Syntheses and Biological Evaluation of Costunolide, Parthenolide and their Fluorinated Analogs

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ABSTRACT

Inspired by the biosynthesis of sesquiterpene lactones (SLs), herein we report the asymmetric total synthesis of germacrane ring (**24**). The synthetic strategy features a selective aldol reaction between β,γ-unsaturated chiral sulfonylamide **15a** and aldehyde **13**, as well as the intramolecular α-alkylation of sulfone **21** to construct 10-membered carbocylic ring. The key intermediate **24** can be used to prepare the natural products costunolide and parthenolide (PTL), which are the key precursors for transformation into other SLs. Furthermore, the described synthetic sequences are amenable to the total synthesis of SL analogs, such as trifluoromethylated analogs (**32** and **45**). Analogs **32** and **45** maintained high activities against a series of cancer cell lines comparing to their parent PTL and costunolide, respectively. In addition, **32** showed enhanced tolerance to acidic media comparing with PTL. To our surprise, PTL and **32** showed comparable half-lives in rat plasma and in the presence of human liver microsomes.

INTRODUCTION

Germacranolides, a type of sesquiterpene lactone (SL) having a 10,5-ring structure, are present in several plant families (Figure 1).[1] They are the key precursor for transformation into other SLs with a variety of polycyclic skeletons, such as guaianolides,[2] eudesmanolides,[3] and so on[4] (Figure 2). However, only recently have they attracted extraordinary research interest due to their anticancer bioactivity.[5] In particular, the SLs costunolide (**1**) and parthenolide (PTL, **2**) are two small molecules that can selectively kill cancer stem cells.[6] Cancer stem cells are defined as cells that are able to both extensively self-renew and differentiate into progenitor cells; moreover, increasing evidence supports that cancer stem cells are responsible for the initiation, metastasis, and treatment resistance of many types of tumors.[6a,7] Thus, the germacranolides are a class of promising scaffolds that can treat cancer from its source.

The total synthesis of germacranolides has attracted intense research efforts for decades, but only a few synthetic approaches to racemic germacranolides have been published.[8] The total synthesis of a diastereoisomer of PTL was achieved via a Pd-catalyzed macrocyclization to form the 10-membered germacrane ring system.[9] Recently, our group reported the first total synthesis of **2**, with the formation of the 10-membered carbocylic ring by a macrocyclic stereocontrolled Barbier reaction. However, although various reaction conditions were extensively investigated, the desired 6,7-*trans*-10-membered ring system was achieved with low selectivity.[10] The preliminary structure–activity relationship (SAR) of PTL analogs was investigated and showed the following: (1) the *Z* or *E* configuration of the 1,10-double bond has little or no effect on the anti-cancer activity; (2) the change from *trans* to *cis* at the C6 and C7 site of the lactone ring results in a moderate decrease of the activity;[10] (3) introducing a polar hydroxyl group at either

the C9 or C14 position leads to a complete loss of activity, but the substitution of a large aromatic substituent has a beneficial effect on the activity.[11]

Despite these exciting bioactivity features, some germacranolides suffer from serious pharmacological and pharmacokinetic drawbacks that limit their clinical use, including poor bioavailability, poor toxicology profiles such as off-target effects, and low metabolic stability.[6a,12] The dimethylamino Michael adduct dimethylamino-PTL can effectively increase the oral bioavailability and have acceptable toxicology profiles,[13] but stability problems such as epoxidation of the electron-rich 1,10-double bond, hydroxylation of the two allylic sites (C9, C14) by cytochrome P450 enzymes,[11] and possible transannular cyclization in acidic media[2,14] have been described. In addition, the P450-catalyzed oxidation products exhibit significantly decreased activity or a complete loss of activity.[11] These findings directed our attention to study the substitution of the 14-methyl group with an electron-withdrawing group to protect against oxidation by cytochrome P450 oxidases. The introduction of a fluorine group into drug molecules often has positive effects by enhancing membrane permeability, promoting electrostatic interactions with target proteins, and increasing metabolic stability towards oxidative metabolism.[15]

Yet, the lack of available synthetic routes limits the optimization of germacranolides and their evaluation in spite of our recent total synthesis of **2** with low 6,7-*trans* diastereoselectivity.[10] Herein, we report a more general and highly stereocontrolled total synthetic approach that can rapidly provide SLs with various carbocyclic skeletons. Based on this route, the natural products **1**, **2**, and their fluorinated analogs were synthesized, and the SARs of these analogs were determined.

RESULTS AND DISCUSSION

Retrosynthetic analysis and total synthesis of 1 and 2

Inspired by the biosynthetic route of SLs (Figure 2),[16] the 6,7-*trans*-germacrane ring system (**24**) was proposed to be the key common intermediate. We planned to utilize an intramolecular *α*-alkylation as the key step to build up the 10-membered carbocycle (Scheme 1). The key common intermediate **24** would be conceived by intramolecular *α*-alkylation of sulfone **21**. Sulfone **21** could be readily manipulated from **16a**, which would be prepared by the aldol reaction of compound **10** and aldehyde **13**.

As shown in Scheme 2, the synthesis started with known compound **7**, which was readily obtained from hydroxypropanone, according to a reported procedure.[17] A Horner-Wadsworth-Emmons (HWE) reaction of ketone **7** and Oppolzer's chiral phosphonate **8** was proposed to generate compound **10**.[18] However, when the HWE reaction was performed with various bases (e.g., NaH, LiHMDS, or NaHMDS), most of the starting materials were recovered, and only a trace of the desired product was detected. Thus, an alternate strategy was attempted. The HWE reaction of ketone **7** and triethyl phosphonoacetate, followed by ester hydrolysis, was proposed to generate acid **9**. Unfortunately, the hydrolysis procedure led to cleavage of the TBS protecting group. The desired acid **9** was finally obtained by the HWE reaction of ketone **7** and diethylphosphonoacetic acid. According to a reported procedure,[19] compound **10** was readily prepared from compound **9** in 58% yield over two steps.

The aldehyde **13** was obtained by oxidation of the reported alcohol **12**[20] with MnO_2 in CH_2Cl_2 in 88% yield (Scheme 3). With aldehyde **13** in hand, the next step was the aldol reaction of compound **10** and aldehyde **13** to yield compound **16a**. Unfortunately, the regioselectivity of

the enolate at the γ-carbon of **10** with $TiCl_4$ and *N*,*N*-diisopropylethylamine (*i*-Pr_2NEt) was poor, and desired compound **16a** was obtained as a minor product. Alternatively, compound **10** was first treated with LiHMDS, followed by the addition of aldehyde **13**; however, this reaction procedure produced an inseparable mixture of **14** and **15b** (3:1), based on ^{1}H-NMR. Finally, **16a** was prepared in two steps as follows: compound **10** was first treated with LiHMDS (prepared by *n*-BuLi and HMDS) and then quenched with aq. NH_4Cl to obtain **15** (**15a**:**15b** = 10:1), presumably through a chelated transition state to selectively remove the proton in γ_2 carbon;[21] next, compound **15** and aldehyde **13** were treated with $TiCl_4$ and *i*-Pr_2NEt in CH_2Cl_2 to afford the desired 6,7-stereochemistry, generating **16a** as the major product in 47% yield and **16b** in 12% yield (Scheme 3).

As shown in Scheme 4, selective cleavage of the TBS protecting group of compound **16a** was achieved with HCl in ethanol at 0 °C.[22] The resulting crude product was treated with 2-methoxypropene to produce acetonide **17**. After the reduction of **17**, the crude product was treated with diphenyl disulfide/*n*-Bu_3P to obtain thioether **18**.[23] Using H_2O_2/$(NH_4)_6Mo_7O_{24}$ in *t*-BuOH and pyridine, thioether **18** was oxidized to compound **19** in 86% yield.[24] The TBDPS group of compound **19** was removed with tetrabutylammonium fluoride, affording alcohol **20** in 95% yield. Next, alcohol **20** was converted into three halides, **21a**, **21b**, and **21c**, via different reaction conditions (Scheme 4). For the preparation of bromide **21b**, it was necessary to use 2,6-lutidine as the base because complex products were observed otherwise.[25] Iodide **21c** had to be freshly prepared for use in the next step, due to its instability at ambient temperature.

Various cyclization conditions were explored for the cyclization precursors (**21a**, **21b**, and **21c**) to generate the desired 10-membered carbocyclic germacrane ring (Table 1). According to Whitby's method,[26] the slow addition of **21a** (0.02 M in THF) to NaHMDS (3 equiv.) in THF

(0.02 M) did not result in the desired cyclization product **22**. No reaction was observed, even under refluxing conditions with excess base (entries 1 and 2, Table 1). Fortunately, treatment of **21b** or **21c** with NaHMDS (3 equiv.) provided compound **22** in yields of 65% and 28%, respectively (entries 3 and 5, Table 1).[27] At –70 °C, conversion of **21b** to **22** was not complete, and a complex mixture was formed (entry 4, Table 1). When LiHMDS was used as the base, compound **22** was obtained in only 10% yield (entry 6, Table 1). However, when the base was changed to KHMDS, compound **22** was achieved in 82% yield (entry 8, Table 1). When the amount of KHMDS was decreased from 3 equiv. to 2 equiv., only a trace amount of cyclized product **22** was detected (entry 7, Table 1). Finally, increasing the amount of KHMDS to 4 equiv. afforded the best yield (84%) of cyclized product **22** (entry 9, Table 1).

As a mixture of two diastereomers, cyclization product **22** was treated with Mg/MeOH to remove the sulfone moiety, providing compound **23** in 74% yield (Scheme 5).[28] The acetonide group of **23** was removed with pyridinium *p*-toluenesulfonate in MeOH to generate the key intermediate **24** in 78% yield.[14,29] With the key intermediate **24** in hand, oxidation with MnO_2 in CH_2Cl_2 produced the desired **1**.[1a] Alternatively, the key intermediate **24** has been used to yield other SLs. For example, diol **24** can undergo Sharpless epoxidation, followed by oxidation with TEMPO and $PhI(OAc)_2$, to yield **2**.[14]

Semisynthesis of mono- and di-fluorinated analogs of PTL

With **2** in hand, reduction of the α,β-unsaturated double bond with $NaBH_4$ provided compound **25**, and oxidation of the allylic methyl group with SeO_2/*t*-BuOOH yielded alcohol **26** (Scheme 6).[30] In addition, fluorination of **26** employing diethylaminosulfur trifluoride (DAST) in CH_2Cl_2 provided a 3:1 mixture of **27** and **28**, which was recrystallized in ether to give

monofluorinated analogs **27** (31% yield) and **28** (12% yield). Treatment of **26** with Dess-Martin periodinane in the presence of $NaHCO_3$ afforded aldehyde **29**, which was treated with DAST to provide difluorinated analog **30** in 43% yield. Further oxidation of the aldehyde with $NaClO_2$ produced acid **31**. Attempted decarboxylative trifluoromethylation of acid **31** by using bis(2-methoxyethyl)aminosulfur trifluoride[31] or CF_3SO_3Na[32] failed to yield the desired trifluorinated analog **32**.

Retrosynthetic analysis and total synthesis of trifluoromethylated costunolide and PTL

Scheme 7 outlines our retrosynthetic analysis of trifluoromethylated analogs **45** and **32**. Similarly, the 6,7-*trans*-germacrane ring diol (**43**) was proposed to be the key common intermediate, which could be built up by utilizing an intramolecular α-alkylation of sulfone **41**. Sulfone **41** would be conceived by the addition of aldehyde **40** and 3,3,3-trifluoropropene-2-yl lithium, followed by mesylation and bromination. Aldehyde **40** could be readily transformed from β,γ-unsaturated chiral sulfonylamide **15a** and aldehyde **34**.

Similar to the previous synthetic route from aldehyde **13** to alcohol **20**, gram-scale production of alcohol **39** was obtained from alcohol **33** in eight steps.[33] Next, Dess-Martin oxidation produced aldehyde **40** (Scheme 8). Using aldehyde **40** as the substrate, bromide **41** was prepared as a single *Z*-isomer by the addition of the vinyl anion derived from commercially available 2-bromo-3,3,3-trifluoropropene,[34] mesylation, and bromination with NaBr in DMF. The use of 2,2-dimethylpropane was necessary for the bromination reaction to avoid concomitant loss of the acetonide, and the use of LiBr instead of NaBr during bromination not only led to the removal of the acetonide but also produced a mixture of *Z*- and *E*-**41**, with a ratio of approximately 1:1.

With bromide **41** in hand, we explored its cyclization to construct the 10-membered carbocyclic germacrane ring. As shown in Table 2, the previously optimized condition for cyclization reaction in Table 1, i.e. slow addition of bromide **41** to KHMDS in THF (0.02 M), only produced a trace amount of the desired cyclization product **42** (Entry 1, Table 2), and most of the starting material was decomposed. The addition of 4 equiv. of NaHMDS to bromide **41** generated the desired compound **42** in 32% yield (Entry 2, Table 2). Reducing the amount of NaHMDS to 1.5 equiv. reduced the yield of compound **42** to 9% (Entry 3, Table 2). Finally, the desired cyclization product **42** was obtained in 51% yield by the simultaneous addition of bromide **41** (0.02 M in THF) and NaHMDS (0.06 M in THF) (Entry 4, Table 2).

Diol **43** was obtained via the removal of the sulfone moiety and the acetonide, and subsequent oxidation with MnO_2 afforded trifluoromethylated analog **45** (Scheme 9). Treatment of diol **43** with *t*-butyl hydroperoxide and $VO(acac)_2$ in CH_2Cl_2 produced a complex mixture. In contrast, direct epoxidation of compound **45** with *m*-chloroperoxybenzoic acid yielded the desired 4,5-epoxy product **32** in 91% yield. The structure of compound **32** was further confirmed by X-ray analysis (Scheme 9).

Anti-cancer properties in different cancer cell lines

Compounds **1**, **2**, and their analogs (**27**, **28**, **30**, **32**, and **45**) were evaluated against human acute myeloid leukemia cell line KG1a, rat glioma cell line C6, cultured acute myeloid leukemia cell line HL-60, and doxorubicin-resistant cell line HL-60/A. As indicated in Table 3, PTL analogs **27**, **30**, and **32** retained high activities against the cancer cell lines KG1a, C6, HL-60, and HL-60/A, with IC_{50} values between 1.5 μM and 3.4 μM. Costunolide analog **45**, without the 4,5-epoxy moiety, showed approximately 2-fold less potency against the cancer cell lines KG1a,

C6, HL-60, and HL-60/A, compared to its counterpart **32**. Interestingly, reduced activities against the cancer cell lines were observed for 1-monofluorinated PTL (**28**), perhaps due to the conformation change resulting from the rearrangement of the 1,10-double bond from being a part of the ring to being exo to the ring. Based on the above results, the preliminary SARs were as follows: (1) the 4,5-epoxy moiety of PTL shows a moderate effect on the activity; (2) the 1,10-double bond is important for the anti-cancer activity.

