DOI: 10.1002/chem.200802661

# Design, Synthesis, and Biological Evaluation of Artificial Macrosphelides in the Search for New Apoptosis-Inducing Agents

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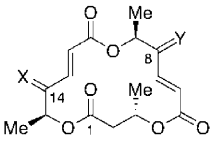
**Abstract:** Various artificial macrosphelides were designed and synthesized, including ring-enlarged analogues and epothilone-hybrid compounds. Syntheses were accomplished in an efficient manner by using a ring-closing metathesis (RCM) strategy in a key macrocyclization step. Biological evaluation of these new macrosphelide-based derivatives revealed that several epothilone hybrids, in which a thiazole-containing side chain was incorporated, exhibited potent apoptosis-inducing activity toward human lymphoma cells. These activities were considerably enhanced relative to those of natural macrosphelide compounds. Structure–activity relationship studies revealed that the "ene-dicarbonyl" substructure is apparently essential for bioactivity.

**Keywords:** anticancer agents · apoptosis · epothilones · macrosphelides · metathesis

## Introduction

Organic molecules derived from natural resources have provided a rich pool of new drugs. Indeed, drugs developed on the basis of natural-product structures account for over 50% of medical supplies in clinical use.[1] Thus, in the field of medicinal chemistry, continuous efforts to screen the biological properties of new natural compounds and subsequently to design drugs based on the lead structures found in this process represent one of the most significant and promising strategies for new drug development.[2] Natural products often possess undesirable properties for practical drugs, such as serious side effects and instability in living cells, even if they exhibit ideal biological activities in vitro, so an "artificial" structure rationally designed by considering the bioactive "natural" product structure (that is, a "non-natural natural product")[3] may provide novel and useful leads for the discovery of new therapeutic agents. In this context, we have been engaged in studies directed toward the design, synthesis, and biological assessment of compounds with a simplified, hybridized, or model structure inspired by various naturally occurring compounds.[4] Some of our recent results from research in this field relate to a group of natural macrolide compounds, the "macrosphelides".[5]

Since the initial isolation and structure elucidation in 1995, 13 natural macrosphelides, A–M have been reported, with the common structural characteristic of a 16-membered trilactone framework (Scheme 1).[6] This class of macrolide compounds has been reported to exhibit potent inhibitory activity against adhesion of human leukemia HL-60 cells to human-umbilical-vein endothelial cells (HUVECs).[6] Adhesion of tumor cells to the vessel-wall endothelia of distant organs is a critical step in tumor metastasis, and it has been reported that macrosphelide B (**2**) can suppress the metastasis of B16-BL6 mouse melanoma cells to the lung in vivo.[7] Moreover, macrosphelide B and related compounds have been found to exert inhibitory activity against tumor-cell




X = Y = α-OH (Macrosphelide A, **1**)
X = O, Y = α-OH (Macrosphelide B, **2**)
X = Y = O (**3**)

Scheme 1. Representative examples of natural macrosphelides.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200802661.

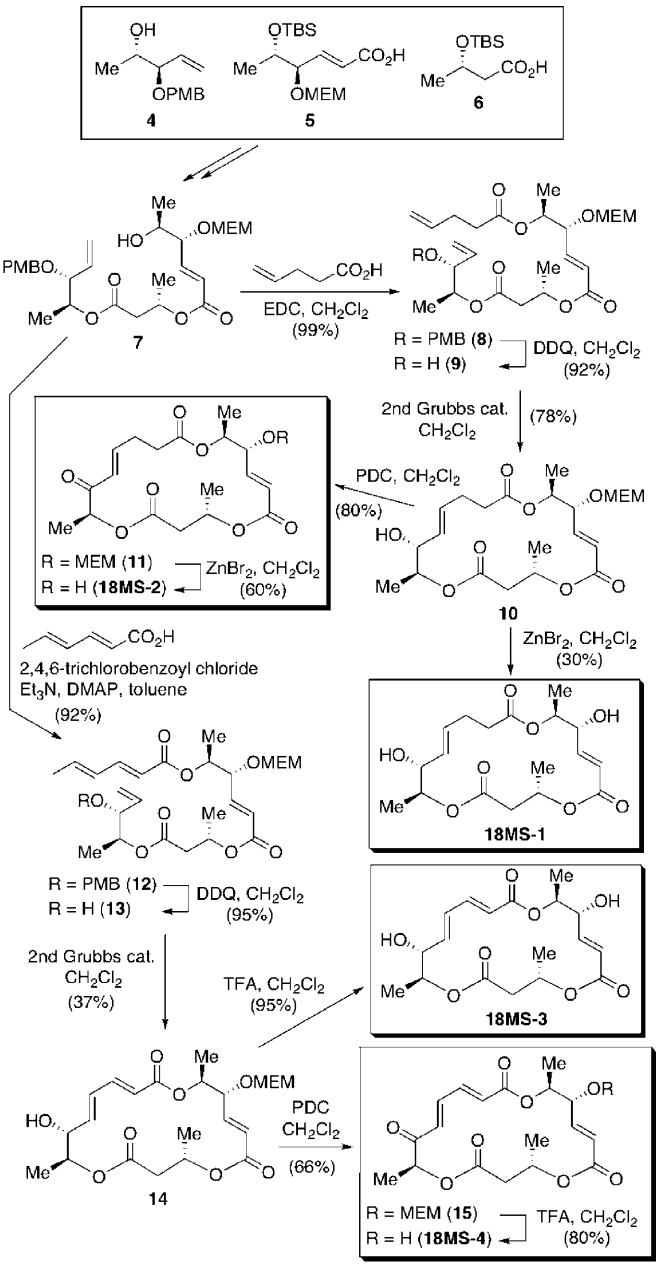
growth (colon 26-L5 adenocarcinoma cells).[8] These studies have revealed that macrosphelides are potential lead compounds for the development of new anticancer chemotherapeutic agents.

