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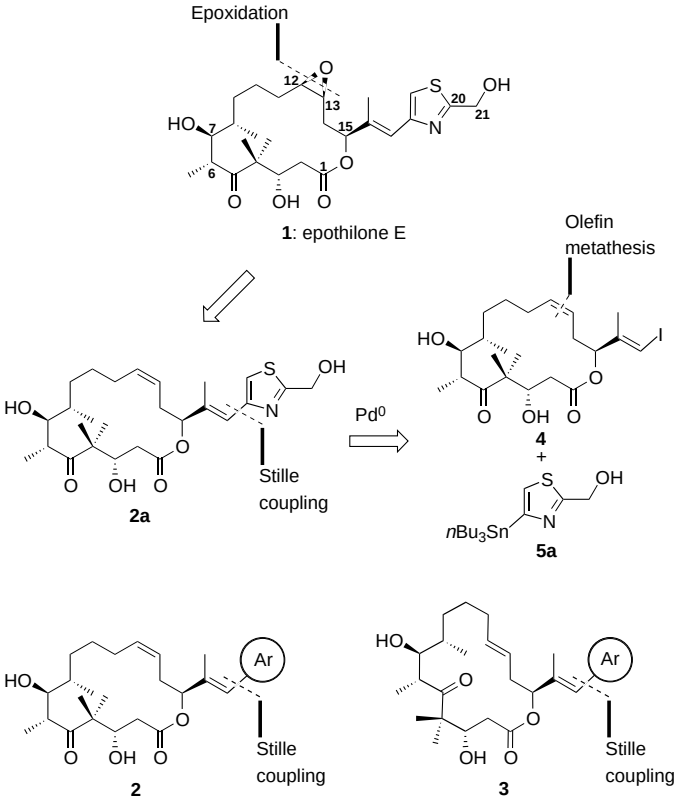
Total Synthesis of Epothilone E and Analogues with Modified Side Chains through the Stille Coupling Reaction**

K. C. Nicolaou,* Yun He, Frank Roschangar, N. Paul King, Dionisios Vourloumis, and Tianhu Li

The epothilones are a growing class of naturally occurring antitumor agents[1–3] whose importance is clearly reflected in the increasing number of publications reporting on their total synthesis,[4–11] analogue construction,[4–16] and biological activity.[1, 3, 4, 5b, 8, 9, 12, 15–17] Here we report the first total synthesis of the naturally occurring epothilone E (**1**, Scheme 1)[16] in



Scheme 1. Retrosynthetic analysis and strategy for the total synthesis of epothilone E (**1**) and analogues with modified side chains. (Ar) = aromatic moiety.

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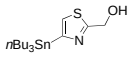
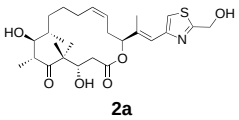
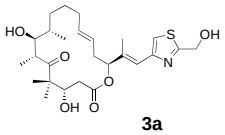
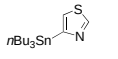
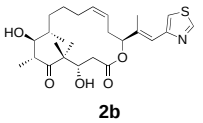
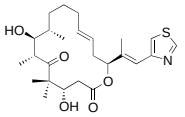
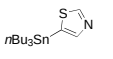
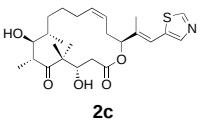
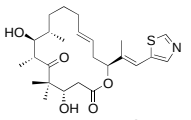
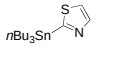
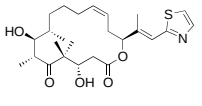
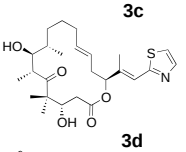
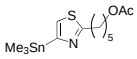
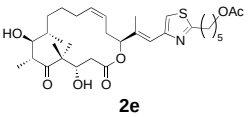
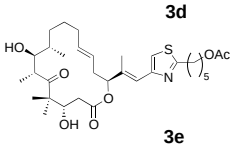
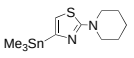
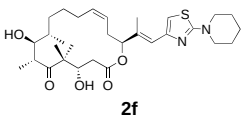
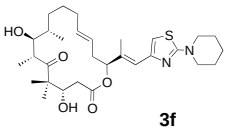
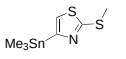
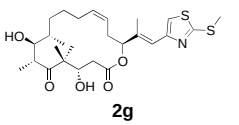
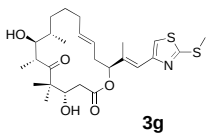
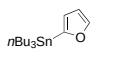
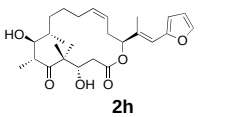
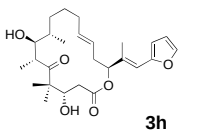
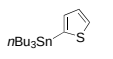
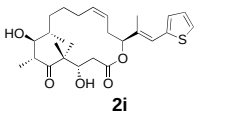
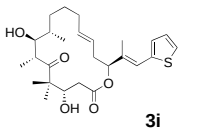
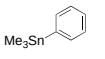
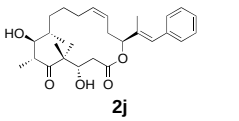
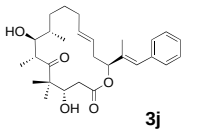
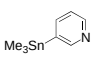
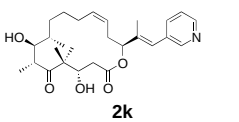
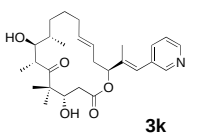
Table 1. Epothilones synthesized according to Scheme 2.

