2.37 (dd, $J$=15.2, 4.7 Hz, 1H), 2.75–2.82 (m, 4H), 2.94 (br s, 1H), 3.73–3.76 (m, 1H), 3.93–3.96 (m, 1H), 3.98–4.03 (m, 2H), 4.18 (qd, $J$= 5.2, 4.9 Hz, 1H), 5.17–5.27 (m, 2H), 5.82 ppm (ddd, $J$=17.2, 10.6, 6.3 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ = −4.9, −4.3, −4.0, −3.6, 14.1, 18.0, 18.2, 19.9, 22.7, 24.7, 25.0, 25.9, 26.1, 26.2, 26.6, 29.3, 29.59, 29.60, 29.66, 29.68, 30.3, 31.9, 36.5, 37.4, 42.0, 45.7, 47.3, 52.0, 66.0, 66.8, 69.10, 71.7, 98.2, 117.0, 137.8 ppm; MS (ESI): $m/z$: 825 $[M+Na]^+$; HRMS: $m/z$: calcd for $C_{43}H_{86}NaO_5S_2Si_2$: 825.5347, found: 825.5284.

**Second linchpin reaction (50)**: The title compound was prepared via the above procedure. $[\alpha]_D^{20}=+12.8$ ($c=0.017$, $CHCl_3$); $^1$H and $^{13}$C NMR were identical to that above; MS (ESI): $m/z$: 826 $[M+Na]^+$; HRMS: $m/z$: calcd for $C_{43}H_{86}NaO_5S_2Si_2$: 825.5347, found: 825.5320.

**Acrylate (*ent*-51)**: Acryloyl chloride (9 mg, 8 μL, 0.1 mmol) was added dropwise to a solution of alcohol (*ent*-**50**) (40 mg, 0.05 mmol) in anhydrous $CH_2Cl_2$ (1 mL) and anhydrous triethylamine (20 mg, 28 μL, 0.20 mmol) at 0°C under an argon atmosphere. The mixture was then stirred for 2 h at 0°C. After this time the mixture was concentrated in vacuo and the residue loaded directly onto a silica gel column. Flash chromatography (PE/EA 30:1) afforded the title compound (35 mg, 82%) as a colorless oil. $[\alpha]_D^{20}=-19.2$ ($c=0.011$, $CHCl_3$); $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ = 0.06 (s, 3H), 0.07 (s, 3H), 0.11 (s, 3H), 0.13 (s, 3H), 0.82–0.88 (m, 21H), 1.23 (s, 23H), 1.34 (s, 3H), 1.39 (s, 3H), 1.42–1.52 (m, 2H), 1.59–1.80 (m, 2H), 1.81–1.94 (m, 3H), 2.10–2.21 (m, 1H), 2.24–2.32 (m, 1H), 2.37 (dd, $J$=11.0, 4.4 Hz, 1H), 2.61–2.87 (m, 5H), 3.70–3.82 (m, 1H), 3.91–4.05 (m, 1H), 4.15–4.33 (m, 2H), 5.14 (dt, $J$= 10.5, 1.6 Hz, 1H), 5.19–5.25 (m, 1H), 5.25–5.34 (m, 1H), 5.73–5.86 (m, 2H), 6.03–6.20 (m, 1H), 6.38 ppm (dd, $J$=17.3, 1.5 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = −5.0, −4.8 −4.1, −3.6, 14.1, 18.0, 18.2, 19.9, 22.7, 24.6, 25.0, 25.9, 26.05, 26.10, 26.6, 29.3, 29.59, 29.64, 29.67, 30.3, 31.9, 36.5, 37.3, 38.7, 45.9, 47.1, 52.4, 66.2, 67.1, 69.1, 72.1, 73.5, 98.2, 116.6, 128.9, 130.6, 136.2, 165.3 ppm; MS (ESI): $m/z$: 879 $[M+Na]^+$; HRMS: $m/z$: calcd for $C_{46}H_{88}NaO_6S_2Si_2$: 879.5453, found: 879.5450.