Chemical stability

Generally, germacranolides are very sensitive to acidic media, and cyclized or rearranged products form under these conditions.[36] Compound **2** was readily converted to micheliolide under acid condition, i.e. *p*-toluenesulfonic acid (*p*TSA) in dichloromethane.[2] With the synthesized fluorinated-PTL analogs (**27**, **28**, **30**, and **32**) in hand, we checked their chemical stability compared with **2**. The synthesized fluorinated-PTL analogs (**27**, **28**, **30**, and **32**) stayed nearly intact over 48 h under the same condition. These results indicated that the introduction of fluorine groups with an electron-withdrawing effect, effectively weakened the nucleophilic ability of the 1,10-double bond to attack the epoxy moiety, thus significantly improved the stability of these fluorinated compounds in acidic media.

Metabolic stability

It has been reported that PTL is unstable under both acidic and basic conditions[2,37] as well as in mouse plasma;[6b] in addition, it is readily oxidized by cytochrome P450 enzymes.[11] The metabolic stability of **2** and its trifluoromethylated analog **32** in the presence of human liver

microsomes was tested. To our surprise, there was no significant difference in the half-lives between **2** (83.5 min) and analog **32** (85.6 min). Next, the half-lives of **2** and analog **32** were evaluated in rat plasma. The half-life of **2** was 16.7 min, and that of analog **32** was 20.3 min (Table 4). These *in vitro* studies suggest that the structure optimization from **2** to trifluoromethylated analog **32** did not improve the metabolic stability of the compound toward cytochrome P450 enzymes of human liver microsomes or rat plasma. Since 11,13-dihydro-PTL (**25**) is inactive against cancer cells,[38] the stability of **25** in rat plasma was also studied. Compound **25** was degraded by only 20% over 420 min in rat plasma.

CONCLUSIONS

In conclusion, the asymmetric synthesis of the 10-membered germacrane ring system (**24**) was achieved. The synthetic strategies featured a selective aldol reaction between the *β*,*γ*-unsaturated chiral sulfonylamide **15a** and aldehyde **13**, as well as efficient intramolecular α-alkylation of sulfone **21b** to construct 10-membered carbocyclic ring. Inspired by the biosynthesis of SLs, the germacranolides **1** and **2**, as key precursors to process into a variety of polycyclic sesquiterpene frameworks, can be prepared via the key intermediate **24**. The described synthetic sequences are amenable to the synthesis of SL analogs, such as trifluoromethylated analogs of **2** and **1**, i.e. **32** and **45**, which maintained high activities against a series of cancer cell lines.

It was reported that **2** suffered from the stability problem in P450 oxidases for the presence of electron-rich 1,10-double bond,[11] and **2** was liable to transannular cyclization with 1,10-double bond nucleophilic attacking the epoxy moiety in acidic media[2]. Therefore, the introduction of electron-withdrawing fluorine groups (i.e. trifluoromethylated analog **32**) showed significantly

enhanced tolerance to acidic media compared to that of **2**. However, to our surprise, **2** and trifluoromethylated analog **32** showed comparable half-lives in rat plasma and in the presence of human liver microsomes. In contrast, the biologically inactive **25** was very stable in rat plasma. Therefore, we presumed that the 1,10-double bond of PTL probably is not the principle metabolic moiety, and the α-methylene-γ-butyrolactone moiety might be responsible for their short half-lives in rat plasma and in the presence of human liver microsomes. The α-methylene-γ-butyrolactone moiety is thought to be responsible for inhibitory action function, since it is a potent Michael reaction acceptor covalently binding to cysteine residues in proteins.[12] Meanwhile, the α-methylene-γ-butyrolactone moiety might be prone to be attacked by cysteine residue. To circumvent the barrier, it is recommended that it could be converted to a prodrug with masking group, such as Mannich-base-prodrug,[6b,13,39] to improve their stability, solubility and bioavailability.

EXPERIMENTAL SECTION

General Chemistry. Unless otherwise mentioned, all reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions. The used solvents were purified and dried according to common procedures. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm Tsingdao silica gel plates (60F-254). Visualization was achieved using UV light, phosphomolybdic acid in ethanol or potassium permanganate in water, each followed by heating. Tsingdao silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. FTIR spectra

were obtained with a Bruker Tensor 27 instrument. All IR samples were prepared as thin film and reported in wave numbers (cm^{-1}). NMR spectra were recorded with a 400 MHz (^1H: 400 MHz, ^{13}C: 100 MHz) spectrometer and referenced to the solvent peak for $CDCl_3$. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br. = broad, m = multiplet), coupling constants and integration. The purity of the final compounds was determined to be ≥ 95% by means of analytical high pressure liquid chromatography (HPLC) on a Shimadzu LD-20A system with an ODS-C18 column (4.6 × 150 mm, 5 μm) eluted at 1 mL/min with Milli-Q water and CH_3CN.

*(E)-4-((tert-Butyldimethylsilyl)oxy)-3-methylbut-2-enoic acid (**9**).* To a stirred solution of diethylphosphonoacetic acid (12.34 g, 62.93 mmol) in dry THF (125 mL) at 0 ºC was added NaHMDS (2 M in THF, 63.0 mL, 126.0 mmol) under Ar atmosphere. After stirring for 0.5 h, the mixture became a dark yellow jelly; then dry THF (250 mL) was added. After the jelly was dissolved, compound **7** (14.23 g, 75.53 mmol) was slowly added. After stirring for 4 h, the mixture was adjusted to pH = 4 with aqueous $KHSO_4$ (0.5 M) and extracted with ethyl acetate (3 × 500 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified by silica gel column [petroleum ether (PE)/EtOAc (EA) = 20:1–8:1] to afford compound **9** (11.67 g, 80%) as a colorless oil. IR (KBr) 3069, 2986, 2930, 2856, 1587, 1470,1308, 1217, 1110, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.70 (s, 1H), 5.95 (s, 1H), 4.05 (s, 2H), 1.97 (s, 3H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 160.4, 113.0, 67.2, 26.00, 18.5, 15.8, –5.4; HRMS (ESI) calcd for $C_{11}H_{23}O_3Si(M+H)^+$ 231.1411, found 231.1411.

*(E)-4-((tert-Butyldimethylsilyl)oxy)-1-((3aR,6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-3-methylbut-2-en-1-one (**10**).* To a stirred solution of

compound **9** (6.34 g, 27.52 mmol) in dry toluene (75 mL) at 0 ºC was added oxalyl chloride (2.83 mL, 33.02 mmol), then added *N*, *N*-dimethylformamide (0.05 mL). The mixture was stirred for 1.5 h at room temperature. The solvent was removed under vacuum at 25 ºC to give the acid chloride. To a suspension of NaH (60% in mineral oil, 1.21 g, 30.27 mmol) in dry toluene (50 mL) at 0 ºC was added (+)-Camphorsultam (6.52 g, 30.27 mmol) under Ar atmosphere and stirred for 3 h at room temperature and followed by addition of the acid chloride in dry toluene (30 mL) at 0 ^{o}C. The mixture was stirred for 2 h at room temperature, followed by addition of saturated aqueous NH_4Cl, and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified by silica gel column [PE:EA = 25:1–8:1] to give compound **10** (6.90 g, 59%) as a colorless oil. $[\alpha]_D^{26}$ +54.6^{o} (*c* 1.0, $CHCl_3$); IR (KBr) 2953, 2859, 1679, 1461, 1371, 1327, 1274, 1240, 1130, 845, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (s, 1H), 4.00 (s, 2H), 3.76 (s, 1H), 3.36 (d, *J* = 13.7 Hz, 1H), 3.28 (d, *J* = 13.7 Hz, 1H), 2.02–1.92 (m, 2H), 1.90 (s, 3H), 1.81–1.66 (m, 3H), 1.32–1.16 (m, 2H), 1.03 (s, 3H), 0.81 (s, 3H), 0.79 (s, 9H), –0.04 (s, 3H), –0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 159.1, 112.8, 66.8, 64.6, 52.7, 47.9, 47.3, 44.4, 38.5, 32.5, 26.3, 25.6, 20.6, 19.6, 17.9, 16.0, –5.7, –5.9; HRMS (ESI) calcd for $C_{21}H_{37}NNaO_4SSi$ $(M+Na)^+$ 450.2105, found 450.2100.

*(2E,6E)-8-((tert-Butyldiphenylsilyl)oxy)-3,7-dimethylocta-2,6-dienal (**13**).* To a stirred solution of compound **12** (16.48 g, 40.32 mmol) in dry CH_2Cl_2 (400 mL) was added MnO_2 (8.77 g, 100.82 mmol). After the mixture was refluxed for 4 h, another portion of MnO_2 (8.77g, 100.82 mmol) was added. After another 2 h, the mixture was filtered through a short pad of Celite with CH_2Cl_2. The filtrate was concentrated under reduced pressure to an oily crude product, which was purified by column chromatography [PE:EA = 10:1–8:1] to give compound **13** (15.09 g,

88%) as a colorless oil. IR (KBr) 2961, 2914, 2848, 1761, 1452, 1257, 1044, 981, 926, 848, 790 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.02 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 7.3 Hz, 4H), 7.47–7.38 (m, 6H), 5.93 (d, J = 8.0 Hz, 1H), 5.45 (s, 1H), 4.07 (s, 2H), 2.28 (s, 4H), 2.19 (s, 3H), 1.62 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 163.7, 135.6, 135.4, 133.8, 129.7, 127.7, 127.5, 122.2, 68.7, 40.4, 26.9, 25.2, 19.4, 17.7, 13.6; HRMS (ESI) calcd for $C_{26}H_{38}NO_2Si$ $(M+NH_4)^+$ 424.2666, found 424.2666.

*3-(((tert-Butyldimethylsilyl)oxy)methyl)-1-((3aR,6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)but-3-en-1-one (**15a**).* To a stirred solution of hexamethyldisilazane (11.9 mL, 56.96 mmol) in dry THF (50 mL) at –78 ºC was added *n*-BuLi (2.5 M in hexane, 22.8 mL, 57.00 mmol) under Ar atmosphere. After 0.5 h, compound **10** (16.2 g, 37.97 mmol) in dry THF (50 mL) was slowly added and soon the solution became yellow. After stirred for 1 h at –78 ºC, the reaction solution was quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified by silica gel column [PE:EA = 25:1–8:1] to yield compound **15a** (14.4 g, 89 %) as a colorless oil. IR (KBr) 3092, 2885, 1768, 1412, 1126, 1003, 985, 962, 819 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.21 (s, 1H), 4.98 (s, 1H), 4.18–4.08 (m, 2H), 3.86–3.79 (m, 1H), 3.52–3.35 (m, 4H), 2.07–2.01 (m, 2H), 1.89–1.80 (m, 3H), 1.41–1.30 (m, 2H), 1.11 (s, 3H), 0.94 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 141.1, 113.5, 65.5, 65.3, 52.9, 48.4, 47.8, 44.7, 39.1, 38.4, 32.9, 26.5, 25.9, 20.9, 19.9, 18.4, –5.3, –5.4; HRMS (ESI) calcd for $C_{21}H_{38}NO_4SSi(M+H)^+$ 428.2285, found 428.2290.

*Aldol reaction of **10** and aldehyde **13**.* Compound **10** (214 mg, 0.5 mmol) was dissolved in anhydrous CH_2Cl_2 (6 mL) under argon atmosphere and the solution was cooled to –78 °C. $TiCl_4$

(1.0 M, 0.55 mL, 0.55 mmol) was added and the yellow solution was stirred 5 min. *N*,*N*-Diisopropylethylamine (0.17 mL, 1 mmol) was added dropwise and the deep purple solution was stirred at –78 °C for 1 h. Freshly prepared aldehyde **13** (325 g, 0.8 mmol) in 1 mL of CH_2Cl_2 was added dropwise. The solution was stirred at –78 °C for 2 h, quenched with saturated aqueous NH_4Cl, and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were concentrated to give a crude residue, which was purified by silica gel column [PE:EA = 25:1–12:1] to obtain compound **16a** (105 mg, 25%) and **16b** (165 mg, 40%).

Compound **16a**: Colorless oil; $[\alpha]_D^{26}$ +21.6° (*c* 1.0, $CHCl_3$); IR (KBr) 2953, 2857, 1691, 1464, 1336, 1258, 1109, 839, 778, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.64 (m, 4H), 7.39 (m, *J* = 13.8, 4.7 Hz, 6H), 5.44–5.38 (m, 2H), 5.35 (s, 1H), 5.26 (d, *J* = 8.6 Hz, 1H), 4.84 (t, *J* = 8.4 Hz, 1H), 4.31 (d, *J* = 13.4 Hz, 1H), 4.22 (d, *J* = 13.4 Hz, 1H), 4.04 (s, 2H), 3.81 (dd, *J* = 7.3, 4.8 Hz, 1H), 3.76 (d, *J* = 8.1 Hz, 1H), 3.44 (d, *J* = 13.8 Hz, 1H), 3.35 (d, *J* = 13.8 Hz, 1H), 3.21 (s, 1H), 2.18–2.09 (m, 2H), 2.04–1.95 (m, 3H), 1.93–1.80 (m, 4H), 1.75 (s, 3H), 1.61 (s, 3H), 1.32–1.23 (m, 2H), 1.06 (s, 9H), 1.02 (s, 3H), 0.93 (s, 12H), 0.11 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 142.4, 140.4, 135.7, 134.1, 134.0, 129.6, 127.7, 124.8, 124.5, 115.8, 69.2, 69.2, 65.8, 64.8, 55.7, 53.2, 48.3, 47.8, 44.6, 39.5, 38.0, 32.8, 27.0, 26.6, 26.2, 26.0, 20.8, 20.0, 19.4, 18.4, 17.1, 13.6, –5.3, –5.4; HRMS (ESI) calcd for $C_{47}H_{75}N_2O_6SSi_2$ $(M+NH_4)^+$ 851.4879, found 851.4852.

Compound **16b**: Colorless oil; $[\alpha]_D^{25}$ –27.6° (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.67 (m, 4H), 7.42–7.35 (m, 6H), 6.38 (s, 1H), 5.41 (t, *J* = 7.1Hz, 1H), 5.32 (d, *J* = 8.7 Hz, 1H), 4.86–4.78 (dd, *J* = 8.4, 7.2 Hz, 1H), 4.36 (s, 1H), 4.04 (s, 2H), 3.89–3.81 (m, J = 6.9, 5.3 Hz, 1H), 3.42 (d, *J* = 13.7 Hz, 1H), 3.34 (d, *J* = 13.7 Hz, 1H), 2.61 (s, 1H), 2.18–2.06 (m, 4H), 2.01 (m, 2H), 1.87 (m, 3H), 1.74 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H), 1.33 (m, 2H), 1.13 (s, 3H), 1.06 (s,

9H), 0.94 (s, 12H), 0.16 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 140.3, 139.1, 135.6, 134.0, 133.9, 129.5, 127.6, 124.6, 124.4, 108.4, 69.1, 67.6, 64.6, 52.9, 50.8, 48.4, 47.7, 45.0, 39.6, 39.1, 33.0, 26.9, 26.4, 26.3, 25.7, 21.0, 19.9, 19.3, 18.2, 17.0, 15.5, 13.5, -5.0, -5.3; HRMS (ESI) calcd for $C_{47}H_{71}NNaO_6SSi_2$ $(M+Na)^+$856.4433 , found 856.4425.