On the other hand, the role of apoptotic cell death has been increasingly recognized as an important aspect in anticancer chemotherapy, and consequently, regulation of apoptosis has been a significant research target in this field.[9] We recently confirmed that macrosphelide B (**2**) and its oxidized derivative, diketomacrosphelide (**3**), can induce apoptotic cell death in human lymphoma U937 cells at 10 μM drug concentration and that these compounds also act as effective sensitizers for hyperthermia-induced apoptosis.[10] This is the first report on the anticancer potential of macrosphelides as an index of apoptosis. These intriguing findings prompted us to design several artificial molecules based on the macrosphelide structure, for the purpose of exploring new lead compounds with improved bioactivities and superior properties for practical medicines. During the investigations, we noted a significant improvement in the apoptosis-inducing activity of this series of compounds, by means of producing "non-natural" macrosphelides.[11] In this paper, we describe the full details of the synthetic studies and biological evaluation of 1) ring-expanded (18-membered) macrosphelide analogues, 2) hybridized macrosphelides with epothilones, and 3) 12,13-dihydro-macrosphelides and their epothilone hybrids.[12]

## Results and Discussion

As the manifold biological activities of macrolides are difficult to ascribe to their intimate stereochemistries and array of functional groups, it is necessary to continue the synthesis of various derivatives of these molecules in the hope of pinpointing more precisely the aspects of stereochemistry and functionality that are important for biological activity. In this context, investigation of the bioactivities of ring-enlarged (18-membered) analogues of natural (16-membered) macrosphelides, which preserve the natural array of functionality, may provide additional guidance for the future design of macrosphelide-based apoptosis inducers. We have thus undertaken the synthesis and biological evaluation of several 18-membered macrosphelide analogues. We previously reported the total synthesis of natural macrosphelides A, B, and E based on a ring-closing metathesis (RCM) strategy.[13] It is anticipated that the broad applicability of RCM for the construction of macrocyclic compounds would make 18-membered analogues accessible.[14]

The synthetic pathway for **18MS-1**–**18MS-4** is summarized in Scheme 2. Previously reported compound **7**,[13] which can be assembled from readily available chiral building blocks **4**–**6**, was used as a common intermediate for the synthesis of the 18-membered analogues. For the preparation of RCM substrate **9** to construct the 18-membered ring, alcohol **7** was acylated by dehydrative condensation with 4-pentenoic acid, and this was followed by treatment with DDQ to



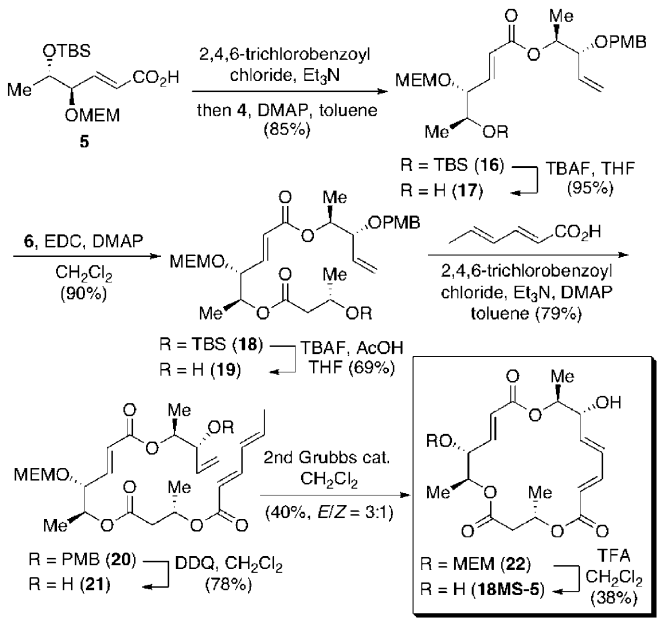

Scheme 2. Synthesis of 18-membered macrosphelides **18MS-1**–**18MS-4**. DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMAP: 4-dimethylaminopyridine; EDC: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride; MEM: (2-methoxyethoxy)methyl; PDC: pyridinium dichromate; PMB: *para*-methoxybenzyl; TBS: *tert*-butyldimethylsilyl; TFA: trifluoroacetic acid.

remove the PMB group. Compound **9**, thus obtained, was subjected to the RCM reaction by using Grubbs second-generation ruthenium complex[15] as a catalyst in $CH_2Cl_2$ to form the 18-membered ring **10** in 78% yield. Removal of the MEM group from **10** or PDC oxidation followed by treatment with $ZnBr_2$ afforded the desired compounds **18MS-1** or **18MS-2**, respectively. Another RCM substrate, **13**, possessing a dienone structure, was prepared by using the esterification protocol[16] of Yamaguchi and co-workers