**Acrylate 51**: The title compound was prepared via the above procedure. $[\alpha]_D^{20}=+12.3$ ($c=0.011$, $CHCl_3$); $^1$H and $^{13}$C NMR were identical to that above; MS (ESI): $m/z$: 879 $[M+Na]^+$; HRMS: $m/z$: calcd for $C_{46}H_{88}NaO_6S_2Si_2$: 879.5453, found: 879.5449.

**Lactone *ent*-52**: To a degassed solution of acrylate (*ent*-**51**) (238 mg, 0.278 mmol) in anhydrous toluene (3 mL) was added Hoveyda–Grubb's 2nd generation catalyst (17 mg, 0.03 mmol, 10 mol%) in a microwave vessel under an argon atmosphere. After microwave irradiation [$T$ = 150°C; Hold: 4 h; power: 150 W] the mixture was concentrated in vacuo. The residue was subjected to flash chromatography on silica gel (PE/EA 10:1) affording the title compound (150 mg, 65%) as a colorless oil. $[\alpha]_D^{20}=+48.3$ ($c=0.013$, $CHCl_3$); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ = 0.08 (s, 6H), 0.13 (s, 6H), 0.86 (m, 21H), 1.09–1.18 (m, 1H), 1.23 (s, 22H), 1.35 (s, 3H), 1.41 (s, 3H), 1.44–1.45 (m, 2H), 1.64 (ddd, $J$=14.0, 7.5, 4.1 Hz, 1H), 1.77 (ddd, $J$=14.1, 7.5, 4.1 Hz, 1H), 1.81–1.89 (m, 3H), 1.99 (dd, $J$=14.6, 6.8 Hz, 1H), 2.41–2.44 (m, 3H), 2.69 (ddd, $J$=14.6, 6.8, 2.9 Hz, 1H), 2.74–2.92 (m, 3H), 3.76–3.79 (m, 1H), 4.02–4.03 (m, 1H), 4.22–4.23 (m, 1H), 4.25–4.27 (dd, $J$=5.1, 2.9 Hz, 1H), 4.76–4.80 (m, 1H), 6.04 (d, $J$=9.6 Hz, 1H), 6.80 ppm (dd, $J$=9.6 Hz, 5.3 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz): $\delta$ = −4.4, −4.0, −3.9, −3.6, 14.1, 18.0, 18.1, 19.8, 22.6, 24.5, 24.9, 25.9, 26.0, 26.1, 26.5, 29.3, 29.6, 30.3, 36.5, 37.4, 40.5, 45.4, 47.1, 51.9, 64.4, 65.8, 67.0, 69.1, 78.7, 98.2, 122.3, 144.6, 163.3 ppm; MS (ESI): $m/z$: 851 $[M+Na]^+$; HRMS: $m/z$: calcd for $C_{44}H_{84}NaO_6S_2Si_2$: 851.5140, found: 851.5129.

**Lactone 52**: The title compound was prepared via the above procedure. $[\alpha]_D^{20}=-59.8$ ($c=0.018$, $CHCl_3$); $^1$H and $^{13}$C NMR were identical to that above; HRMS: $m/z$: calcd for $C_{44}H_{84}NaO_6S_2Si_2$: 851.5140, found: 851.5134.