*Syntheses of compounds **16a** and **16b** from **15a**.* Compound **15a** (1.2 g, 2.81 mmol) was dissolved in anhydrous CH_2Cl_2 (15 mL) under argon atmosphere and the solution was cooled to –78 °C. $TiCl_4$ (3.0 mL, 3.0 mmol) was added and the yellow solution was stirred 5 min. *N*,*N*-Diisopropylethylamine (1.3 mL, 7 mmol) was added dropwise and the deep purple solution was stirred at –78 °C for 1 h. Freshly prepared aldehyde **13** (1.7 g, 4.2 mmol) in 5 mL of CH_2Cl_2 was added dropwise. The solution was stirred at –78 °C for 2 h, quenched with saturated aqueous NH_4Cl, and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were concentrated to give a crude residue, which was purified by silica gel column [PE:EA = 25:1–15:1] to obtain compound **16a** (1.1 g, 47%) and **16b** (280.8 mg, 12%).

*((4R,5S)-4-((1E,5E)-7-((tert-Butyldiphenylsilyl)oxy)-2,6-dimethylhepta-1,5-dien-1-yl)-2,2-dimethyl-6-methylene-1,3-dioxepan-5-yl)((3aR,6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)methanone (**17**).* To a solution of compound **16a** (3.7 g, 4.44 mmol) in CH_2Cl_2 (10 mL) and EtOH (75 mL) at 0 ºC was added a solution of conc. HCl (1 mL) in EtOH (20 mL). After stirring for 0.5 h, the mixture was concentrated at 30 ºC under reduced pressure and the remaining water was removed by azeotropy with toluene to give the crude diol. To a stirred solution of diol and pyridinium *p*-toluenesulfonate (56 mg, 0.22 mmol) in dry DMF (30 mL) at 0 ºC was added 2-methoxypropene (0.54 mL, 5.77 mmol). The mixture was warmed to room temperature and stirred for 4 h, added 50 mL ethyl acetate (50 mL) and saturated aqueous $NaHCO_3$ (20 mL), and extracted with *tert*-butyl methyl ether (3 × 100 mL).

The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified by silica gel column [PE:EA = 10:1–4:1] to provide compound **17** (2.3 g, 74% for two steps) as an oil. $[\alpha]_D^{25}$ +27.6° (*c* 0.5, $CHCl_3$); IR (KBr) 2938, 1765, 1251, 1129, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 6.7 Hz, 4H), 7.39 (m, *J* = 13.8, 6.9 Hz, 6H), 5.42 (t, *J* = 6.5 Hz, 1H), 5.37 (d, *J* = 9.6 Hz, 1H), 5.11 (s, 1H), 4.98 (t, *J* = 9.4 Hz, 1H), 4.90 (s, 1H), 4.37 (d, *J* = 13.0 Hz, 1H), 4.05 (s, 2H), 4.02 (d, *J* = 13.4 Hz, 1H), 3.96 (d, *J* = 7.1 Hz, 1H), 3.80 (t, *J* = 6.1 Hz, 1H), 3.46 (d, *J* = 13.8 Hz, 1H), 3.37 (d, *J* = 13.8 Hz, 1H), 2.21–2.06 (m, 4H), 2.03 (m, 2H), 1.86 (m, 3H), 1.72 (s, 3H), 1.62 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 1.33 (m, 2H), 1.11 (s, 3H), 1.06 (s, 9H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 144.4, 139.3, 135.7, 134.1, 134.0, 129.6, 127.7, 124.6, 123.7, 115.4, 101.5, 69.2, 69.0, 66.9, 65.3, 57.5, 53.2, 48.1, 47.8, 44.6, 39.6, 38.7, 33.0, 26.9, 26.5, 26.4, 25.4, 25.0, 20.8, 20.0, 19.4, 17.2, 13.6; HRMS (ESI) calcd for $C_{44}H_{65}N_2O_6SSi$ $(M+NH_4)^+$ 777.4327, found 777.4306.

*tert-Butyl(((2E,6E)-7-((4R,5S)-2,2-dimethyl-6-methylene-5-((phenylthio)methyl)-1,3-dioxepan-4-yl)-2,6-dimethylhepta-2,6-dien-1-yl)oxy)diphenylsilane (**18**).* To a suspension of $LiAlH_4$ (47 mg, 1.24 mmol) in dry THF (1 mL) at 0 °C was added a solution of compound **17** (630 mg, 0.83 mmol) in THF (4 mL). After stirring at 0 °C for 1 h, saturated aqueous NH_4Cl (0.2 mL) were added slowly. The mixture was dried over Na_2SO_4, filtered through Celite pad and silica gel pad, and washed with a mixture of CH_2Cl_2 and EtOH (10:1). The solvent was removed under reduced pressure to afford an oily crude product. To a solution of the above crude and diphenyl disulfide (362 mg, 1.66 mmol) in toluene (8 mL) was added *n*-Bu_3P (0.42 mL, 1.66 mmol) and the mixture was stirred at ambient temperature for 18 h. It was then directly purified by a column of silica gel (PE:EtOAc = 20:1) to provide compound **18** (490 mg, 92%) as an oil.

$[\alpha]_D^{26}$ –10.2° (*c* 0.5, $CHCl_3$); IR (KBr) 2973, 2934, 2856, 1763, 1439, 1247, 1136, 967 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72–7.65 (m, 4H), 7.44–7.34 (m, 6H), 7.28–7.20 (m, 4H), 7.16–7.09 (m, 1H), 5.40 (t, *J* = 6.4 Hz, 1H), 5.22 (d, *J* = 9.3 Hz, 1H), 5.05 (s, 1H), 4.92 (s, 1H), 4.54 (dd, *J* = 9.3, 7.8 Hz, 1H), 4.32 (d, *J* = 14.2 Hz, 1H), 4.26 (d, *J* = 14.2 Hz, 1H), 4.04 (s, 2H), 3.15–3.04 (m, 2H), 2.58 (q, *J* = 7.7 Hz, 1H), 2.11 (m, 2H), 2.03 (m, 2H), 1.75 (s, 3H), 1.59 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 138.7, 137.1, 135.7, 134.4, 134.0, 129.7, 128.9, 128.8, 127.7, 125.8, 125.2, 124.0, 114.2, 101.8, 70.2, 69.1, 66.5, 52.4, 39.6, 34.1, 27.0, 26.2, 26.0, 24.5, 19.4, 17.3, 13.6; HRMS (ESI) calcd for $C_{40}H_{56}NO_3SSi$ $(M+NH^4)^+$ 658.3745, found 658.3732.

*tert-Butyl(((2E,6E)-7-((4R,5S)-2,2-dimethyl-6-methylene-5-((phenylsulfonyl)methyl)-1,3-dioxepan-4-yl)-2,6-dimethylhepta-2,6-dien-1-yl)oxy)diphenylsilane (**19**).* Compound **18** (470 mg, 0.73 mmol) was dissolved in *t*-BuOH (3 mL) and pyridine (1 mL). The mixiture was cooled to 0 °C, and a mixture of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (544 mg, 0.44 mmol) in 30% H_2O_2 (0.9 mL) was added dropwise. The cooling bath was removed and the reaction mixture was stirred at room temperature for 4 h. Sat. aq. $Na_2S_2O_3$ (0.1 mL), $NaHCO_3$ (5 mL), H_2O (5 mL) and EtOAc (15 mL) were added. The organic layers were separated, and the aqueous phase was extracted with EtOAc (2 × 15 mL). The combined organic phase was washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified by silica gel column (PE:EA = 8:1–4:1) to afford sulfone **19** (422 mg, 86%) as a colorless oil. $[\alpha]_D^{26}$ –26.5° (*c* 0.5, $CHCl_3$); IR (KBr) 2952, 2930, 2858, 1696, 1652, 1253, 1117, 839, 777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.85 (m, 2H), 7.70 (dd, *J* = 7.8, 1.5 Hz, 4H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 2H), 7.47–7.36 (m, 6H), 5.41 (dd, *J* = 7.0, 6.0 Hz, 1H), 5.10 (d, *J* = 9.0 Hz, 1H), 5.02 (s, 1H), 4.99 (s, 1H), 4.37 (dd, *J* = 9.3, 6.9 Hz, 1H), 4.25 (d, *J* = 14.5 Hz, 1H), 4.11 (d, *J* =

14.5 Hz, 1H), 4.07 (s, 2H), 3.56 (dd, *J* = 14.6, 9.8 Hz, 1H), 3.21 (dd, *J* = 14.6, 3.6 Hz, 1H), 2.84 (m, 1H), 2.16 –2.07 (m, 2H), 2.00 (m, 2H), 1.68 (d, *J* = 0.6 Hz, 3H), 1.62 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 139.8, 139.7, 135.7, 134.5, 133.9, 133.7, 129.7, 129.2, 128.2, 127.7, 124.3, 123.8, 115.2, 102.0, 69.9, 69.0, 65.9, 56.7, 47.5, 39.5, 27.0, 26.2, 25.6, 24.4, 19.4, 17.2, 13.7; HRMS (ESI) calcd for $C_{40}H_{56}NO_5SSi$ $(M+NH_4)^+$ 690.3643, found 690.3645.

*(2E,6E)-7-((4R,5S)-2,2-Dimethyl-6-methylene-5-((phenylsulfonyl)methyl)-1,3-dioxepan-4-yl)-2,6-dimethylhepta-2,6-dien-1-ol (**20**).* A mixture of compound **19** (422 mg, 0.63 mmol) in THF (1 mL) and TBAF in THF (0.2 M, 3.9 mL, 0.78 mmol) was stirred overnight at room temperature. The solution was quenched with aqueous ammonium chloride solution and then extracted with ethyl acetate. The organic layer was dried over Na_2SO_4, and concentrated to give an oily crude product, which was purified by silica gel column (PE:EA = 2:1–1:1) to afford **20** (235 mg, 86%) as a colorless oil. $[\alpha]_D^{27}$ –34.0^o (*c* 1.0, $CHCl_3$); IR (KBr) 3528, 3066, 2987, 2926, 2863, 1447, 1306,1152, 1072, 793, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 7.4 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 2H), 5.32 (br t, *J* = 6.8 Hz, 1H), 5.08 (d, *J* = 9.0 Hz, 1H), 4.93 (s, 1H), 4.90 (s, 1H), 4.33 (dd, *J* = 9.4, 6.8 Hz, 1H), 4.17 (d, *J* = 14.5 Hz, 1H), 3.99 (d, *J* = 14.5 Hz, 1H), 3.95 (s, 2H), 3.48 (dd, *J* = 14.5, 9.5 Hz, 1H), 3.17 (dd, *J* = 14.5, 3.8 Hz, 1H), 2.87–2.78 (m, 1H), 2.23 (br s, 1H), 2.11 (m, 2H), 2.07–1.98 (m, 2H), 1.63 (d, *J* = 0.8 Hz, 3H), 1.62 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5, 139.7, 139.0, 135.6, 133.8, 129.2, 128.1, 124.9, 124.6, 115.1, 102.0, 69.8, 68.5, 65.7, 56.6, 47.5, 39.1, 25.6, 25.3, 24.2, 16.8, 13.8; HRMS (ESI) calcd for $C_{24}H_{38}NO_5S(M+NH_4)^+$ 452.2465, found 452.2457.

*(4R,5S)-4-((1E,5E)-7-Bromo-2,6-dimethylhepta-1,5-dien-1-yl)-2,2-dimethyl-6-methylene-5-((phenylsulfonyl)methyl)-1,3-dioxepane (**21b**).* To a solution of **20** (100 mg, 0.232 mmol) , CBr_4

(137.3 mg, 0.414 mmol, 1.8 eq) and 2,6-lutidine (0.08 mL,0.69 mmol) in CH_2Cl_2 (2 mL) was added a solution of triphenylphosphine (108.6 mg, 0.414 mmol) in CH_2Cl_2 (1 mL) at 0 °C under Ar atmosphere. The reaction mixture was stirred at that temperature for 30 min, and then directly purified by a silica gel column (CH_2Cl_2:EA = 10:1) to provide **21b** (104 mg, 91%) as an oil. $[\alpha]_D^{27}$ –54.2° (*c* 1.0, $CHCl_3$); IR (KBr) 3064, 2986, 2922, 2856, 1446, 1306, 1216, 1153, 1072, 796, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.7 Hz, 2H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 5.56 (t, *J* = 6.8 Hz, 1H), 5.13 (d, *J* = 9.3 Hz, 1H), 4.97 (s, 1H), 4.95 (s, 1H), 4.36 (dd, *J* = 9.1, 6.9 Hz, 1H), 4.22 (d, *J* = 14.5 Hz, 1H), 4.06 (d, *J* = 14.5 Hz, 1H), 3.97 (s, 2H), 3.53 (dd, *J* = 14.5, 9.6 Hz, 1H), 3.18 (dd, *J* = 14.5, 3.7 Hz, 1H), 2.95–2.79 (m, 1H), 2.19–2.09 (m, 2H), 2.07–1.98 (m, 2H), 1.75 (s, 3H), 1.66 (s, 3H), 1.36 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 140.0, 138.8, 133.8, 132.6, 130.5, 129.3, 128.2, 125.1, 115.1, 102.1, 69.9, 65.8, 56.8, 47.6, 41.8, 38.8, 26.5, 25.7, 24.4, 17.0, 14.9; HRMS (ESI) calcd for $C_{24}H_{37}NBrO_4S(M+NH_4)^+$ 514.1621, found 514.1611.

*(5aS,8E,12E,13aR)-2,2,8,12-Tetramethyl-5-methylene-6-(phenylsulfonyl)-4,5,5a,6,7,10,11,13a-octahydrocyclodeca[d][1,3]dioxepine (**22**).* A solution of **21b** (0.02 M in THF, 8.5 mL) was slowly added (about one drop per second) to KHMDS (1.0 M in THF, 0.68 mL, 0.68 mmol, 4 eq) in dry THF (34 mL) at 0 °C. The resulting yellow solution was continued to stir for 15 min at 0 °C, followed by addition of saturated aqueous NH_4Cl. The reaction mixture was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude, which was purified by silica gel column [PE:EA = 15:1–8:1] to afford compound **22** (59.4 mg, 84%) as a mixture of diastereoisomers. HRMS (ESI) calcd for $C_{24}H_{33}O_4S$ $(M+H)^+$ 417.2094, found 417.2100.

*(5aS,8E,12E,13aR)-2,2,8,12-Tetramethyl-5-methylene-4,5,5a,6,7,10,11,13a-octahydrocyclodeca[d][1,3]dioxepine (**23**).* A mixture of **22** (59.4 mg, 0.142 mmol) and activated magnesium turnings (68 mg, 2.85 mmol) in THF (0.5 mL) and MeOH (2.5 mL) was stirred at room temperature for 8 h under Ar atmosphere. EtOAc (10 mL) was added to the reaction mixture. The reaction was quenched with saturated aqueous NH_4Cl (5 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic solution was washed with saturated brine, dried over Na_2SO_4, and concentrated to give a crude, which was purified on silica gel column [PE:EA = 100:1–40:1] to afford compound **23** (29.0 mg, 74%) as a colorless oil. $[\alpha]_D^{27}$ +46.7° (*c* 0.3, $CHCl_3$); IR (KBr) 3069, 2982, 2923, 2859, 1444, 1372, 1217, 1074, 1014, 892, 846 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.82 (br d, J = 12.0 Hz, 1H), 4.79 (s, 2H), 4.74 (d, J = 9.5 Hz, 1H), 4.45–4.38 (m, 2H), 4.25 (d, J = 14.0 Hz, 1H), 2.38–2.20 (m, 4H), 2.17–1.85 (m, 4H), 1.65 (m, 1H), 1.64 (d, J = 1.0 Hz, 3H), 1.49 (s, 3H), 1.41 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 137.3, 136.3, 132.0, 126.2, 110.4, 102.1, 72.2, 67.2, 58.9, 42.8, 39.3, 32.9, 27.1, 26.1, 24.1, 17.2, 16.7; HRMS (ESI) calcd for $C_{18}H_{28}NaO_2$ $(M+Na)^+$ 299.1982, found 299.1985.