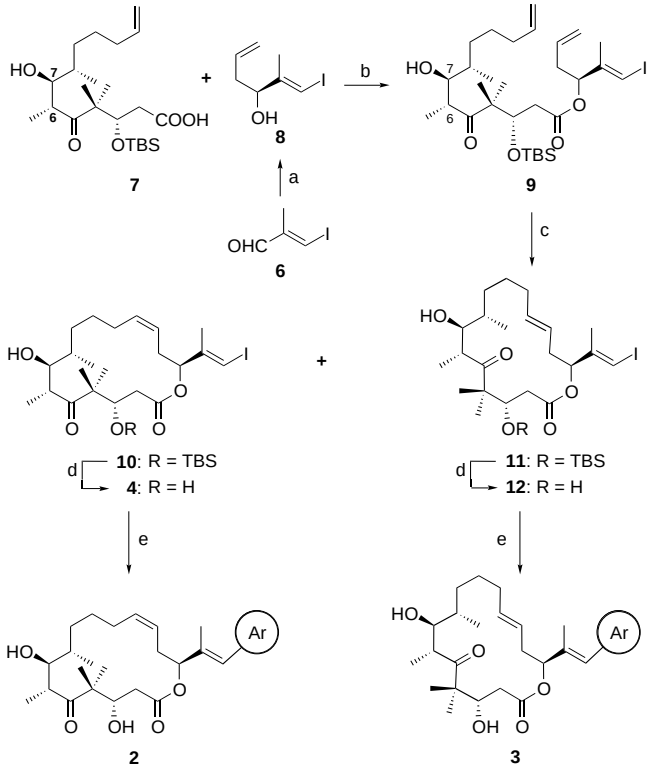
Entry	5	Procedure[a]	2	Yield [%]	3	Yield [%]
1	 **5a**	A	 **2a**	76	 **3a**	88
2	 **5b**	A	 **2b**	70	 **3b**	74
3	 **5c**	A	 **2c**	73	 **3c**	66
4	 **5d**	A	 **2d**	84	 **3d**	88
5	 **5e**	A	 **2e**	82	 **3e**	84
6	 **5f**	A	 **2f**	72	 **3f**	44
7	 **5g**	A	 **2g**	44	 **3g**	72
8	 **5h**	B	 **2h**	87	 **3h**	92
9	 **5i**	B	 **2i**	88	 **3i**	94
10	 **5j**	B	 **2j**	86	 **3j**	89
11	 **5k**	A	 **2k**	42	 **3k**	46

[a] See Scheme 2.