**EBC-23 (60)**: To a solution of *ent*-**52** (130 mg, 0.157 mmol) in $CH_2Cl_2$ (5.3 mL) at 0°C was added a solution of aqueous hydrogen fluoride (0.8 mL, 50%) dissolved in acetonitrile (2.6 mL). The reaction mixture was then stirred for 8 h at RT. Additional aqueous hydrogen fluoride (0.8 mL, 50%) was added to the mixture and stirring continued for another 8 h. The reaction was quenched by adding $NaHCO_3$ solution (5 mL) and was extracted with $Et_2O$ (2×5 mL). The combined organic phase was washed with $NaHCO_3$ solution (5 mL), dried over $Na_2SO_4$, and concentrated. Treatment of above mixture in 75% aqueous acetonitrile (12 mL) with CAN (353 mg, 0.028 mmol) at room temperature for 30 min, followed by dilution with water (10 mL) and extraction with ether (2×10 mL). The filtrate was washed with brine (5 mL), dried over $Na_2SO_4$ and concentrated in vacuo. The residue was subjected to flash chromatography on silica gel (petroleum ether/EtOAc 1:1) affording EBC-23 (**1**) (38 mg, 54%) as a white solid. $[\alpha]_D^{20}=+16.3$ ($c=0.034$, $CHCl_3$); $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 0.84 (t, $J$=13.97 Hz, 3H), 1.23 (s, 23H), 1.47–1.52 (m, 2H), 1.56–1.65 (m, 3H), 1.75–1.79 (m, 1H), 1.97–2.05 (m, 2H), 2.27–2.31 (dd, $J$=15.0, 2.6 Hz, 1H), 2.51–2.56 (dd, $J$= 14.9, 6.8 Hz, 1H), 3.05(ws, 1H), 3.76–3.81 (m, 1H), 4.11 (m, 1H), 4.34–4.39 (m, 1H), 4.49–4.51 (t, $J$=4.77 Hz, 1H), 5.02–5.04 (ddd, $J$=6.9, 4.5, 2.6 Hz, 1H), 6.20–6.22 (d, $J$=9.90 Hz, 1H), 6.87–6.90 ppm (dd, $J$=9.9, 5.1 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta$ = 14.1, 22.7, 25.4, 29.3, 29.59, 29.62, 29.64, 29.66, 29.67, 31.9, 37.7, 38.7, 42.2, 47.7, 64.2, 67.8, 68.9, 71.8, 78.8, 106.6, 124.6, 138.6, 161.0 ppm; HRMS: $m/z$: calcd for $C_{26}H_{44}NaO_6$: 475.3030, found: 475.3037.

***ent*-EBC-23 (60)**: The title compound was prepared via the above procedure. $[\alpha]_D^{20}=-16.6$ ($c=0.027$, $CHCl_3$); $^1$H and $^{13}$C NMR were identical to that above; HRMS: $m/z$: calcd for $C_{26}H_{44}NaO_6$: 475.3030, found: 475.3034.

**Assays**: Inhibition of cell growth was quantitated by dilution of compounds into cell cultures seeded the previous day in 96-well plates (3000–5000 cells/well in RPMI 1640 medium containing 10% fetal calf serum). After 6 days the cultures were fixed in ethanol and stained with sulforhodamine B for comparison with untreated controls (absorbance at 540 nm, measured on an ELISA reader).

For the mouse xenograft model, 2 million DU145 human prostate cancer cells were injected subcutaneously into each of four sites on the flanks of nude (BALB/c nu-/nu-) mice. Tumor growth was monitored with callipers and volume calculated with the formula: length × (breadth)$^2$/2.

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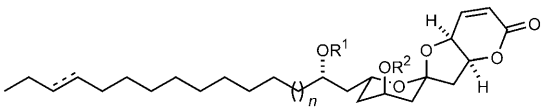


**(Bio)Synthesizing anticancer agents in the rain down under**: Compounds EBC-23, 24, 25, 72, 73, 75 and 76 (see figure) were isolated from the fruit of *Cinnamomum laubatii* in the Australian tropical rainforests. EBC-23 was synthesized stereoselectively to confirm the deduced relative stereochemistry and determine the absolute stereochemistry. Key to the total synthesis was a series of Tietze–Smith linchpin reactions. EBC-23 inhibited the growth of an androgen-independent prostate tumor cell line in the mouse model, indicating potential for the treatment of refractory solid tumors in adults.

**Anticancer Agents**

*L. Dong, H. Schill, R. L. Grange, A. Porzelle, J. P. Johns, P. G. Parsons, V. A. Gordon, P. W. Reddell, C. M. Williams** ..... ▮▮▮▮–▮▮▮▮

**Anticancer Agents from the Australian Tropical Rainforest: Spiroacetals EBC-23, 24, 25, 72, 73, 75 and 76**