*(1R,2E,6E,10S)-10-(3-Hydroxyprop-1-en-2-yl)-3,7-dimethylcyclodeca-2,6-dienol (**24**).* To a solution of **23** (10.7 mg, 0.04 mmol) in MeOH (0.3 mL) was added ethylene glycol (0.2 mL) and PPTS (2.4 mg, 0.01 mmol) at room temperature. After stirring for 20 min, the reaction was immediately poured into sat. aq. $NaHCO_3$ and extracted with EtOAc. The organic layers were dried over Na_2SO_4 and concentrated. Purification by column chromatography (50% EA in hexane) afforded diol **24** (7.1 mg, 78%) as a clear oil. $[\alpha]_D^{25}$ +77.7° (*c* 0.6, $CHCl_3$); IR (KBr) 3076, 2924, 2857, 1445, 1262, 899, 802 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.15 (s, 1H), 5.01 (s, 1H), 4.79 (d, J = 10.9 Hz, 1H), 4.67 (d, J = 9.5 Hz, 1H), 4.16 (m, 3H), 2.67 (br s, 1H), 2.40–

2.32 (m, 1H), 2.22 (m, 3H), 2.11 (m, 2H), 1.94 (m, 1H), 1.80–1.67 (m, 3H), 1.66 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 138.1, 135.1, 133.0, 126.9, 112.3, 71.5, 65.5, 55.0, 41.7, 39.6, 32.3, 26.0, 17.1, 16.5; HRMS (ESI) calcd for $C_{15}H_{25}O_2$ $(M+H)^+$ 237.1849, found 237.1853.

*(+)-Costunolide (**1**).* To a stirred solution of compound **24** (49 mg, 0.2 mmol) in CH_2Cl_2 (4 mL) was added MnO_2 (180 mg, 2 mmol). After the mixture was stirred for 24 h at room temperature, another portion of MnO_2 (180 mg, 2 mmol) was added. After another 24 h, the mixture was filtered through a short pad of Celite and washed with CH_2Cl_2. The filtrate was concentrated under reduced pressure to an oily crude product, which was purified by flash chromatography [PE/EA = 40:1–10:1] to give compound **1** (40 mg, 82%) as an amorphous white solid. $[\alpha]_D^{21}$ +120° (*c* 0.1, $CHCl_3$), lit. $[\alpha]_D$ = +128° (*c* 0.34, $CHCl_3$)[1a]; IR (KBr) 3070, 2930, 2856, 1669, 1428, 1376, 1216, 1110, 823, 739, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (d, *J* = 3.6 Hz, 1H), 5.51 (d, *J* = 3.2 Hz, 1H), 4.84 (d, *J* = 11.0 Hz, 1H), 4.72 (d, *J* = 9.9 Hz, 1H), 4.55 (t, *J* = 9.3 Hz, 1H), 2.56 (m, 1H), 2.44 (dd, *J* = 13.2, 5.9 Hz, 1H), 2.34–1.97 (m, 6H), 1.68 (s, 3H), 1.65 (m, 1H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 141.6, 140.2, 137.1, 127.3, 127.1, 119.8, 82.0, 50.5, 41.1, 39.5, 28.1, 26.3, 17.4, 16.2; HRMS (ESI) calcd for $C_{15}H_{21}O_2$ $(M+H)^+$ 233.1536, found 233.1538.

*Melampomagnolide B (**26**).* A solution of **2** (1.0 g, 4.3 mmol) in dichloromethane (20 mL) was treated with SeO_2 (324 mg, 2.4 mmol) and pre-dried *t*-BuOOH (70% in H_2O, 1.48 mL, 10.8 mmol) over Na_2SO_4. The mixture was refluxed gently for 10 h, and stirred for 4 days at room temperature. The reaction mixture was diluted with dichloromethane (20 mL) and the organic layer was washed with sat. aqueous $Na_2S_2O_3$, brine and dried over anhydrous Na_2SO_4 . The solvent was removed under vacuum to get the crude, which was purified by column

chromatography [PE:EA = 2:1–1:2] to give the alcohol **26** (810 mg, 72%) as a white solid. mp 171–173 ^{o}C; $[\alpha]_D^{21}$ –33.9^{o} (*c* 1.0, $CHCl_3$); IR (KBr) 3466, 3096, 2957, 2867, 1747, 1309, 1151, 818 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (d, *J* = 3.4 Hz, 1H), 5.63 (t, *J* = 8.1 Hz, 1H), 5.54 (d, *J* = 3.1 Hz, 1H), 4.14 (d, *J* = 12.7 Hz, 1H), 4.05 (d, *J* = 12.7 Hz, 1H), 3.84 (t, *J* = 9.3 Hz, 1H), 2.84 (d, *J* = 9.4 Hz, 1H), 2.81 (m, 1H), 2.47–2.35 (m, 3H), 2.31–2.24 (m, 1H), 2.20–2.10 (m, 2H), 1.98 (br s, 1H), 1.63 (t, *J* = 11.2 Hz, 1H), 1.53 (s, 3H), 1.07 (t, *J* = 12.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 139.6, 138.9, 127.2, 120.4, 81.3, 65.6, 63.4, 60.3, 42.8, 36.8, 25.6, 24.0, 23.7, 18.0. HRMS (ESI) calcd for $C_{15}H_{20}NaO_4$ [M + Na^+] 287.1254; found, 287.1259.

*(1aR,7aS,10aS,10bS,E)-5-(Fluoromethyl)-1a-methyl-8-methylene-2,3,6,7,7a,8,10a,10b-octahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-9(1aH)-one (**27**) and (1aR,7aS,10aS,10bS)-4-fluoro-1a-methyl-5,8-dimethylenedecahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-9(1aH)-one (**28**)*. The solution of the alcohol **26** (94 mg, 0.356 mmol) in dry CH_2Cl_2 (20 mL) was cooled to –75 ^{o}C and DAST (0.22 mL, 1.78 mmol) was added under Ar. The cooling bath was removed, and the reaction mixture was stirred at room temperature for 2 h. Sat. aqueous $NaHCO_3$ (5 mL) was added, and the organic layer was separated, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography [PE:EA = 5:1–2:1] to yield a 3:1 mixture of **27** and **28** (68.3 mg, 72%), which was recrystallized in ether to get **27** (29.3 mg, 31%) as an oil and **28** (11.3 mg, 12%) a white solid.

Compound **27**: $[\alpha]_D^{17}$ –44.78^{o} (*c* 0.3, $CHCl_3$); IR (KBr) 3098, 2960, 2856, 1768, 1458, 1261, 1093, 1030, 805 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (d, *J* = 3.5 Hz, 1H), 5.75 (dd, *J* = 13.0, 7.8 Hz, 1H), 5.54 (d, *J* = 3.2 Hz, 1H), 4.90 (dd, *J* = 48.4, 10.6 Hz, 1H), 4.77 (dd, *J* = 47.3, 10.6 Hz, 1H), 3.85 (t, *J* = 9.4 Hz, 1H), 2.95–2.86 (m, 1H), 2.84 (d, *J* = 9.4 Hz, 1H), 2.42 (m, 3H), 2.34–2.13 (m, 3H), 1.72–1.65 (m, 1H), 1.54 (s, 3H), 1.11 (t, *J* = 12.3 Hz, 1H); ^{13}C NMR (100

MHz, $CDCl_3$) δ 169.5, 138.8, 136.0 (d, J = 14.2 Hz), 132.3 (d, J = 10.9 Hz), 120.2, 86.7 (d, J = 164.9 Hz), 81.0, 63.3, 60.0, 42.8 (d, J = 2.9 Hz), 36.5 (d, J = 4.3 Hz), 26.0, 24.7, 23.8, 18.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –209.79 (t, J = 47.9 Hz); HRMS (ESI) calcd for $C_{15}H_{19}FNaO_3$ [M + Na^+] 289.1210; found, 289.1215.

Compound **28**: mp 220–221 ^{o}C; $[\alpha]_D^{17}$ –63.97^o (*c* 0.2, $CHCl_3$); IR (KBr) 2960, 2856, 1766, 1456, 1260, 1097, 1022, 862 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (d, J = 3.5 Hz, 1H), 5.54 (d, J = 3.2 Hz, 1H), 5.51 (dd, J = 6.0, 2.1 Hz, 1H), 5.21 (s, 1H), 4.91 (ddd, J = 45.1, 10.8, 4.4 Hz, 1H), 3.78 (t, J = 9.5 Hz, 1H), 3.29 (m, 1H), 2.82 (d, J = 9.2 Hz, 1H), 2.56–2.41 (m, 2H), 2.26–2.13 (m, 3H), 2.09–1.95 (m, 1H), 1.80 (m, 1H), 1.50 (s, 3H), 1.07 (t, J = 12.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 143.7 (d, J = 14.9 Hz), 139.2, 119.7 (d, J = 7.9 Hz), 119.7, 98.5 (d, J = 164.6 Hz), 79.8, 63.7, 60.2, 42.7, 32.4 (d, J = 12.9 Hz), 28.0 (d, J = 26.1 Hz), 24.1, 23.3, 18.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ –155.23 (d, J = 53.1 Hz); HRMS (ESI) calcd for $C_{15}H_{19}FNaO_3$ [M + Na^+] 289.1210; found, 289.1209.

*(1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-carbaldehyde (**29**).* To a solution of the alcohol **26** (66.0 mg, 0.25 mmol) in dry CH_2Cl_2 (3 mL) was added $NaHCO_3$ (210.0 mg, 2.5 mmol) followed by the addition of Dess-Martin periodinane (156.9 mg, 0.37 mmol) in portions at 0^{o}C. The mixture was stirred for 2 h at room temperature, and quenched by the addition of sat. aqueous $Na_2S_2O_3$ (3 mL), H_2O (3 mL) and CH_2Cl_2 (5 mL). The mixture was stirred until the phases became clear. The two phases were separated, and the organic layer was washed with brine, dried over Na_2SO4, and concentrated to afford the residue, which was purified by flash chromatography [PE:EA = 4:1–2:1] to give the aldehyde **29** (60.5 mg, 92%) as a white foam. $[\alpha]_D^{20}$ –57.0^o (*c* 0.6, $CHCl_3$); IR (KBr) 3064, 2936, 2852, 1767, 1679, 1456, 1262, 812 cm^{-1}; ^{1}H

NMR (400 MHz, $CDCl_3$) δ 9.46 (d, J = 1.2 Hz, 1H), 6.68 (t, J = 8.3 Hz, 1H), 6.18 (d, J = 3.5 Hz, 1H), 5.54 (d, J = 3.1 Hz, 1H), 3.78 (t, J = 9.4 Hz, 1H), 2.93 (m, 1H), 2.70 (d, J = 9.5 Hz, 1H), 2.62–2.43 (m, 4H), 2.41–2.25 (m, 2H), 1.64–1.55 (m, 1H), 1.54 (s, 3H), 1.26–1.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.2, 169.4, 153.9, 143.8, 138.2, 120.8, 81.2, 63.0, 59.6, 42.2, 36.0, 25.0, 24.9, 22.4, 17.9; HRMS (ESI) calcd for $C_{15}H_{18}NaO_4$ [M + Na^+] 285.1097; found, 285.1100

*(1aR,7aS,10aS,10bS,E)-5-(Difluoromethyl)-1a-methyl-8-methylene-2,3,6,7,7a,8,10a,10b-octahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-9(1aH)-one (**30**).* The solution of **29** (39.0 mg, 0.18 mmol) in dry CH_2Cl_2 (0.1 mL) was cooled to 0 ^oC and DAST (0.22 mL, 1.8 mmol) was added under Ar. The cooling bath was removed and the mixture was stirred at room temperature for 3 days. CH_2Cl_2 (10 mL) and Sat. aqueous $NaHCO_3$ (5 mL) was added, and the organic layer was separated, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography [PE:EA = 5:1–2:1] to yield compound **30** (18.3 mg, 43%) as a white solid. mp 102–103 ^oC; $[\alpha]_D^{21}$ –63.79^o (*c* 0.13, $CHCl_3$); IR (KBr) 2960, 2855, 1769, 1459, 1261, 1093, 1022, 802 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (d, J = 3.3 Hz, 1H), 6.04 (dd, J = 56.9, 54.4 Hz, 1H), 5.95 (t, J = 8.0 Hz, 1H), 5.53 (d, J = 3.0 Hz, 1H), 3.85 (t, J = 9.4 Hz, 1H), 3.09–2.98 (m, 1H), 2.82 (d, J = 9.4 Hz, 1H), 2.57–2.19 (m, 6H), 1.73–1.62 (m, 1H), 1.56 (s, 3H), 1.14 (td, J = 12.6, 3.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 138.7, 135.0 (t, J = 10.8 Hz), 134.8 (t, J = 20.0 Hz), 120.3, 118.9 (t, J = 238.0 Hz), 80.9, 63.3, 59.7, 42.8 (d, J = 5.6 Hz, 1H), 36.1, 26.5, 23.7, 22.7, 18.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –107.39 (dd, J = 301.6, 57.1 Hz, 1F), –116.33 (dd, J = 301.5, 54.3 Hz, 1F); HRMS (ESI) calcd for $C_{15}H_{18}F_2NaO_3$ [M + Na^+] 307.1116; found, 307.1118.

*(1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-9-oxo-1a,2,3,6,7,7a,8,9,10a,10b-decahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-5-carboxylic acid (**31**).* To a mixure of

aldehyde **29** (50.0 mg, 0.19 mmol), $NaH_2PO_4 \cdot 2H_2O$ (118mg, 0.76 mmol) and 2-methyl-2-butene (0.2 mL, 1.9 mmol) in *t*-BuOH (2 mL) and H_2O (0.5 mL) was added $NaClO_2$ (68.7 mg, 0.76 mmol) at 0 ^oC. After stirring for 1 h at the temperature, the mixture was extracted with EtOAc (3 × 10 mL) and H_2O (5 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated to give the residue, which was purified by column chromatography [PE:EA = 1:1–1:4] to yield compound **31** (46.7 mg, 88%) as a white solid. mp 213–214 ^oC; $[\alpha]_D^{20}$ –80.4^o (*c* 0.13, $CHCl_3$); IR (KBr) 3222, 3090, 2926, 2859, 1746, 1714, 1460, 1229, 807, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (t, *J* = 8.7 Hz, 1H), 6.22 (d, *J* = 3.2 Hz, 1H), 5.55 (d, *J* = 3.0 Hz, 1H), 3.81 (t, *J* = 9.4 Hz, 1H), 2.80 (dd, *J* = 13.8, 7.8 Hz, 2H), 2.72–2.56 (m, 2H), 2.45 (m, 3H), 2.25 (m, 1H), 1.67–1.58 (m, 1H), 1.56 (s, 3H), 1.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 169.6, 144.3, 138.5, 132.6, 120.6, 81.7, 62.9, 59.7, 42.3, 35.9, 25.9, 24.7, 23.5, 18.0; HRMS (ESI) calcd for $C_{15}H_{17}O_5$ [M – H^+] 277.1081; found, 277.1087.