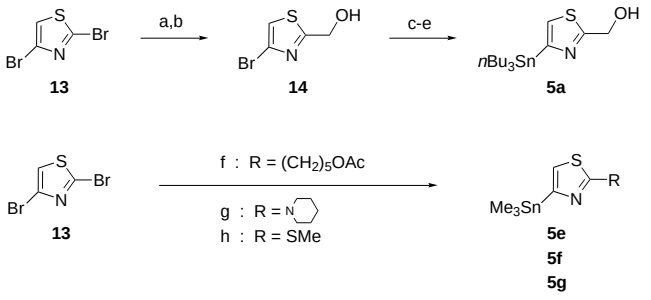
which an olefin metathesis reaction[4a, 5b, 6a, 7, 10, 13, 18, 19] is used to form the macrocycle and a Stille coupling[20] to construct the side chain. In addition, the developed strategy was applied to the synthesis of an analogue library containing a variety of aromatic systems in place of the 2-methylthiazole moiety of natural epothilone A (see Table 1). Scheme 1 outlines, in retrosynthetic format, the highly convergent metathesis/Stille coupling strategy towards epothilone E (**1**) and the new epothilones represented by structures **2** and **3**. The utilization of a common advanced intermediate (e.g. **4**) gives this Stille strategy a distinct advantage in delivering rapidly a plethora of side chain modified epothilone analogues for biological screening.

The epothilones shown in Table 1 were constructed as summarized in Scheme 2. Thus, alcohol **8**, prepared in 91% yield by addition of (+)-allyldiisopinocampheyl borane [(+)-Ipc_2B(allyl)] to the known aldehyde **6**,[21] was coupled with carboxylic acid **7**[10] (3:2 mixture with its C6,C7 diastereomer) with DCC and 4-DMAP to afford ester **9** (49% yield, after chromatographic separation from its C6,C7 diastereomer). Exposure of **9** to catalytic amounts of $[RuCl_2(=CHPh)(PCy_3)_2]$ in CH_2Cl_2 at ambient temperature resulted in a mixture of (*Z*) and (*E*) cycloolefins, which were chromatographically separated on silica gel (flash column, hexanes/ethyl acetate 9/1): **10** [R_f = 0.47, (hexanes/ethyl acetate 82/18), 35% yield]; **11** [R_f = 0.53, (hexanes/ethyl acetate 82/18), 30% yield]. Desilylation of **10** and **11** was then achieved with HF·Py in THF, leading to diols **4** (Table 2) (84%) and **12** (85%), respectively.

The required stannanes were either commercially available (**5h**, **i**), synthesized according to literature procedures (**5b–d**, **5j**, **k**),[22] or prepared by the sequences shown in Scheme 3. For the synthesis of epothilone E (**1**), dibromide **13**[23] was selectively metalated with *n*BuLi and then treated, in the presence of HMPA, with dimethylformamide (DMF); after reduction with $NaBH_4$ alcohol **14** was obtained in 63% overall yield. Protection of **14** as a silyl ether (TBSCl, imidazole, 96% yield) followed by a second metalation (*n*BuLi), exposure to nBu_3SnCl (85% yield), and desilylation with TBAF furnished stannane **5a** (95% yield). The synthesis of stannane **5e** required: 1) Sonogashira coupling of dibromide **13** with 4-pentyn-1-ol ($[Pd(PPh_3)_4]$/CuI, iPr_2NH, 70°C, 83% yield);[24] 2) chemoselective hydrogenation of the triple bond (cat. PtO_2/H_2, 100% yield); 3) acetate formation (Ac_2O, pyridine, 83% yield); and 4) reaction with $Me_3SnSnMe_3$/cat. $[Pd(PPh_3)_4]$ (toluene, 100°C, 93% yield). Stannane **5f** was prepared from dibromide **13** by reaction with piperidine (60°C, 100% yield), followed by palladium-catalyzed coupling with $Me_3SnSnMe_3$ ($[Pd(PPh_3)_4]$, toluene, 80°C, 100% yield). Similarly, **5g** was obtained from **13** by reaction with NaSMe (EtOH, 25°C, 94% yield) followed by the coupling (100% yield).