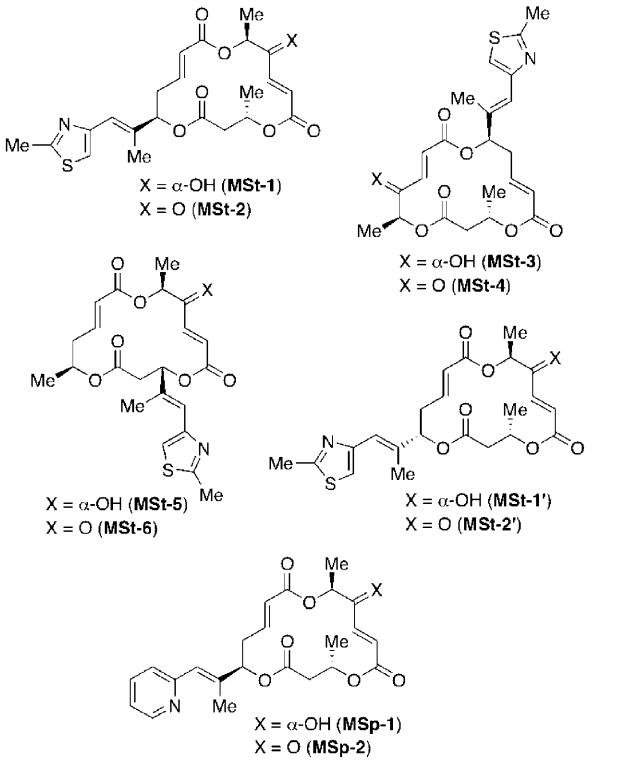
followed by oxidative removal of the PMB group. RCM with this compound was rather sluggish, probably due to steric congestion (disubstituted olefin), and the desired macrocycle **14** was obtained in 37% yield, accompanied by recovered starting material. Neither 16-membered products nor geometrical isomers could be detected. Similarly to the above procedures, compound **14** was successfully converted into **18MS-3** and **18MS-4**.

Alteration of the ring-closure position provides structural isomers beyond the above **18MS** compounds. For example, the synthesis of **18MS-5**, an isomer of **18MS-3**, was conveniently accomplished by simple modification of the connecting pattern of chiral blocks **4**–**6** (Scheme 3). Successive esterification–deprotection sequences of these chiral blocks and 2,4-pentadienoic acid gave the RCM substrate **21** with high efficiency. In contrast to the cases depicted in Scheme 2, the RCM reaction of **21** afforded a mixture of geometric isomers, with predominant formation of the *E* isomer. This mixture was allowed to react with TFA to remove the MEM group, and **18MS-5** could be isolated in a pure form after chromatographic separation.




Scheme 3. Synthesis of 18-membered macrosphelide **18MS-5**. TBAF: tetra-*n*-butylammonium fluoride; THF: tetrahydrofuran.

We previously reported that macrosphelides with a thiazole side chain, which is an important component of epothilones, a potent antitumor natural macrolide,[17] exhibit enhanced apoptosis-inducing activity relative to that of the parent natural macrosphelides (**1**–**3**). These "hybridized" macrosphelides (**MSt-1**–**MSt-6**, Scheme 4) were efficiently synthesized by assembly of chiral blocks such as **5** and **6**, followed by RCM cyclization.[11] In a preliminary biological evaluation, it was revealed that **MSt-2** showed the most potent bioactivity among the six hybrid compounds.[11] These results encouraged us to synthesize and evaluate a




Scheme 4. Macrosphelide analogues hybridized with epothilones.

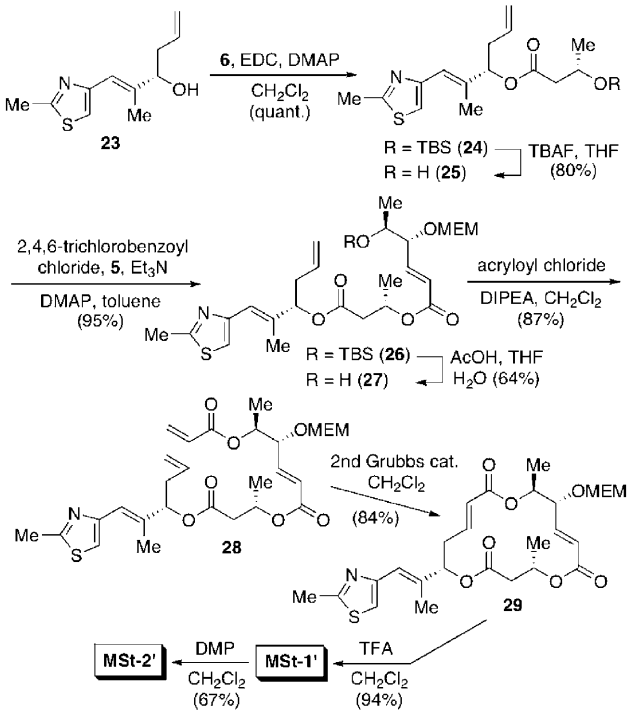
C15 diastereomer (**MSt-2′**) and a pyridyl analogue (**MSp-2**) of **MSt-2**, as well as their synthetic precursors **MSt-1′** and **MSp-1**.