*(E)-6-((tert-Butyldiphenylsilyl)oxy)-3-methylhex-2-enal (**34**).* The title compound **34** (23.4 g, 92%) was prepared from **33** (25.5 g, 69.2 mmol) according to a procedure similar to that described for the synthesis of **13**. IR (KBr) 3069, 2933, 2858, 1641, 1378, 1109, 823, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.00 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 6.6 Hz, 4H), 7.49–7.34 (m, 6H), 5.91 (d, *J* = 8.0 Hz, 1H), 3.70 (t, *J* = 6.0 Hz, 2H), 2.33 (t, *J* = 6.0 Hz,, 2H), 2.15 (s, 3H), 1.75 (m, 2H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.3, 164.0, 135.6, 133.7, 129.7, 127.7, 127.4, 63.0, 37.0, 30.1, 26.9, 19.2, 17.6; HRMS (ESI) calcd for $C_{23}H_{30}NaO_2Si$ [M + Na^+] 389.1907; found, 389.1908.

*(2S,3R,E)-2-(3-((tert-Butyldimethylsilyl)oxy)prop-1-en-2-yl)-8-((tert-butyldiphenylsilyl)oxy)-1-((3aR,6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)-3-hydroxy-5-methyloct-4-en-1-one (**35**).* The title compound **35** (11.0 g, 43%) was prepared from

15 (13.8g, 32.3 mmol) according to a procedure similar to that described for the synthesis of **16a**. $[\alpha]_D^{21}$ +10.6° (*c* 1.0, $CHCl_3$); IR (KBr) 3454, 3069, 2999, 2856, 1692, 1335, 1109, 838, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.66 (m, 4H), 7.42–7.37 (m, 6H), 5.39 (s, 1H), 5.35 (s, 1H), 5.24 (d, *J* = 8.8 Hz, 1H), 4.83 (t, *J* = 8.6 Hz, 1H), 4.31 (d, *J* = 13.4 Hz, 1H), 4.22 (d, *J* = 13.4 Hz, 1H), 3.82–3.72 (m, 2H), 3.66 (t, *J* = 6.3 Hz, 2H), 3.44 (d, *J* = 13.7 Hz, 1H), 3.35 (d, *J* = 13.8 Hz, 1H), 3.22 (br s, 1H), 2.07 (m, 2H), 1.98 (m, 1H), 1.83 (m, 4H), 1.73 (s, 3H), 1.68 (m, 2H), 1.29 (m, 2H), 1.05 (s, 9H), 1.02 (s, 3H), 0.93 (s, 12H), 0.11 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 142.4, 140.3, 135.6, 134.1, 129.5, 127.6, 124.7, 115.7, 69.1, 65.8, 64.8, 63.9, 55.6, 53.1, 48.2, 47.7, 44.6, 37.9, 35.9, 32.7, 30.9, 26.9, 26.5, 26.0, 20.7, 19.9, 19.3, 18.4, 17.0, -5.39, -5.43; HRMS (ESI) calcd for $C_{44}H_{67}NNaO_6SSi_2[M + Na^+]$ 816.4120 ; found, 816.4122.

*((4R,5S)-4-((E)-5-((tert-Butyldiphenylsilyl)oxy)-2-methylpent-1-en-1-yl)-2,2-dimethyl-6-methylene-1,3-dioxepan-5-yl)((3aR,6S,7aS)-8,8-dimethyl-2,2-dioxidohexahydro-1H-3a,6-methanobenzo[c]isothiazol-1-yl)methanone (**36**)*. The title compound **36** (2.44 g, 75%) was prepared from **35** (3.54 g, 4.46 mmol) according to a procedure similar to that described for the synthesis of compound **17**. $[\alpha]_D^{21}$ +9.4° (*c* 1.0, $CHCl_3$); IR (KBr) 2937, 2897, 1690, 1336, 1109, 709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 6.6 Hz, 4H), 7.39 (m, 6H), 5.33 (d, *J* = 9.6 Hz, 1H), 5.10 (s, 1H), 4.95 (t, *J* = 9.4 Hz, 1H), 4.88 (s, 1H), 4.36 (d, *J* = 13.0 Hz, 1H), 4.01 (d, *J* = 13.0 Hz, 1H), 3.94 (m, 1H), 3.76 (t, *J* = 6.3 Hz, 1H), 3.65 (t, *J* = 6.5 Hz, 2H), 3.45 (d, *J* = 13.8 Hz, 1H), 3.34 (d, *J* = 13.8 Hz, 1H), 2.13–2.00 (m, 4H), 1.84 (d, *J* = 5.5 Hz, 3H), 1.68 (s, 3H), 1.64 (m, 2H), 1.37 (s, 6H), 1.29 (m, 2H), 1.09 (s, 3H), 1.04 (s, 9H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 144.3, 139.1, 135.6, 134.1, 129.5, 127.6, 123.6, 115.4, 101.4, 68.9, 66.9, 65.2, 63.9, 57.3, 53.1, 48.0, 47.7, 44.6, 38.6, 35.9, 32.9, 31.1, 26.9, 26.4, 25.3, 24.9, 20.7, 19.9, 19.3, 17.1; HRMS (ESI) calcd for $C_{41}H_{57}NNaO_6SSi$ $[M + Na^+]$ 742.3568; found, 742.3570.

*tert-Butyl(((E)-5-((4R,5S)-2,2-dimethyl-6-methylene-5-((phenylthio)methyl)-1,3-dioxepan-4-yl)-4-methylpent-4-en-1-yl)oxy)diphenylsilane (**37**).* Compound **37** (1.87g, 81%) was prepared as an oil from **36** (2.78g, 3.86 mmol) according to a procedure similar to that described for the synthesis of **18** from **17**. $[\alpha]_D^{21}$ +3.4^o (*c* 1.0, $CHCl_3$; IR (KBr) 3069, 2932, 2858, 1428, 1378, 1109, 822, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 6.6 Hz, 4H), 7.39 (m, 6H), 7.24 (m, 4H), 7.11 (t, *J* = 6.6 Hz, 1H), 5.20 (d, *J* = 9.3 Hz, 1H), 5.05 (s, 1H), 4.92 (s, 1H), 4.52 (dd, *J* = 9.0, 8.0 Hz, 1H), 4.32 (d, *J* = 14.1 Hz, 1H), 4.26 (d, *J* = 14.1 Hz, 1H), 3.63 (t, *J* = 6.3 Hz, 2H), 3.14–3.02 (m, 2H), 2.56 (br q, *J* = 7.6 Hz, 1H), 2.09 (m, 2H), 1.71 (s, 3H), 1.67–1.60 (m, 2H), 1.40 (s, 3H), 1.35 (s, 3H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 138.6, 137.1, 135.6, 134.1, 129.6, 128.9, 128.8, 127.7, 125.8, 125.2, 114.1, 101.8, 70.1, 66.5, 63.7, 52.4, 36.1, 34.0, 30.9, 26.9, 25.9, 24.4, 19.3, 17.1; HRMS (ESI) calcd for $C_{37}H_{48}NaO_3SSi$ [M + Na^+] 623.2986; found, 623.2988.

*tert-Butyl(((E)-5-((4R,5S)-2,2-dimethyl-6-methylene-5-((phenylsulfonyl)methyl)-1,3-dioxepan-4-yl)-4-methylpent-4-en-1-yl)oxy)diphenylsilane (**38**).* The title compound **38** (1.83 g, 93%) was prepared from **37** (1.87 g, 3.11 mmol) according to a procedure similar to that described for the synthesis of compound **19**. $[\alpha]_D^{21}$ –20.7^o (*c* 1.0, $CHCl_3$); IR (KBr) 3069, 2931, 2857, 1428, 1378, 1080, 800, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88– 7.84 (m, 2H), 7.67 (m, 4H), 7.62–7.57 (m, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.46–7.36 (m, 6H), 5.07 (d, *J* = 9.3 Hz, 1H), 5.01 (s, 1H), 4.98 (s, 1H), 4.34 (dd, *J* = 9.3, 6.9 Hz, 1H), 4.24 (d, *J* = 14.5 Hz, 1H), 4.08 (d, *J* = 14.4 Hz, 1H), 3.65 (t, *J* = 6.3 Hz, 2H), 3.54 (dd, *J* = 14.6, 9.8 Hz, 1H), 3.19 (dd, *J* = 14.6, 3.6 Hz, 1H), 2.84–2.76 (m, 1H), 2.04 (m, 2H), 1.65 m, 2H), 1.63 (d, *J* = 0.9 Hz, 3H), 1.36 (s, 3H), 1.30 (s, 3H), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 139.7, 139.6, 135.6, 134.0, 133.7, 129.6, 129.2, 128.2,

127.7, 124.3, 115.2, 101.9, 69.9, 65.9, 63.7, 56.6, 47.4, 36.0, 30.8, 26.9, 25.6, 24.3, 19.3, 17.0; HRMS (ESI) calcd for $C_{37}H_{48}NaO_5SSi$ [M + Na^+] 655.2884; found, 655.2888.

*(E)-5-((4R,5S)-2,2-Dimethyl-6-methylene-5-((phenylsulfonyl)methyl)-1,3-dioxepan-4-yl)-4-methylpent-4-en-1-ol (**39**).* The title compound **39** (673 mg, 93%) was prepared from **38** (1.10 g, 1.74 mmol) according to a procedure similar to that described for the synthesis of compound **20**. $[\alpha]_D^{20}$ –38.0° (*c* 1.0, $CHCl_3$); IR (KBr) 3534, 3067, 2934, 2868, 1447, 1305, 1217, 910, 797 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.4 Hz, 2H), 7.65 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H), 5.17 (d, *J* = 9.2 Hz, 1H), 4.99 (s, 1H), 4.95 (s, 1H), 4.39 (dd, *J* = 9.2, 6.9 Hz, 1H), 4.24 (d, *J* = 14.5 Hz, 1H), 4.09 (d, *J* = 14.5 Hz, 1H), 3.63 (t, *J* = 6.3 Hz, 2H), 3.51 (dd, *J* = 14.5, 9.3 Hz, 1H), 3.22 (dd, *J* = 14.5, 3.9 Hz, 1H), 2.90–2.81 (m, 1H), 2.13–2.04 (m, 2H), 1.91–1.76 (m, 2H), 1.69 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 139.7, 139.5, 133.8, 129.2, 128.1, 124.8, 115.0, 102.0, 69.8, 65.8, 62.4, 56.8, 47.3, 36.1, 30.3, 25.6, 24.3, 16.8; HRMS (ESI) calcd for $C_{21}H_{30}NaO_5S$ [M + Na^+] 417.1706; found, 417.1708.

*(E)-5-((4R,5S)-2,2-Dimethyl-6-methylene-5-((phenylsulfonyl)methyl)-1,3-dioxepan-4-yl)-4-methylpent-4-enal (**40**).* The title compound **40** (81.0 mg, 84%) was prepared from **39** (96.8 mg, 0.246 mmol) according to a procedure similar to that described for the synthesis of compound **29**. $[\alpha]_D^{20}$ –21.7° (*c* 1.0, $CHCl_3$); IR (KBr) 3066, 2923, 2855, 1722, 1447, 1262, 1021, 800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 7.88 (d, *J* = 7.4 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 2H), 5.15 (d, *J* = 9.2 Hz, 1H), 5.00 (s, 1H), 4.94 (s, 1H), 4.39 (dd, *J* = 9.2, 6.7 Hz, 1H), 4.25 (d, *J* = 14.6 Hz, 1H), 4.10 (d, *J* = 14.5 Hz, 1H), 3.51 (dd, *J* = 14.5, 9.3 Hz, 1H), 3.20 (dd, *J* = 14.5, 4.1 Hz, 1H), 2.88–2.79 (m, 1H), 2.56 (t, *J* = 7.6 Hz, 2H), 2.40–2.25 (m, 2H), 1.69 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 144.6, 139.6, 137.5,

133.7, 129.2, 128.0, 125.2, 114.9, 101.9, 69.6, 65.6, 56.6, 47.3, 41.6, 31.4, 25.5, 24.2, 17.0; HRMS (ESI) calcd for $C_{21}H_{32}NO_5S$ [M + NH_4^+] 410.1996; found, 410.1999.

*(4R,5S)-4-((1E,5Z)-6-(Bromomethyl)-7,7,7-trifluoro-2-methylhepta-1,5-dien-1-yl)-2,2-dimethyl-6-methylene-5-((phenylsulfonyl)methyl)-1,3-dioxepane (**41**).* To a solution of 2-bromo-3,3,3-trifluoroprop-1-ene (0.24 mL, 2.30 mmol) in dry Et_2O (8 mL) was added dropwise *t*-BuLi (2.3 mL, 1.0 M in hexane, 2.30 mmol) at –105 °C under Ar atmosphere. After stirring for an additional 15 min, a solution of aldehyde **40** (182.0 mg, 0.46 mmol) in Et_2O (5.2 mL) was slowly added at the same temperature. The reaction mixture was allowed to warm up to –50 °C over 2 h. After the reaction was quenched with aqueous NH_4Cl (2 mL), the product was extracted with EtOAc. The combined extracts were washed with brine, and dried over $NaSO_4$. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (PE:EA = 2:1) to give epimeric alcohols. MsCl (62 μL, 0.80 mmol) was added to a stirred solution of the above epimeric alcohols and Et_3N (0.42 mL, 3.18 mmol) in dry CH_2Cl_2 (6 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and then poured into a mixture of EtOAc (20 mL), H_2O (3 mL) and sat. aqueous $NaHCO_3$ (2 mL). The organic layers were separated, dried (Na_2SO_4), and concentrated under reduced pressure to give crude, which was crudely purified by flash column chromatography (PE:EA = 2:1) to give the mesylates. The mesylates were dissolved in DMF (4 mL) and 2,2-dimethylpropane (1 mL), and NaBr (185.2 mg, 1.80 mmol) was added. The mixture was stirred at 25 °C for 24 h. The mixture was poured into a mixture of EtOAc (20 mL) and sat. aqueous $NaHCO_3$ (10 mL). The organic layers were separated, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography [PE:EA = 8:1–5:1] to give 138.5 mg of bromide **41** (54% over 3 steps). $[\alpha]_D^{17}$ –28.7° (*c* 0.5, $CHCl_3$); IR (KBr) 3065, 2924, 2858, 1448, 1320, 1121, 800 cm^{-1}; ^1H NMR

(400 MHz, $CDCl_3$) δ 7.88 (d, J = 7.3 Hz, 2H), 7.65 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.6 Hz, 2H), 5.21 (d, J = 8.9 Hz, 1H), 4.99 (s, 1H), 4.95 (s, 1H), 4.40 (dd, J = 9.2, 6.5 Hz, 1H), 4.24 (d, J = 14.6 Hz, 1H), 4.09 (d, J = 14.6 Hz, 1H), 4.03 (s, 2H), 3.54 (dd, J = 14.4, 9.2 Hz, 1H), 3.22 (dd, J = 14.5, 4.2 Hz, 1H), 2.94–2.85 (m, 1H), 2.37 (m, 2H), 2.22–2.12 (m, 2H), 1.72 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 140.1 (q, J = 5.2 Hz), 139.8, 137.4, 133.7, 129.2, 128.1, 127.2 (q, J = 29.6 Hz), 125.9, 123.4 (q, J = 273.4 Hz), 114.8, 102.0, 69.7, 65.6, 56.9, 47.4, 37.4, 25.9, 25.5, 24.3, 21.0, 17.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –66.83 (s); HRMS (ESI) calcd for $C_{24}H_{30}BrF_3NaO_4S$ [M + Na^+] 573.0892; found, 573.0895.