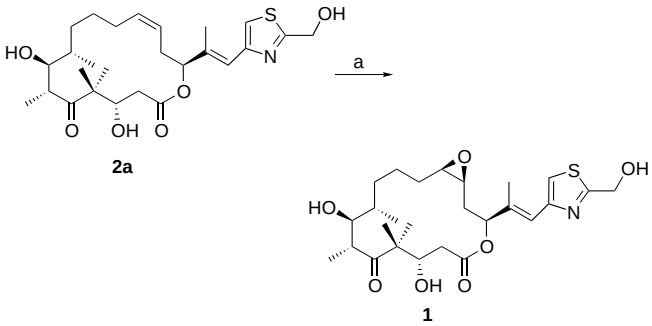
Scheme 2. Synthesis of intermediates **4** and **12** and desoxyepothilones **2** and **3**. a) 1.2 equiv (+)-Ipc$_2$B(allyl), Et$_2$O, −100°C, 0.5 h, 91%; b) 2.0 equiv **8**, 1.5 equiv DCC, 1.5 equiv 4-DMAP, toluene, 25°C, 12° h, 49% **9** and 33% of its (6*S*,7*R*) diastereomer; c) 10 mol% [RuCl$_2$(=CHPh)(PCy$_3$)$_2$], CH$_2$Cl$_2$, 25°C, 20 h, 35% **10** and 30% **11**; d) 10 equiv HF·Py, THF, 25°C, 30 h, **4** (84%); **12** (85%); e) procedure A: 1.5 equiv **5**, 10 mol% [Pd(PPh$_3$)$_4$], toluene, 100°C, 20 min; procedure B: 1.5 equiv **5**, 10 mol% [Pd(MeCN)$_2$Cl$_2$], DMF, 25°C, 10 h, see Table 1. TBS = *tert*-butyldimethylsilyl; DCC = dicyclohexylcarbodiimide; 4-DMAP = 4-dimethylaminopyridine; Py = pyridine.



Scheme 3. Preparation of stannanes **5a**, **5f**, **5g**, and **5e**. a) 1.1 equiv *n*BuLi, 1.2 equiv DMF, 1.1 equiv HMPA, −78→25°C, 2 h, 72%; b) 2.0 equiv NaBH$_4$, MeOH, 25°C, 20 min, 88%; c) 1.5 equiv TBSCl, 2.0 equiv imidazole, 25°C, 0.5 h, 96%; d) 1.2 equiv *n*BuLi, 1.2 equiv *n*Bu$_3$SnCl, −78→25°C, 2 h, 85%; e) 1.2 equiv TBAF, THF, 25°C, 20 min, 95%; f) 1. 2.0 equiv HCC(CH$_2$)$_3$OH, 0.05 equiv [Pd(PPh$_3$)$_4$], 0.1 equiv CuI, *i*Pr$_2$NH, 70°C, 2 h, 83%; 2. H$_2$, 0.1 equiv PtO$_2$, EtOH, 25°C, 4 h; 100%; 3. Ac$_2$O, pyridine, 25°C, 83%; 4. 10 equiv Me$_3$SnSnMe$_3$, 0.1 equiv [Pd(PPh$_3$)$_4$], toluene, 100°C, 3 h, 93%; g) 1. 10 equiv piperidine, 60°C, 6 h, 100%; 2. 10 equiv Me$_3$SnSnMe$_3$, 0.05 equiv [Pd(PPh$_3$)$_4$], toluene, 80°C, 3 h, 100%; h) 1. 3.0 equiv NaSMe, EtOH, 25°C, 2 h, 94%; 2. 10 equiv Me$_3$SnSnMe$_3$, 0.05 equiv [Pd(PPh$_3$)$_4$], toluene, 80°C, 3 h, 100%. HMPA = hexamethylphosphoramide; TBAF = tetra-*n*-butylammonium fluoride.

Attachment of the aromatic moieties onto the macrocyclic framework of vinyl iodides **4** and **12** was performed with the aromatic stannanes shown in Table 1 by means of palladium-catalyzed Stille couplings under conditions A ([Pd(PPh$_3$)$_4$], toluene, 100°C) or B ([Pd(MeCN)$_2$Cl$_2$], DMF, 25°C). Table 1 includes a selection of the synthesized epothilone A analogues, the coupling method, and the yields.

Epothilone E (**1**) (Table 2) was synthesized from its deoxy analogue **2a** (Table 2) by epoxidation with H$_2$O$_2$/KHCO$_3$/CH$_3$CN in methanol[13] as shown in Scheme 4 (65% yield, based on 50% conversion). Synthetic **1** exhibited identical ^{1}H and ^{13}C NMR spectra to those of the natural substance.[25] Epothilone E (**1**) exhibited 52% tubulin polymerization as compared to 76% for epothilone A, 98% for epothilone B, and 50% for Taxol in the filtration–colorimetric tubulin polymerization assay.[3]



Scheme 4. Synthesis of epothilone E (**1**). a) 33 equiv H$_2$O$_2$, 60 equiv CH$_3$CN, 9.0 equiv KHCO$_3$, MeOH, 25°C, 4 h, 65% (based on 50% conversion).

Table 2. Physical data for compounds **4**, **2a**, and **1**.