The synthetic pathway for **MSt-2**, which we have already established utilizing RCM,[11] is a good guideline for the syntheses of the new hybrid compounds. Common chiral blocks (**5** and **6**) and chiral homoallylic alcohols **23**[11] and **31** are requisite parts for assembling **MSt-2′** and **MSp-2**, respectively. Scheme 5 illustrates the synthesis of **MSt-1′** and **MSt-2′**. Thiazole-containing chiral alcohol **23**, chiral carboxylic acids **6** and **5**, and acryloyl chloride were connected by a repeated esterification and deprotection sequence to provide RCM substrate **28** in satisfactory yields. RCM of this compound proceeded smoothly, and removal of the MEM group and Dess–Martin oxidation gave **MSt-1′** and **MSt-2′**.

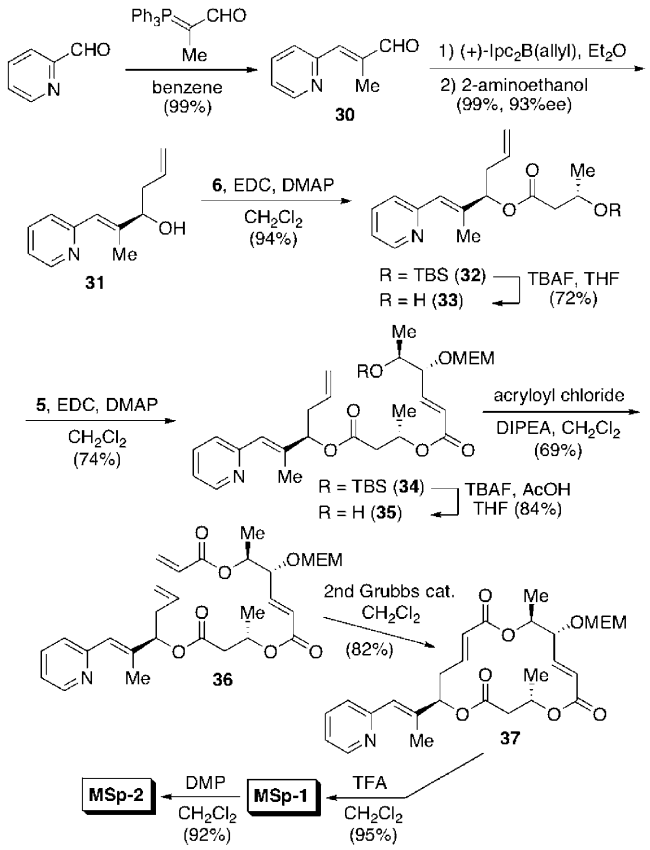
For the synthesis of pyridyl analogues **MSp-1** and **MSp-2**, pyridine-containing chiral alcohol **31** was prepared (Scheme 6). A Wittig reaction of 2-formylpyridine gave homologous aldehyde **30**, which was then subjected to an asymmetric allylation reaction with (+)-diisopinocampheylallylborane to afford **31** in a nearly quantitative yield. The optical purity of **31** (93% *ee*) was determined by Mosher's ester analysis. Subsequent transformation of **31** into **MSp-1** and **MSp-2** was performed according to the above synthetic procedure (Scheme 5), with slight modifications (**33** to **35**), to accomplish the synthesis.

Most of the naturally occurring macrosphelides have a common 16-membered framework with 3 esters and 2 double bonds at the 6,7- and 12,13-positions. Among these

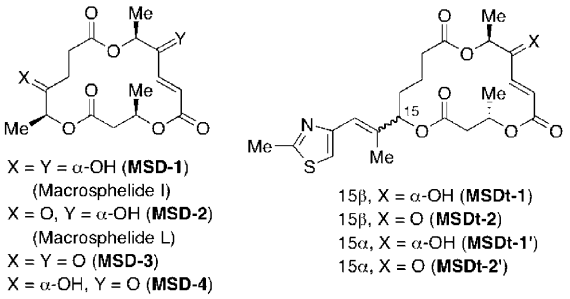



Scheme 5. Synthesis of hybrid compounds **MSt-1′** and **MSt-2′**. DIPEA: *N,N*-diisopropylethylamine; DMP: Dess–Martin periodinane.




Scheme 6. Synthesis of hybrid compounds **MSp-1** and **MSp-2**. (+)-Ipc$_2$B-(allyl): (+)-diisopinocampheylallylborane.

compounds, two macrosphelides with a different unsaturation mode (12,13-dihydro-type framework) have been isolated, and these are designated macrosphelides I and L (Scheme 7). Macrosphelide L exhibits potent cell–cell adhesion (HL-60 and HUVEC) inhibitory activity ($IC_{50}=5.6$ μM; other natural macrosphelides: $IC_{50}=8.6$–$36.5$ μM),[18] and macrosphelide I has been reported to show cytotoxicity against P388 lymphocytic leukemia cells.[6d] However, the action of these compounds toward apoptotic cell death is unknown. With great interest in the biological profile of this series of macrosphelides, we undertook the synthesis of natural macrosphelides I and L (**MSD-1** and **MSD-2**), their analogues (**MSD-3** and **MSD-4**), and four derivatives with a thiazole side chain (**MSDt-1**, **MSDt-2**, **MSDt-1′**, and **MSDt-2′**).