*(5aS,8E,12E,13aR)-2,2,12-Trimethyl-5-methylene-6-(phenylsulfonyl)-8-(trifluoromethyl)-4,5,5a,6,7,10,11,13a-octahydrocyclodeca[d][1,3]dioxepine (**42**).* To a stirred solvent of THF (23 mL) in ice-salt bath (–15 ^{o}C) was added simultaneously a solution of **41** (0.02 M in THF, 11.8 mL, 0.236 mmol) and NaHMDS (0.06 M in THF, 11.8 mL, 0.708mmol) drop by drop. The resulting dark red solution was continued to stir for 5 min, followed by addition of saturated aqueous NH_4Cl. The reaction mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with saturated brine, dried over Na_2SO_4, and concentrated to give an oily crude, which was purified by silica gel column [PE:EA = 8:1–5:1] to afford compound **42** (60.3 mg, 54%) as a white foam. $[\alpha]_D^{20}$ –184.8^o (*c* 0.1, $CHCl_3$); IR (KBr) 3079, 2924, 2855, 1448, 1261, 1105, 1020, 803 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ7.87 (d, J = 7.6 Hz, 2H), 7.63 (t, J = 7.6 Hz, 1H), 7.55 (t, J = 7.6 Hz, 2H), 6.21 (t, J = 8.2 Hz, 1H), 5.51 (t, J = 10.0 Hz, 1H), 5.08 (d, J = 15.4 Hz, 1H), 5.03 (s, 1H), 5.00 (d, J = 9.9 Hz, 1H), 4.96 (s, 1H), 4.40 (d, J = 15.3 Hz, 1H), 3.83 (dt, J = 13.3, 4.4 Hz, 1H), 3.21 (dd, J = 10.0, 3.2 Hz, 1H), 2.58 (t, J = 13.9 Hz, 1H), 2.26–2.14 (m, 2H), 2.12–2.01 (m, 2H), 1.89 (d, J = 0.8 Hz, 3H), 1.86 (m, 1H), 1.46 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 139.5, 135.6 (q, J = 6.1 Hz), 133.8, 132.8, 130.6,

129.3, 128.5 (q, J = 28.0 Hz), 128.2, 124.1 (q, J = 274.5 Hz), 112.8, 101.7, 68.2, 67.0, 64.7, 52.0, 36.3, 27.1, 25.4, 24.8, 24.3, 17.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ –63.4 (s); HRMS (ESI) calcd for $C_{24}H_{29}F_3NaO_4S$ [M + Na^+] 493.1631; found, 493.1635.

*(3aS,6E,10E,11aR)-10-Methyl-3-methylene-6-(trifluoromethyl)-3,3a,4,5,8,9-hexahydrocyclodeca[b]furan-2(11aH)-one (**45**).* Compound **45** (21.2 mg, 25%) was prepared as amorphous white solid from **42** (173 mg, 0.386 mmol) according to a procedure similar to that described for the synthesis of **1** from **22**. $[\alpha]_D^{20}$ +42.4^o (*c* 0.1, $CHCl_3$); IR (KBr) 2923, 2855, 1764, 1456, 1262, 1109, 807 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.17 (m, 2H), 5.44 (s, 1H), 5.12 (d, J = 10.2 Hz, 1H), 4.60 (t, J = 9.9 Hz, 1H), 2.71 (t, J = 8.9 Hz, 1H), 2.36–2.25 (m, 4H), 2.20–2.11 (m, 1H), 2.08–1.96 (m, 2H), 1.88 (s, 3H), 1.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 139.6, 138.3, 133.3 (q, J = 6.3 Hz), 131.4 (q, J = 27.1 Hz), 126.0, 124.5 (q, J = 274.7 Hz), 119.0, 80.6, 45.0, 37.4, 25.7, 24.7, 22.8, 17.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ –64.3 (s); HRMS (ESI) calcd for $C_{15}H_{17}F_3NaO_2$ [M + Na^+] 309.1073; found, 309.1075.

*(1aR,7aS,10aS,10bS,E)-1a-Methyl-8-methylene-5-(trifluoromethyl)-2,3,6,7,7a,8,10a,10b-octahydrooxireno[2',3':9,10]cyclodeca[1,2-b]furan-9(1aH)-one (**32**).* To a solution of **45** (10.5 mg, 36.7 μmol) in dichloromethane (1 mL) was added *m*-CPBA (85%, 14.9 mg, 73.4 μmol) at room temperature. After 1 h, another portion of *m*-CPBA (85%, 29.8 mg, 146.8 μmol) was added. After being continued to stir for 3 h at 25 ^{o}C, the reaction mixture was diluted with dichloromethane (5 mL) and quenched with sat. aqueous $Na_2S_2O_3$, and then the organic layer was washed with sat. aqueous $NaHCO_3$, brine and dried over Na_2SO_4. The solvent was removed under vacuum to give the crude, which was purified by column chromatography [PE:EA = 8:1–5:1] to provide compound **32** (10.0 mg, 91%) as white solid. $[\alpha]_D^{17}$ –93.2^o (*c* 0.1, $CHCl_3$); IR (KBr) 2960, 2852, 1771, 1464, 1261, 1099, 1023, 803 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.31

(t, J = 8.6 Hz, 1H), 6.23 (d, J = 3.5 Hz, 1H), 5.53 (d, J = 3.2 Hz, 1H), 3.85 (t, J = 9.4 Hz, 1H), 2.97 (m, 1H), 2.79 (d, J = 9.4 Hz, 1H), 2.54–2.51 (m, 2H), 2.49–2.38 (m, 1H), 2.38–2.29 (m, 2H), 2.27–2.19 (m, 1H), 1.76–1.66 (m, 1H), 1.55 (s, 3H), 1.20–1.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 138.43, 134.6 (q, J = 6.1 Hz), 130.6 (q, J = 27.7 Hz), 124.2 (q, J = 274.6 Hz), 120.4, 80.8, 63.1, 59.6, 42.5 (q, J = 2.0 Hz), 35.9, 26.2, 23.6, 23.2, 18.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ –64.47 (s); HRMS (ESI) calcd for $C_{15}H_{17}F_3NaO_3$ [M + Na^+] 325.1022; found, 325.1026.

Materials and Experimental Procedure for the Stability Study of compound 32 and PTL. The HPLC−MS/MS system consisted of a UltiMate 3000 × 2 Dual-Gradient HPLC system (Sunnyvale, CA, USA) and a triple quadrupole API4000$^+$ mass spectrometer from Applied Biosystems (Ontario, Canada). All solvents and chemicals were of HPLC grade and purchased from Fisher Scientific (Tustin, CA). Drug-free heparinised rat plasma was collected from male Sprague-Dawley rats (body weight: 220–250 g) obtained from the Laboratory Animal Center, Academy of Military Medical Science (Beijing, China). The animal facilities and protocols were approved by the Institutional Animal Care and Use Committee of Nankai University. All procedures were carried out in accordance with the Guidelines for Animal Experimentation of Nankai University (Tianjin, China). 20 μL PTL (**2**) and **32** solutions were respectively placed in 980 μL rat blank plasma. The tubes were then incubated in a bath incubator at 37 ^{o}C. Samples were removed at predetermined time intervals. The human liver microsomes (HLM), NADPH System Solution A and B were obtained from BD Gentest^{TM} (Woburn, MA, USA). 500 μL potassium phosphate buffer (pH = 7.4), 290 μL H_2O, 50 μL NADPH System Solution A, 10 μL NADPH System Solution B and 50 μL HLM were mixed and preincubated at 37 ^{o}C for 10 min. Then the above incubation mixture 900 μL and 20 μg/mL PTL or **32** solution 100 μL were mixed

and incubated at 37 ^{o}C. The reactions were terminated by the addition of isometric Buspirone (I.S.) in acetonitrile solution at predetermined time intervals. The concentration of PTL and **32** was analyzed by HPLC−MS/MS, respectively.

SUPPORTING INFORMATION

Copies of the NMR spectra of all new compounds, metabolic stability of compound **32** and PTL, and X-ray data of compound **32**. This material is available free of charge via the Internet at http://pubs.acs.org/.

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NOTES

The authors declare no competing financial interest.

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ABBREVIATIONS USED

SL, sesquiterpene lactone; PTL, parthenolide; DMAPT, dimethylaminoparthenolide; TBDPS, *tert*-butyldiphenylsilyl; HMDS, Hexamethyldisilazane; LiHMDS, lithium hexamethyldisilazide; NaHMDS, sodium hexamethyldisilazide; *i*-Pr_2NEt, *N*,*N*-diisopropylethylamine; KHMDS, potassium hexamethyldisilazide; TEMPO, 2,2,6,6-Tetramethylpiperidinooxy; DAST, diethylaminosulfur trifluoride

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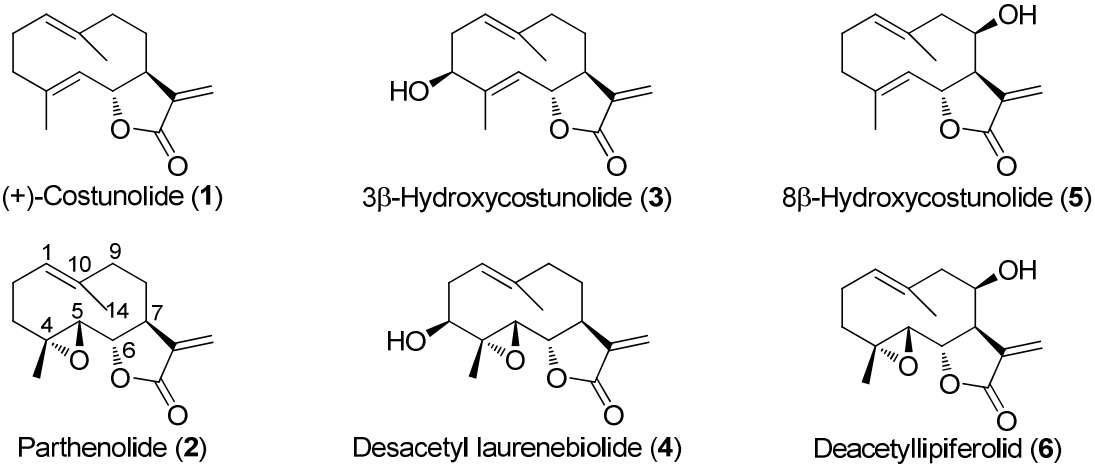


Figure 1. Selected naturally occurring germacranolides.

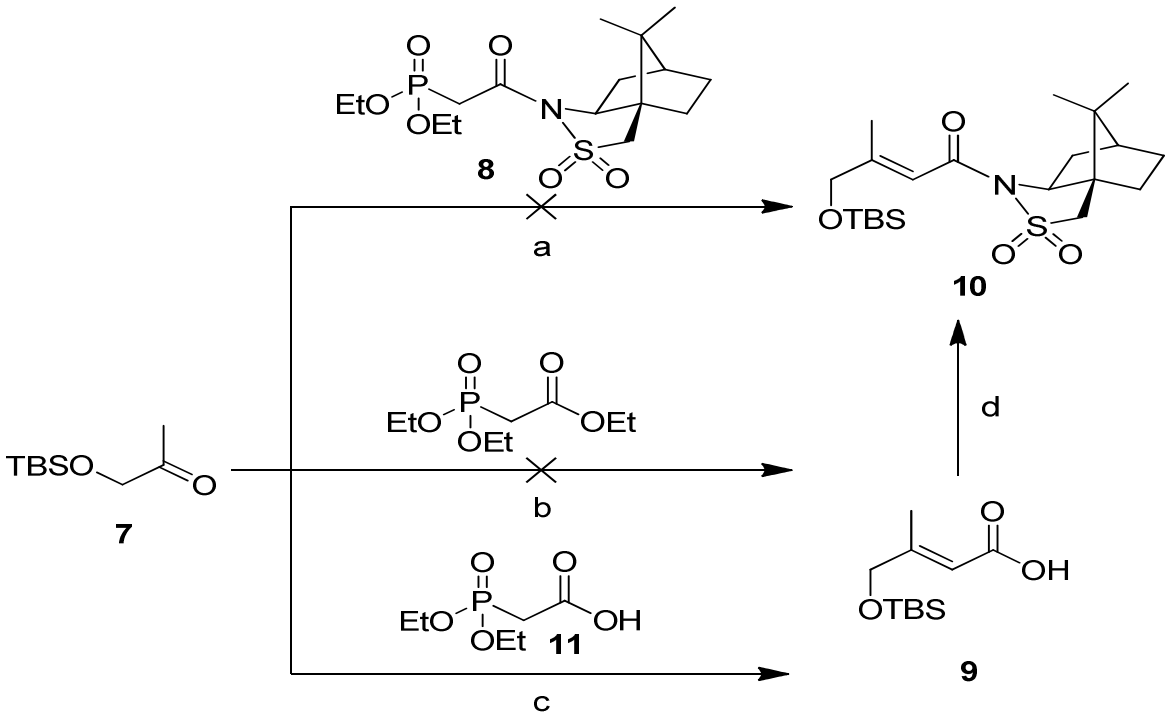
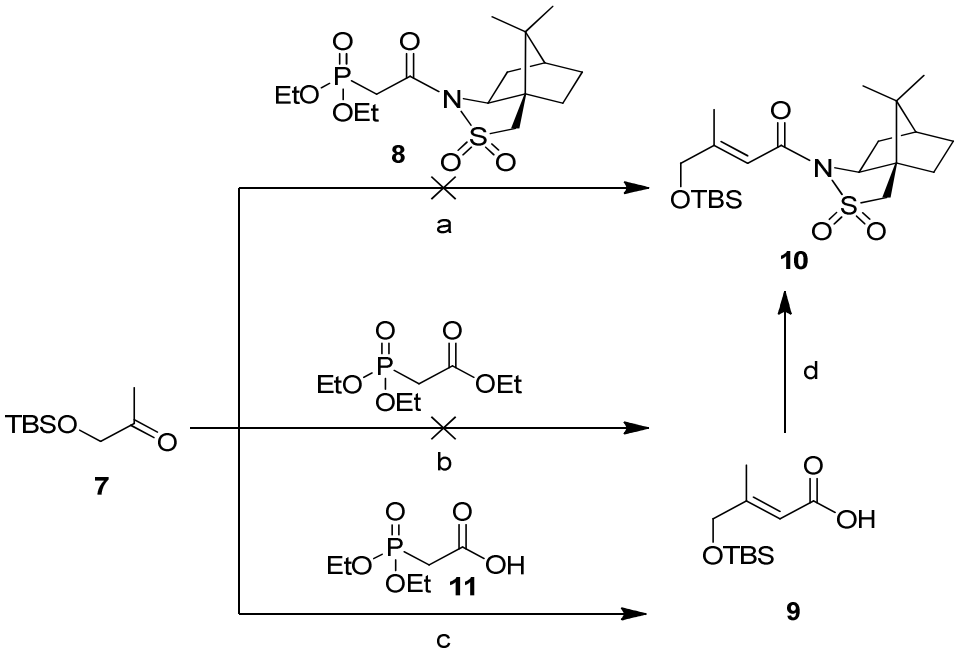
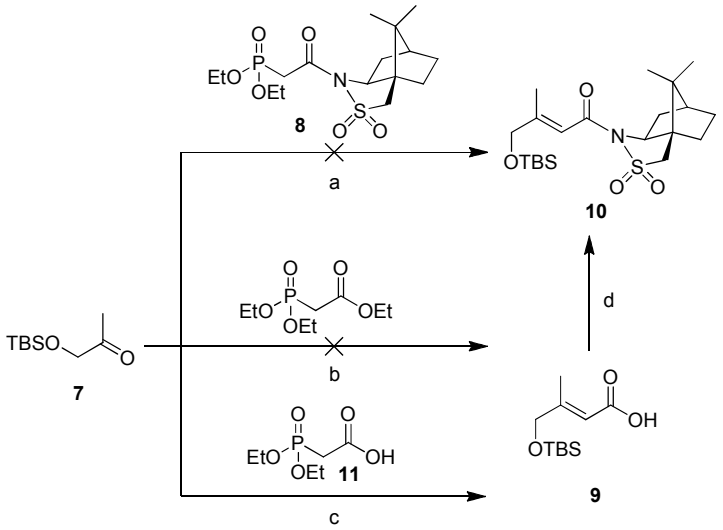


Figure 2. Presumed biosynthetic pathway of various SLs.