4: R_f = 0.21 (silica gel, EtOAc/hexanes, 1/3); $[\alpha]_{22}^{D} = -53.1$ (c = 1.37 in CHCl$_3$); IR (film): $\tilde{\nu}$ = 3499 (br), 2930, 1732, 1688, 1469, 1379, 1259, 1149, 1093, 1048, 1006, 732 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 6.43 (s, 1H, IC*H*=C(CH$_3$)), 5.44 (ddd, J = 10.5, 10.5, 4.5 Hz, 1H, C*H*=CHCH$_2$), 5.34 (dd, J = 9.5, 2.0 Hz, 1H, CO$_2$CH), 5.32 (ddd, J = 10.5, 10.5, 5.5 Hz, 1H, C*H*=CHCH$_2$), 4.07 (ddd, J = 11.0, 6.0, 3.0 Hz, 1H, (CH$_3$)$_2$CC*H*(OH)), 3.73 (ddd, J = 2.5, 2.5, 2.5 Hz, 1H, C*H*OH(CHCH$_3$)), 3.10 (qd, J = 7.0, 2.5 Hz, 1H, CH$_3$C*H*(C=O)), 2.84 (d, J = 2.5 Hz, 1H, CH(CH$_3$)CHO*H*CH(CH$_3$)), 2.66 (ddd, J = 15.0, 9.5, 9.5 Hz, 1H, =CHC*H*$_2$CHO), 2.51 (dd, J = 15.5, 11.0 Hz, 1H, CH$_2$COO), 2.42 (dd, J = 15.5, 3.0 Hz, 1H, CH$_2$COO), 2.35 (d, J = 6.0 Hz, 1H, (CH$_3$)$_2$CHOH), 2.21–2.12 (m, 2H), 2.05–1.97 (m, 1H), 1.88 (s, 3H, ArCH=CC*H*$_3$), 1.76–1.70 (m, 1H), 1.70–1.62 (m, 1H), 1.32 (s, 3H, C(CH$_3$)$_2$), 1.18 (d, J = 7.0 Hz, 3H, C*H*$_3$CH(C=O)), 1.10 (s, 3H, C(CH$_3$)$_2$), 1.35–1.05 (m, 3H), 0.99 (d, J = 7.0 Hz, 3H, C*H*$_3$CHCH$_2$); ^{13}C NMR (125.7 MHz, CDCl$_3$): δ = 219.9, 170.0, 145.3, 133.8, 124.0, 80.2, 77.3, 74.1, 72.8, 52.7, 42.0, 38.8, 38.4, 32.5, 31.2, 27.5, 27.4, 22.2, 20.8, 19.7, 15.5, 13.6; HRMS (FAB): m/z calcd for C$_{22}$H$_{35}$CsIO$_5$ (M+Cs$^+$): 639.0584, found: 639.0604

2a: R_f = 0.29 (silica gel, EtOAc/hexanes, 1/1); $[\alpha]_{22}^{D} = -44.2$ (c = 0.60 in CHCl$_3$); IR (film): $\tilde{\nu}$ = 3387 (br), 2925, 2859, 1730, 1688, 1508, 1461, 1256, 1183, 1150, 1061, 980, 755 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.12 (s, 1H, ArH), 6.61 (s, 1H, ArC*H*=C(CH$_3$)), 5.45 (ddd, J = 10.5, 10.5, 4.5 Hz, 1H, C*H*=CHCH$_2$), 5.38 (ddd, J = 10.5, 10.5, 5.0 Hz, 1H, C*H*=CHCH$_2$), 5.31 (d, J = 8.5 Hz, 1H, CO$_2$CH), 4.92 (d, J = 4.0 Hz, 2H, C*H*$_2$OH), 4.23 (ddd, J = 11.5, 5.5, 2.5 Hz, 1H, (CH$_3$)$_2$CC*H*(OH)), 3.75–3.71 (m, 1H, C*H*OH(CHCH$_3$)), 3.32 (d, J = 5.5 Hz, 1H, C(CH$_3$)$_2$CHOH), 3.25 (t, J = 4.0 Hz, 1H, CH$_2$OH), 3.13 (qd, J = 7.0, 2.0 Hz, 1H, CH$_3$C*H*(C=O)), 3.03 (d, J = 2.0 Hz, 1H, CH$_3$CHCH(O*H*)CHCH$_3$), 2.68 (ddd, J = 15.0, 9.5, 9.5 Hz, 1H, =CHC*H*$_2$CHO), 2.50 (dd, J = 15.0, 11.5 Hz, 1H, CH$_2$COO), 2.35 (dd, J = 15.0, 2.5 Hz, 1H, CH$_2$COO), 2.31–2.24 (m, 1H, =CHC*H*$_2$CHO), 2.24–2.16 (m, 1H), 2.09 (s, 3H, ArCH=CC*H*$_3$), 2.06–1.98 (m, 1H), 1.82–1.73 (m, 1H), 1.72–1.62 (m, 1H), 1.39–1.17 (m, 3H), 1.33 (s, 3H, C(CH$_3$)$_2$), 1.19 (d, J = 7.0 Hz, 3H, C*H*$_3$CH(C=O)), 1.08 (s, 3H, C(CH$_3$)$_2$), 1.00 (d, J =