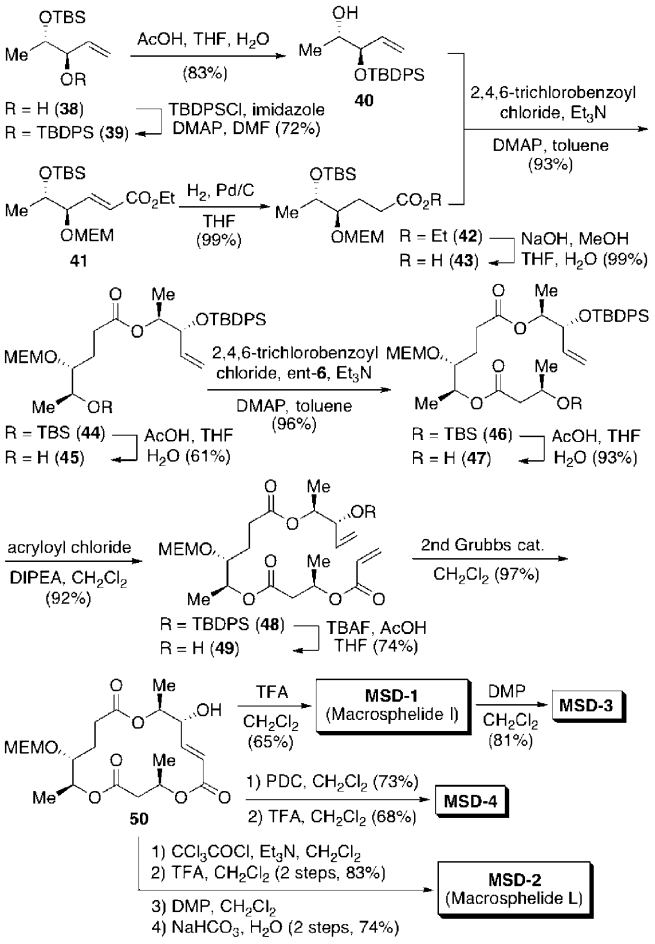

Scheme 7. 12,13-Dihydro-type macrosphelides.

The synthetic routes to macrosphelides I and L, and the related compounds, are depicted in Scheme 8. Chiral alcohol **40** was prepared from known alcohol **38**[13] by protecting-group manipulation. Chiral carboxylic acid **43** containing the 12,13-dihydro structure could be synthesized by hydrogenation of olefin **41**[13] over Pd/C followed by alkaline hydrolysis. These compounds were coupled by using the Yamaguchi esterification to afford **44**, which was further subjected to condensation with ent-**6** after removal of the TBS group. Diester **46** thus obtained was transformed into RCM substrate **49** in three steps. Macrocyclization of **49** proceeded efficiently under RCM conditions to provide **50**, a common intermediate for **MSD-1**–**MSD-4**. After several transformations, the total syntheses of macrosphelides I (**MSD-1**) and L (**MSD-2**) and their analogues (**MSD-3** and **MSD-4**) were completed.

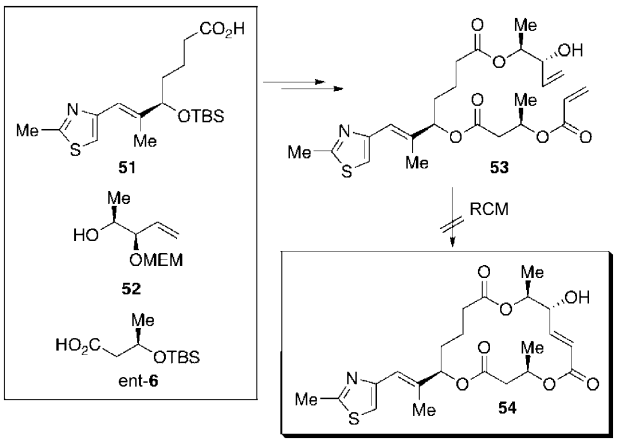
We initially planned to synthesize thiazole-containing MSDts such as **54** from chiral blocks **51**, **52**, and ent-**6** via intermediate **53** (Scheme 9). However, we found, unexpectedly, that cyclization of **53** could not be obtained under various RCM conditions, and only the unchanged starting material and several unidentified products were observed. Although the reasons for that remain unclear, our strategy to reach thiazole-containing MSDts was changed.