Scheme 1. Retrosynthetic analysis of **1** and **2**

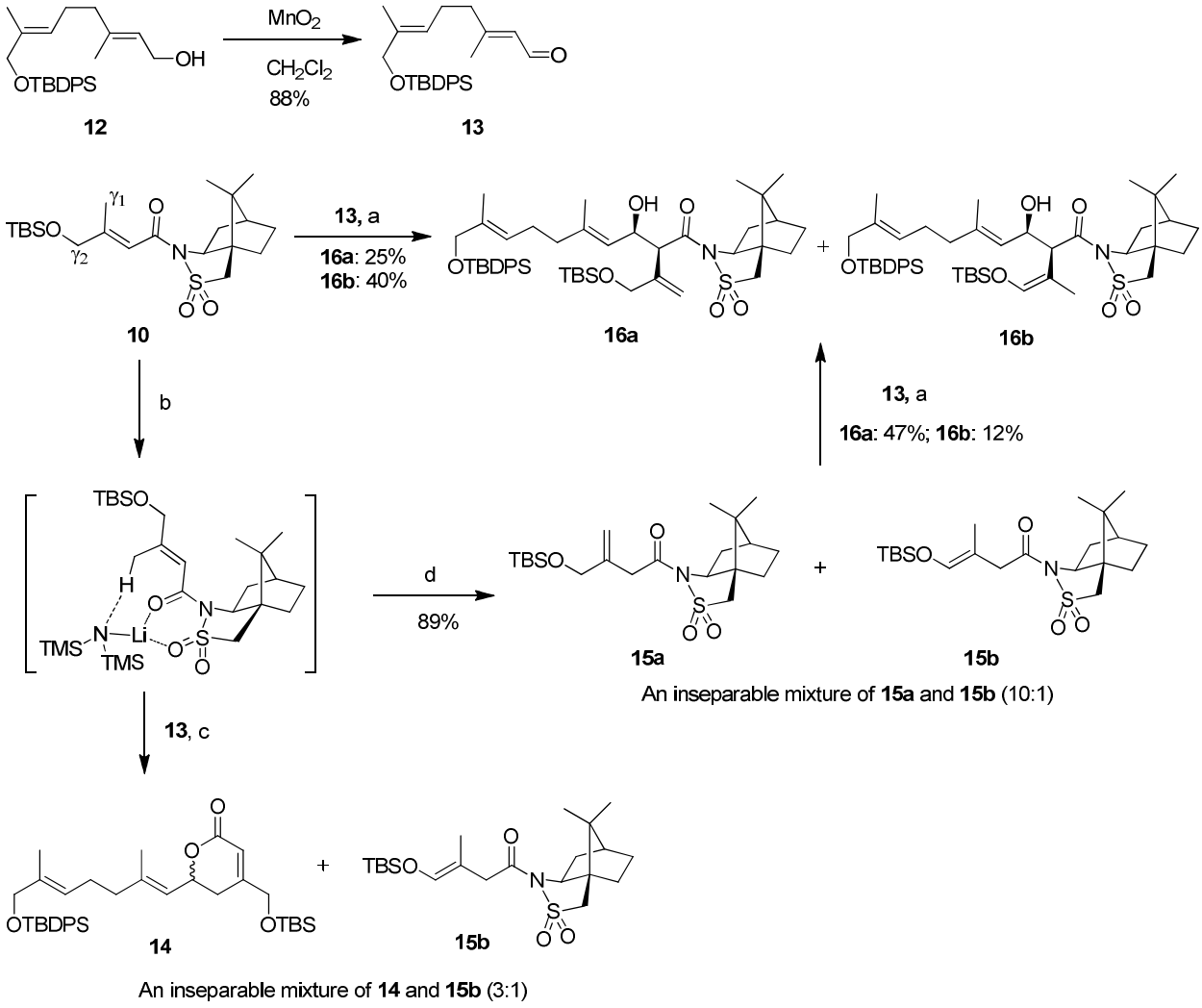


Scheme 2. Synthesis of compound **10**[a]



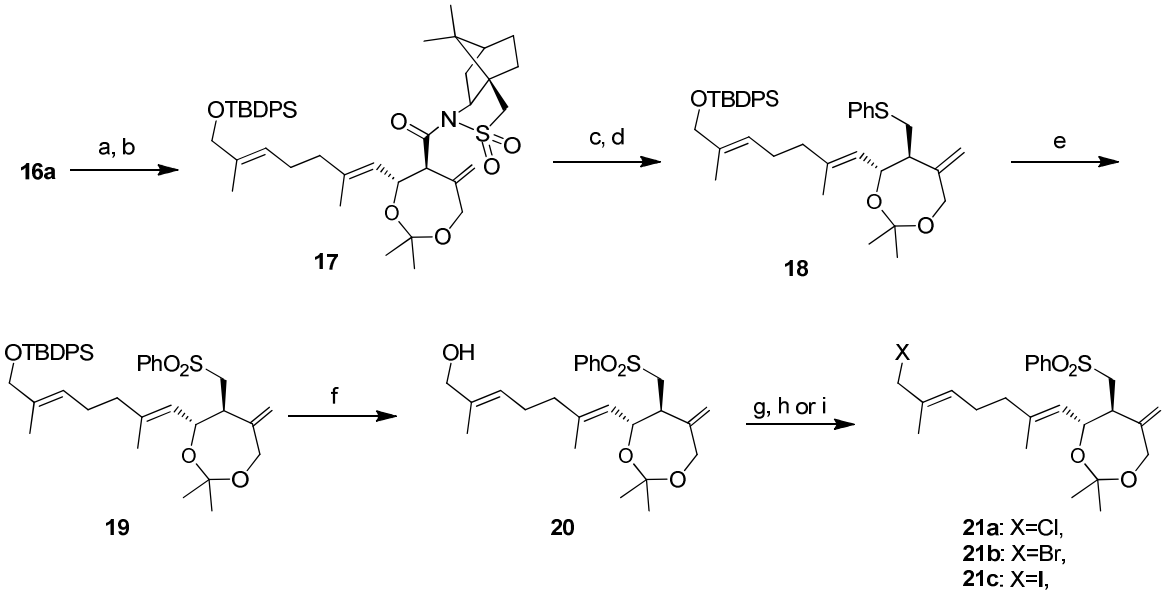
[a]Reagents and conditions: (a) NaH, LiHMDS or NaHMDS, THF, and then the addition of **7**; (b) NaH, THF, r.t., 2 h; then the addition of LiOH, MeOH, and H_2O; (c) NaHMDS, THF, 0 °C to r.t., 80%; (d) $(COCl)_2$, toluene, DMF, r.t., 2 h, then was added to NaH, L-(+)-Camphorsultam, 59%.

Scheme 3. Aldol reaction of **10** and aldehyde **13**[a]



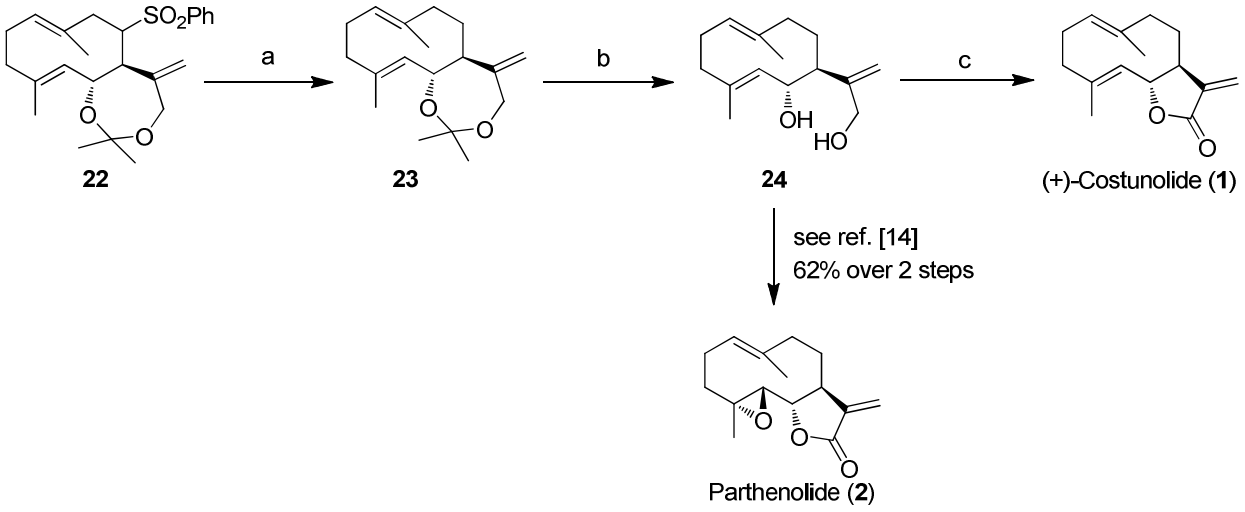
[a]Reagents and conditions: (a) $TiCl_4$, *i*-Pr_2NEt, –78 °C, CH_2Cl_2, and then **13**; (b) *n*-BuLi, HMDS, THF, –78 °C; c) then **13**, –78 °C, 73%; (d) then aq. NH_4Cl, 89%.

Scheme 4. Synthesis of cyclization precursors **21a**, **21b**, and **21c**[a]



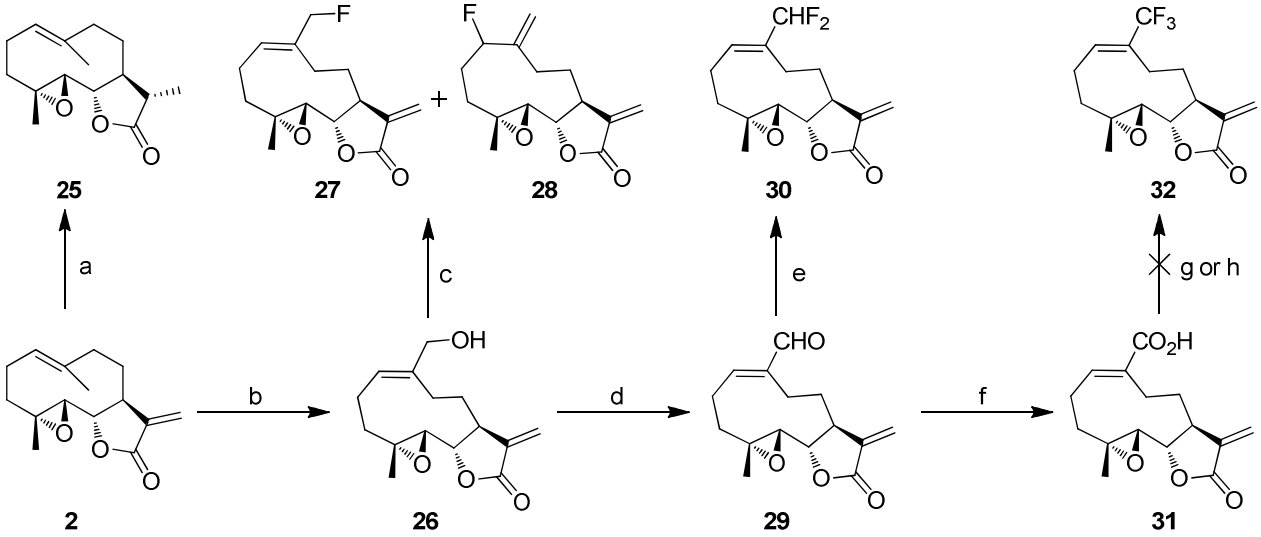
[a]Reagents and conditions: (a) HCl, H_2O, EtOH, 0 °C, 30 min; (b) 2-methoxypropene, PPTS, DMF, r.t., 74% over two steps; (c) $LiAlH_4$, THF, 0 °C, 1 h; (d) PhSSPh, *n*-Bu_3P, toluene, r.t., 15 h; 92% over 2 steps; (e) H_2O_2, $(NH_4)_6Mo_7O_{24}$, *t*-BuOH, pyridine, 86%; (f) TBAF, THF, r.t., 12 h, 95%; (g) CCl_4, P(*n*-Bu)$_3$, r.t. 78%; (h) CBr_4, PPh_3, 2,6-lutidine, 0 °C, 94%; (i) I_2, PPh_3, imidazole, 0 °C, 66%.