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7.0 Hz, 3H, CH_3CHCH$_2$); ^{13}C NMR (125.7 MHz, $CDCl_3$): $\delta = 220.5$, 170.3, 169.9, 152.3, 139.0, 133.5, 124.9, 118.9, 116.5, 78.4, 74.2, 72.2, 61.8, 53.4, 41.7, 39.3, 38.6, 32.4, 31.7, 27.5, 27.4, 22.8, 18.4, 16.0, 15.5, 13.5; HRMS (FAB): *m/z* calcd for $C_{26}H_{39}CsNO_6S$ (M+Cs$^+$): 626.1552, found: 626.1530

1: $R_f = 0.56$ (silica gel, EtOAc/hexanes, 2/1); $[\alpha]_{22}^{D} = -27.5$ ($c = 0.20$ in $CHCl_3$); IR (film): $\tilde{\nu} = 3413$ (br), 2928, 2867, 1731, 1689, 1462, 1375, 1257, 1152, 1061, 978, 756 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.13$ (s, 1H, ArH), 6.61 (s, 1H, ArC*H*=CCH$_3$), 5.46 (dd, 1H, $J = 8.1$, 2.4 Hz, CO$_2$CH), 4.94 (d, $J = 5.2$ Hz, 2H, CH_2OH), 4.16–4.12 (m, 1H, (CH$_3$)$_2$CC*H*(OH)), 3.82–3.78 (m, 1H, C*H*OH(CHCH$_3$)), 3.66 (br. s, 1H, OH), 3.23 (qd, $J = 6.8$, 5.2 Hz, 1H, CH$_3$C*H*(C=O)), 3.04 (ddd, $J = 8.1$, 4.5, 4.5 Hz, 1H, CH$_2$C*H*-O(epoxide)CH), 2.91 (ddd, $J = 7.3$, 4.5, 4.1 Hz, 1H, CH$_2$C*H*-O(epoxide)CH), 2.61 (t, $J = 5.2$ Hz, 1H, CH$_2$OH), 2.55 (dd, $J = 14.7$, 10.4 Hz, 1H, CH$_2$COO), 2.48 (br. s, 1H, OH), 2.45 (dd, $J = 14.7$, 3.2 Hz, 1H, CH$_2$COO), 2.14–2.07 (m, 1H, CH_2CH-O(epoxide)CH), 2.11 (s, 3H, ArCH=CCH_3), 1.91 (ddd, $J = 15.1$, 8.1, 8.1 Hz, 1H, CH_2CH-O(epoxide)CH), 1.78–1.66 (m, 2H, CH_2CH-O(epoxide)CH), 1.52–1.38 (m, 5H), 1.36 (s, 3H, C(CH$_3$)$_2$), 1.18 (d, 3H, $J = 6.8$ Hz, CH_3CH(C=O)), 1.10 (s, 3H, C(CH$_3$)$_2$), 1.01 (d, $J = 7.0$ Hz, 3H, CH_3CHCH$_2$); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta = 220.0$, 170.6, 169.9, 152.3, 137.6, 119.8, 117.0, 76.7, 74.8, 73.6, 62.3, 57.5, 54.4, 52.7, 43.6, 38.9, 36.2, 31.4, 30.4, 27.0, 23.7, 21.3, 21.0, 17.2, 15.6, 14.3; HRMS (FAB): *m/z* calcd for $C_{26}H_{40}NO_7S$ (M+H$^+$): 510.2525, found: 510.2539

The described chemistry opens a convergent and convenient entry into a library of epothilones with varying side chains for biological screening. Further chemical and biological investigations with these and related compounds will be reported in due course.

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