We had already completed the synthesis of several MSts (Scheme 4), so these were likely to be good precursors for the target MSDts, provided that regioselective reduction was possible for these compounds. Thus, we examined hy-

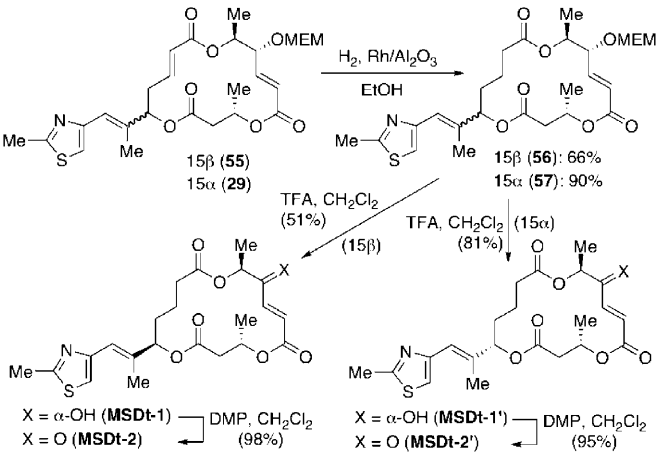



Scheme 8. Total syntheses of macrosphelides I and L, and related compounds. DMF: *N,N*-dimethylformamide; TBDPS: *tert*-butyldiphenylsilyl.




Scheme 9. Initial synthetic plan for **MSDt** compounds.

drogenation of **55**[11] and **29**, after taking into consideration the preliminary results on the highest biological activity of **MSt-2**. Whereas Pd/C and Pt/C were inefficient as catalysts, the required 12,13-dihydro compounds (**56** and **57**) were obtained with exclusive selectivity by using $Rh/Al_2O_3$ in ethanol. These compounds were successfully transformed into **MSDt-1** and **MSDt-2** or **MSDt-1′** and **MSDt-2′**, respectively (Scheme 10).




Scheme 10. Synthesis of **MSDt** compounds.

The artificial macrosphelide analogues (including natural macrosphelides I and L) synthesized in this study were then evaluated for apoptosis-inducing activity. Derivative **3**, which was the most potent apoptosis inducer among the natural macrosphelide series,[10] was used as a positive control for the preliminary evaluation. DNA fragmentation of cells is known to be a feature characteristic of apoptosis, so an initial screening was performed by monitoring DNA fragmentation of human lymphoma cells (U937).[19] The percentage of DNA fragmentation was determined as previously reported.[10] Figure 1A represents the results for the 18-membered macrosphelide series. Although almost no DNA fragmentation was observed for any of the compounds at relatively low drug concentrations (1 μM), **18MS-2** exhibited activity to a degree comparable with that of positive control **3** at 10 μM. On the other hand, the macrosphelide compounds with a thiazole (or pyridine) side chain were mostly found to induce DNA fragmentation more potently at 1 μM than at 10 μM, which suggests that these compounds may exert cytotoxicity at higher concentrations (Figure 1B). **MSt-2** showed particularly potent activity at 1 μM relative to that of the positive control. The 12,13-dihydromacrosphelides (**MSD-1**–**MSD-4**, natural type) were also surveyed for their DNA-fragmentation activity (Figure 1C). Interestingly, natural macrosphelides I (**MSD-1**) and L (**MSD-2**) did not exhibit any activity, whereas their modified derivatives (**MSD-3** and **MSD-4**) induced DNA fragmentation at 10 μM. Figure 1D illustrates a comparison of the results for the 12,13-dihydromacrosphelides having a thiazole side chain with the results for their non-dihydro counterparts (**MSt-2** and **MSt-2′**). Although dihydromacrosphelides **MSDt-2** and **MSDt-2′** exerted much higher activity than their non-dihydro analogues **MSt-2** and **MSt-2′** at 10 μM, **MSt-2** and **MSt-2′** were found to be superior at lower concentrations (1 μM).