Scheme 5. Synthesis of compounds **1** and **2**[a]



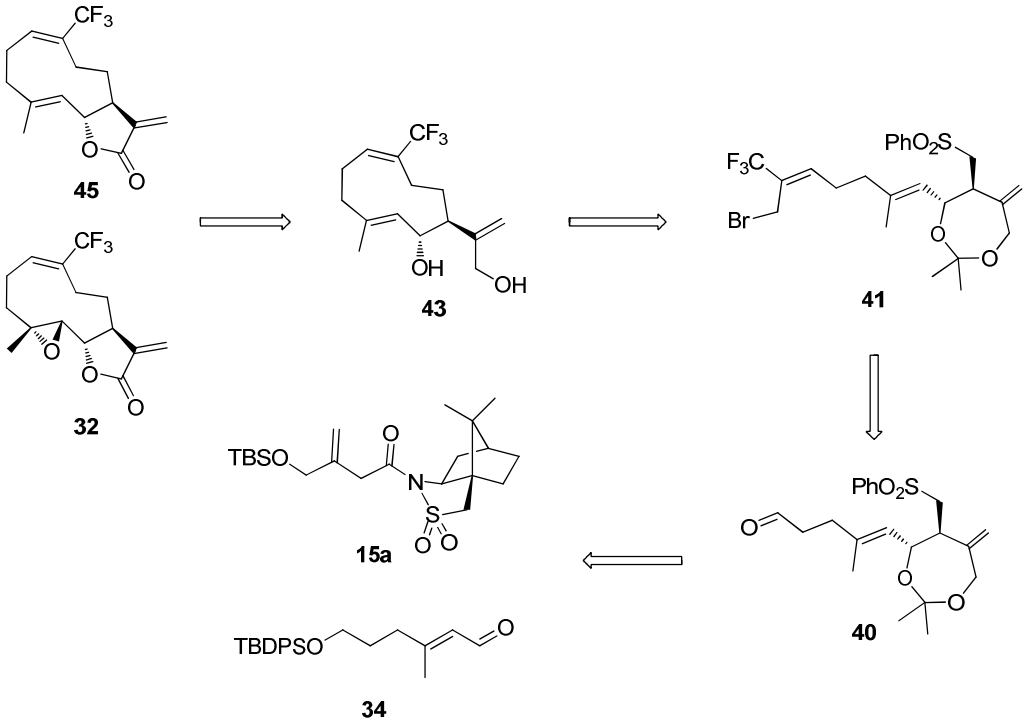
[a]Reagents and conditions: (a) Mg, MeOH, r.t., 16 h, 74%; (b) PPTS, MeOH, $(CH_2OH)_2$, r.t., 20 min, 78%; (c) MnO_2, CH_2Cl_2, r.t., 48 h, 82%.

Scheme 6. Synthesis of diverse derivatives of PTL[a]

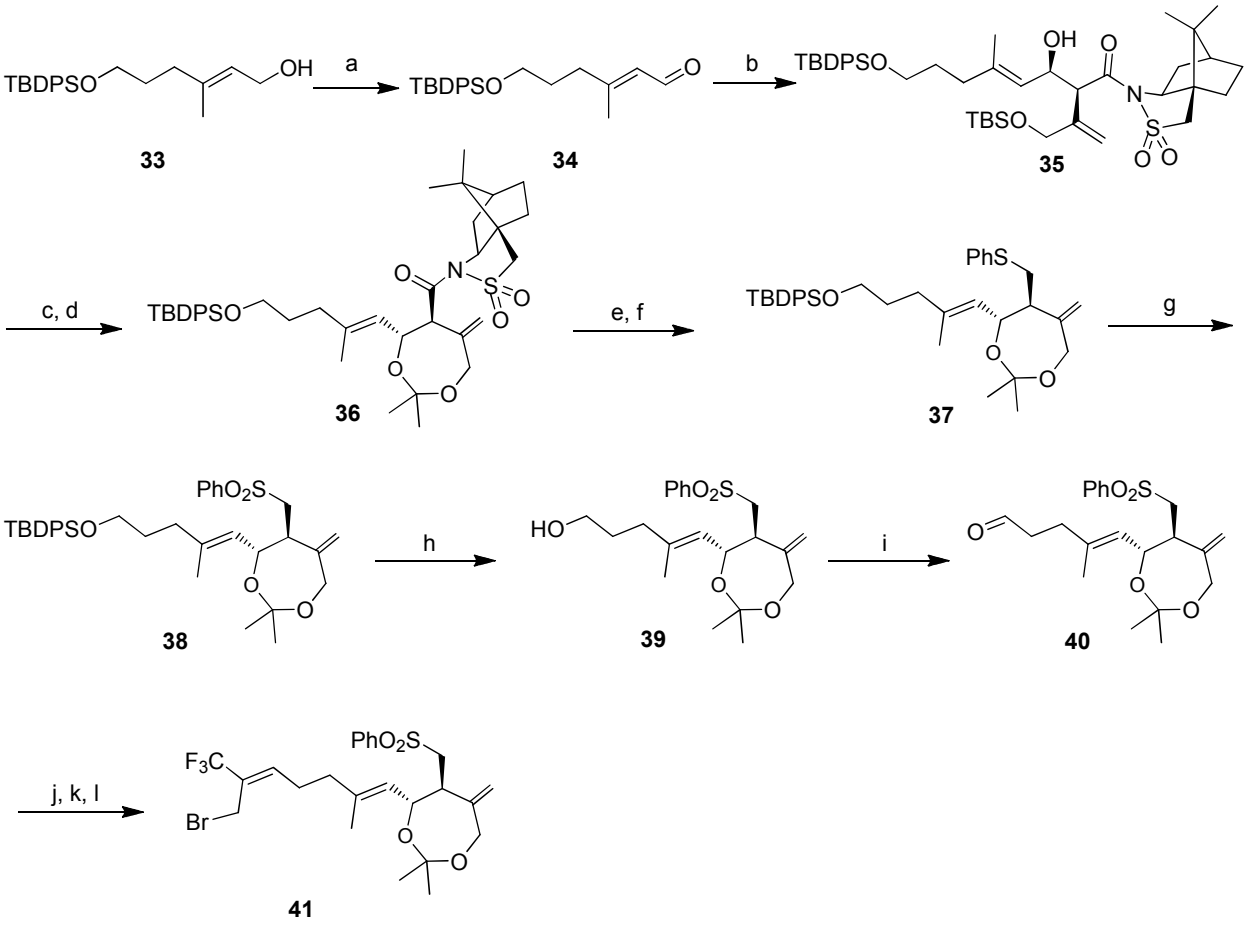


[a]Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C to r.t.; (b) SeO_2, *t*-BuOOH, CH_2Cl_2, 4 d, 72%; (c) DAST, CH_2Cl_2, r.t., 2 h, 31% yield for **27**, 12% yield for **28**; (d) Dess-Matin periodinane, $NaHCO_3$, CH_2Cl_2, r.t, 2 h, 92%; (e) DAST, CH_2Cl_2, r.t., 3 d, 43%; (f) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 0 °C, 1 h, 88%; (g) bis(2-methoxyethyl)aminosulfur trifluoride, r.t. or 80 °C; (h) CF_3SO_2Na, *t*-BuOOH, $CuSO_4$, H_2O, CH_2Cl_2, 50 °C.

Scheme 7. Retrosynthetic analysis of trifluoromethylated costunolide and PTL

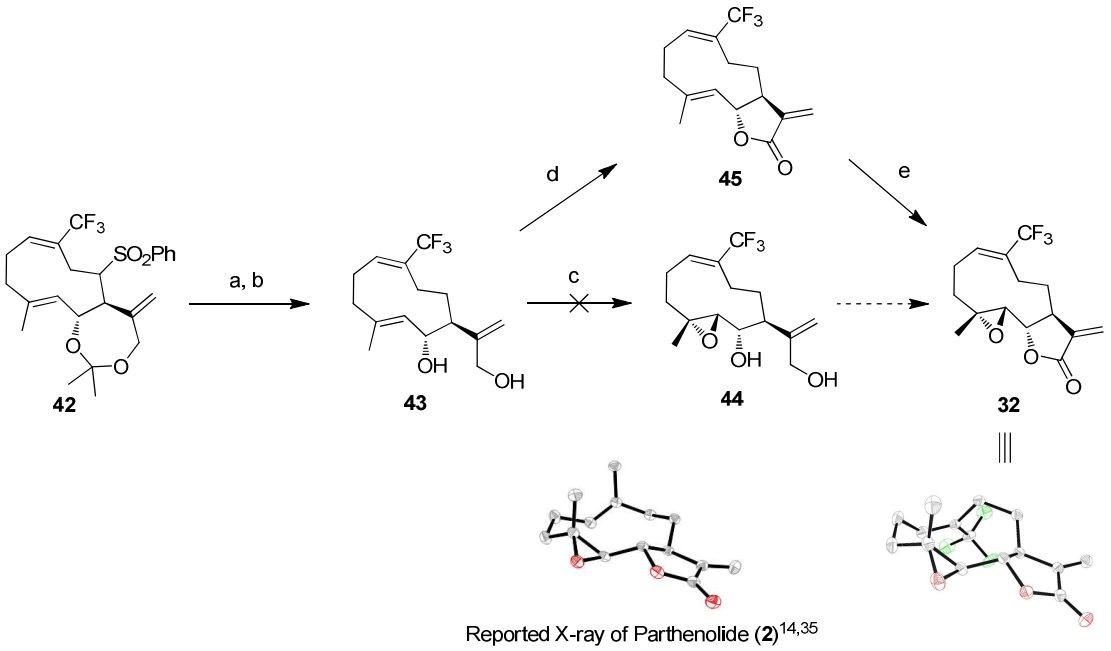


Scheme 8. Synthesis of compound **41**[a]



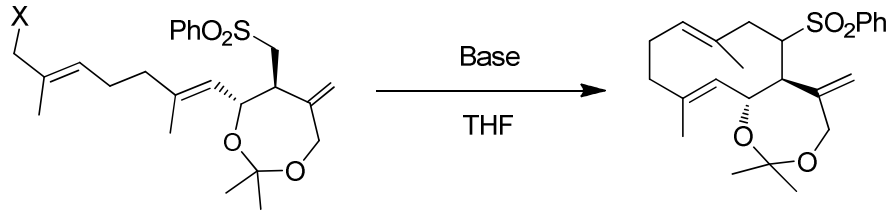
[a]Reagents and conditions: (a) MnO_2, CH_2Cl_2, 92%; (b) **15**, $TiCl_4$, *i*-Pr_2NEt, –78 °C, CH_2Cl_2, and then **34**, 43%; (c) HCl, H_2O, EtOH, 0 °C, 30 min; (d) 2-methoxypropene, PPTS, DMF, r.t., 75% over 2 steps; (e) $LiAlH_4$, THF, 0 °C, 1 h; (f) PhSSPh, *n*-Bu_3P, toluene, r.t., 15 h; 81% over 2 steps; (g) H_2O_2, $(NH_4)_6Mo_7O_{24}$, *t*-BuOH, pyridine, 93%; (h) TBAF, THF, r.t., 12 h, 93%; (i) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, r.t., 2 h, 84%; (j) 2-bromo-3,3,3-trifluoropropene, *t*-BuLi, –105 °C, Et_2O, then **40**; (k) MsCl, TEA, CH_2Cl_2, 0 °C, 2 h; (l) NaBr, 2,2-dimethylpropane, DMF, 25 °C, 24 h. 54% over 3 steps.

Scheme 9. Synthesis of compounds **45** and **32**[a]



[a]Reagents and conditions: (a) Mg, MeOH, r.t., 16 h, 74%; (b) PPTS, MeOH, $(CH_2OH)_2$, r.t., 20 min, 78%, (c) TBHP, $VO(acac)_2$, CH_2Cl_2, 0 °C; (d) MnO_2, CH_2Cl_2, r.t., 8 h, 25% over 3 steps; (e) *m*-CPBA, CH_2Cl_2, 25 °C, 3 h, 91%.

Table 1. Cyclization of compound **21**.



21a: X=Cl
21b: X=Br
21c: X=I

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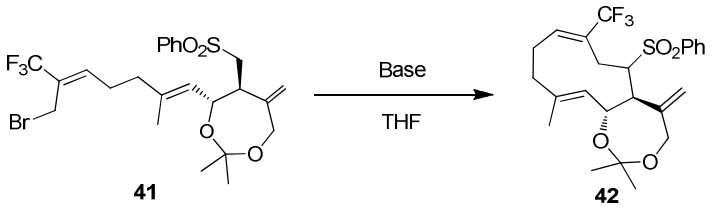
Entry	Substrate	Base	T (°C)	Reaction time (h)	Isolated yield
1	**21a**	NaHMDS, 3 equiv.	0	3	No reaction
2	**21a**	NaHMDS, 4 equiv.	70	3	No reaction
3	**21b**	NaHMDS, 3 equiv.	0	0.5	65%
4	**21b**	NaHMDS, 3 equiv.	–70	2	Slow reaction, complex mixture
5	**21c**	NaHMDS, 3 equiv.	0	0.5	28%
6	**21b**	LiHMDS, 3 equiv.	0	3	10%
7	**21b**	KHMDS, 2 equiv.	0	0.25	trace
8	**21b**	KHMDS, 3 equiv.	0	0.25	82%
9	**21b**	KHMDS, 4 equiv.	0	0.25	84%

Table 2. Cyclization of compound **40**.



Entry	Base	Conditions[a]	T (°C)	Yield
1	0.02 M KHMDS, 4 equiv.	Add **41** dropwise to base	0	trace
2	1.0 M NaHMDS, 4 equiv.	Add base dropwise to **41**	–15 to 0	32%
3	1.0 M NaHMDS, 1.5 equiv.	Add base dropwise to **41**	–15 to r.t.	9%
4	0.06 M NaHMDS, 3 equiv.	Add **41** and base dropwise simultaneously	–15	51%

[a]**41** was used as a 0.02 M solution in THF.

Table 3. Inhibitory effects of compounds **1**, **2**, **27**, **28**, **30**, **32**, and **45** on KG1a, C6, HL-60, and HL-60/A cells.[a]

Compound	IC_{50}[b] (μM)			
	KG1a[c]	C6[d]	HL-60[e]	HL-60/A[f]
1	4.1 ± 1.2	4.1 ± 0.2	2.1 ± 0.1	5.9 ± 1.0
2	2.3 ± 0.4	2.5 ± 0.2	2.0 ± 0.2	2.0 ± 0.3
27	2.9 ± 0.8	2.8 ± 0.6	2.0 ± 0.6	1.5 ± 0.2
28	8.6 ± 0.6	11.3 ± 0.3	11.9 ± 2.0	9.2 ± 0.6
30	1.8 ± 0.6	3.4 ± 0.8	2.0 ± 0.5	2.1 ± 0.1
32	2.0 ± 0.3	3.0 ± 0.8	2.1 ± 0.3	2.0 ± 0.4
45	5.1 ± 0.7	5.4 ± 1.2	5.0 ± 1.0	4.9 ± 0.4

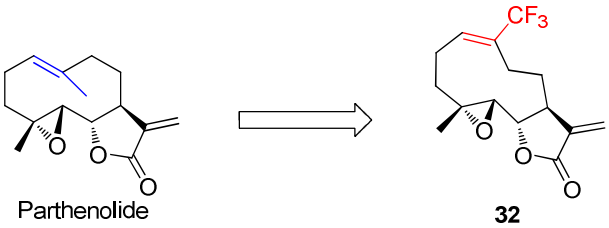
[a]All values are the mean of three independent experiments. [b]IC_{50}: 50% cytotoxic concentration. [c]KG1a: human acute myeloid leukemia cell line. [d]C6: rat glioma cell line. [e]HL-60: cultured acute myeloid leukemia cell line. [f]HL-60/A: doxorubicin-resistant cell line.

Table 4. Half-lives of **2**, **32**, and **25** in rat plasma.

Compound	**2**	**32**	**25**
$t_{1/2}$	16.7 min	20.3 min	>420 min[a]

[a]Only 20% degradation over 420 min.

Table of Contents graphic



Parthenolide **32**

Compared with parthenolide:
1. Similar potency against cancer cell lines
2. Higher stability in acid media
3. Comparable stability in rat plasma and human liver microsomes