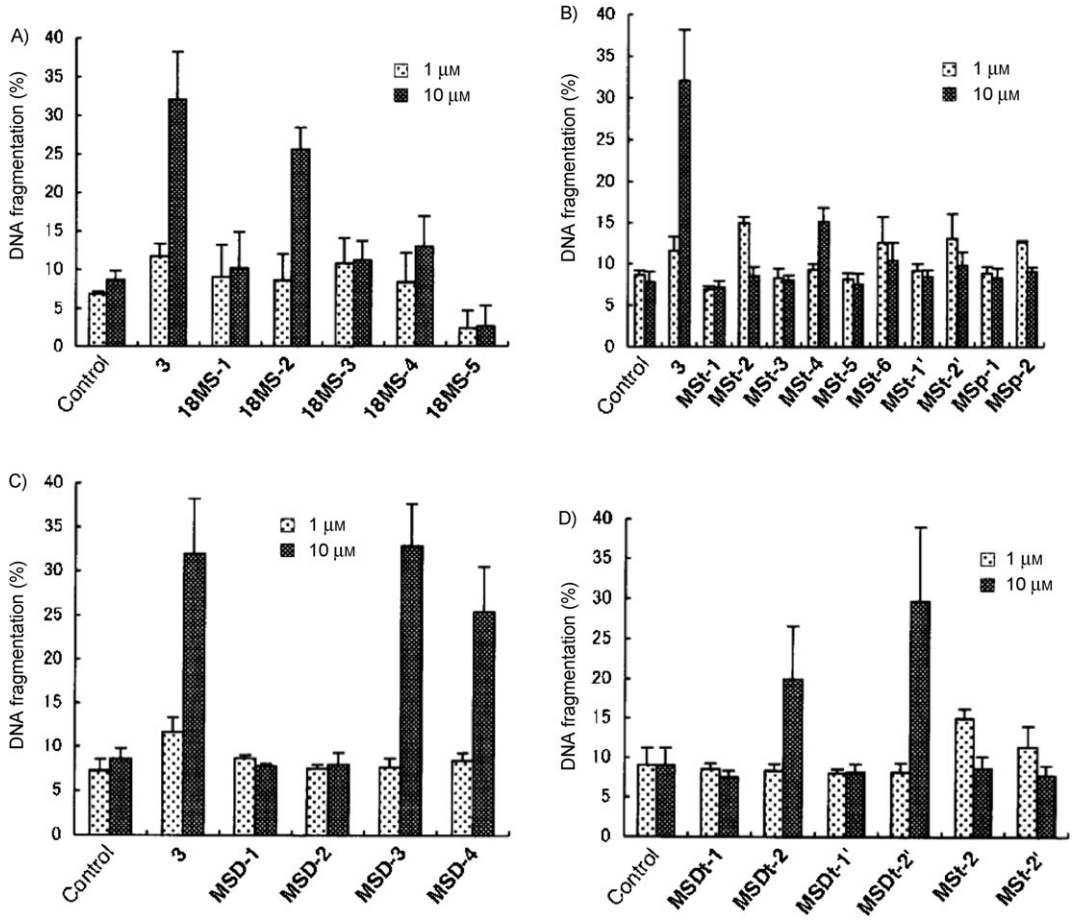



Figure 1. Effects of artificial macrosphelide compounds at 1 and 10 μM concentrations on the DNA fragmentation of human lymphoma U937 cells (incubation time: 12 h). A) 18-Membered macrosphelide analogues; B) hybridized macrosphelides with epothilones; C) 12,13-dihydromacrosphelides (natural type); D) 12,13-dihydromacrosphelides (hybrid type). Results are presented as means ± S.D (number of experiments $n = 3$).

The DNA-fragmentation assay data shown in Figure 1 clearly demonstrate the importance of the oxidation state at the 8- and 14-positions. The presence of a keto group at these positions is likely to enhance the bioactivity of macrosphelide derivatives. Indeed, the derivatives without a carbonyl group at either position (for example, **MSt-1**, **MSt-3**, **MSt-5**, **MSt-1′**, and **MSDt-1**) showed no activity. In other words, the "ene-dicarbonyl" substructure (functional-group array) appears to be essential for bioactivity. This trend also applies in the case of 18-membered analogues (**18MS-2**). In addition, the keto group needs to be conjugated with the olefin, rather than isolated (**MSD-2** versus **MSD-4**). Our recent biological data suggest that the bioactive macrosphelides exert apoptosis-inducing activity by modulating intracellular oxidative stress (see below).[10] In the light of such findings, the conjugated ene-dicarbonyl substructure (electron-deficient conjugation system) may participate in reversible electron-transfer processes leading ultimately to the generation of reactive oxygen species (ROS).

We previously reported that incorporation of a thiazole side chain at the 15-position (epothilone hybrid, **MSt-2**) enhanced apoptosis-inducing activity relative to that of the natural-type macrosphelides.[11] The DNA-fragmentation assay gave the same result at lower concentrations, and the stereochemistry at the 15-position did not have a marked effect on activity (**MSt-2** versus **MSt-2′**). Epothilones are noted for their strong action in the tubulin dynamics of cells (tubulin-dimer stabilizing effect), in which the thiazole side chain can function as a hydrogen-bond acceptor and lead to apoptotic cell death.[17] Structure–activity relationship studies of epothilones have revealed that α-pyridyl analogues of the thiazole moiety exhibit equal or superior bioactivities to those of the natural epothilones.[20] These observations hold true for the present macrosphelide study (**MSt-2** versus **MSp-2**, at 1 μM concentration), which suggests that the epothilones and macrosphelides have a similar mode of action in the intracellular environment. However, we did not observe unambiguous action in tubulin dynamics when several macrosphelide compounds were examined by a tubulin-polymerization/depolymerization assay (data not shown). We recently reported that apoptotic cell death induced by macrosphelide-based derivatives,[10] including **MSt-2**,[21] is regulated by rapid and transient intracellular oxidative stress and subsequent activation of the Fas/caspase-8-dependent signaling pathway.[22] There are several reports on apoptosis induced by epothilones and related compounds

through such caspase–mitochondrial-mediated pathways.[23] Moreover, epothilone-induced apoptotic cell death in a tubulin-polymerization-independent manner has recently been reported.[24] The similarities in the activation mechanisms of apoptotic cell death between macrosphelides and epothilones remain unclear, and further studies are required in order to elucidate the precise molecular mechanisms of macrosphelide-induced apoptosis, as well as the role of the thiazole side chain.[25]

Finally, selected derivatives were screened for apoptosis-inducing activity by using previously reported procedures.[10] Human lymphoma U937 cells were treated with each compound at 1 and 5 μM concentrations for 12 h. This was followed by measurement of early apoptosis and secondary necrosis by Annexin V FITC/PI staining with flow cytometry, and the results are summarized in Figure 2. At concentrations of 5 μM, **18MS-2**, **MSD-3**, **MSD-4**, and **MSt-2′** showed significantly higher apoptosis-inducing activity than natural-type compound **3** (Figure 2A). On the other hand, it was found that **MSt-2** was the most effective apoptosis inducer at the lower dose (1 μM). The other derivatives did not exhibit activity at this concentration (Figure 2B). In addition, the maximum potency of apoptosis and anti-proliferative activity against other cancer cell lines (HCT116 and AGS cells) was observed for **MSt-2** rather than the other derivatives.[21,26] Moreover, human normal dermal fibroblasts were relatively resistant to **MSt-2**.[21] Thus, we believe that **MSt-2** is a potential lead for the development of an anticancer therapeutic agent based on macrosphelides.

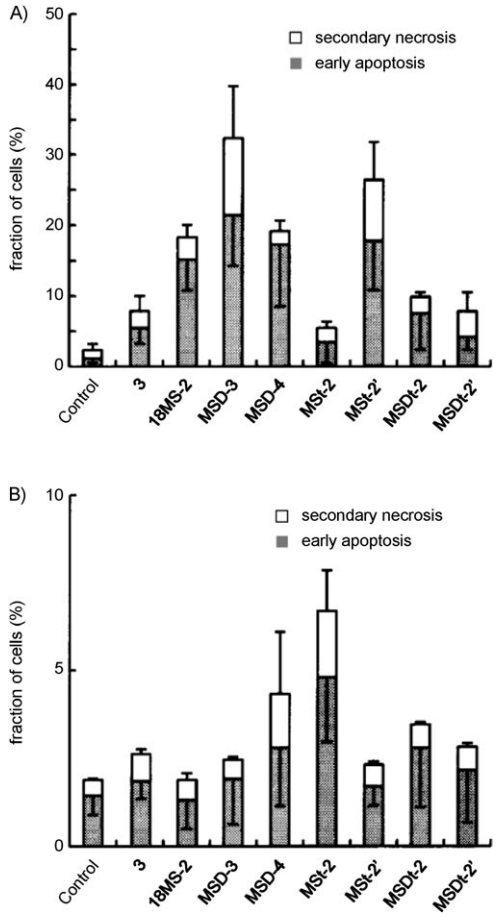



Figure 2. Apoptosis-inducing potency of selected macrosphelide derivatives. U937 cells were treated with A) 5 μM and B) 1 μM concentrations of each compound for 12 h. The percentages of early apoptotic and secondary necrotic cells were measured by flow cytometry by staining with propidium iodide (PI) and annexin V labeled with fluorescein isothiocyanate (FITC). Results are presented as means ± S.D ($n=3$).

## Conclusions

In this study, we synthesized a variety of artificial macrosphelide compounds and evaluated their apoptosis-inducing activity for the purpose of exploring new chemotherapeutic candidates for the treatment of cancer. The syntheses were accomplished with high efficiency by utilizing RCM as a common synthetic technique. Some of the new compounds synthesized here exhibited more potent bioactivity than natural macrosphelides. Thus, the present study is a successful example of a "non-natural natural product strategy" for a new discovery in medicine.

## Experimental Section

**General remarks**: All nonaqueous reactions were carried out under an Ar atmosphere. Reagents were purchased from commercial sources and used as received. Anhydrous solvents were prepared by distillation over $CaH_2$ or were purchased from commercial sources. $^1H$ and $^{13}C$ NMR spectra were obtained on a Varian Gemini 300 instrument, with the chloroform peak as an internal reference. Mass spectra were measured on a JEOL D-200 or JEOL AX 505 mass spectrometer, and the ionization method was electron impact (EI, 70 eV). IR spectra were recorded on a JASCO FT/IR-460Plus spectrometer. Column chromatography was carried out by employing Cica silica gel 60N (spherical, neutral, 40–50 or 63–210 μm). Preparative methods for compounds **4**–**7**, **23**, **38**, **41**, and **55** have already been reported.[11,13] The synthesis of **MSt-1**–**MSt-6** was described in a previous communication.[11]

**General synthetic procedures**

Procedure 1-a: Esterification by using EDC: EDC (4 mmol) was added to a stirred solution of the alcohol (1 mmol), the carboxylic acid (1.2 mmol), and DMAP (0.1 mmol) in $CH_2Cl_2$ (5 mL) at 0 °C under an Ar atmosphere. After continuous stirring of the solution at room temperature for several hours (monitored by TLC), the solvent was evaporated to leave a residue, which was triturated with diethyl ether and filtered through celite. Evaporation of the solvent followed by chromatography on silica gel afforded the corresponding ester.

**Procedure 1-b: Esterification by using the Yamaguchi protocol**: 2,4,6-Trichlorobenzoyl chloride (1.7 mmol) was added to a solution of the carboxylic acid (1.5 mmol) and $Et_3N$ (4 mmol) in toluene (10 mL) at room temperature under an Ar atmosphere, and the resulting mixture was stirred at room temperature for 1 h. The alcohol (1 mmol) and DMAP (2 mmol) were added, and the reaction mixture was stirred for several hours. After the reaction was completed (monitored by TLC), the mixture was diluted with benzene, washed with saturated $NaHCO_3$ and brine, and dried over $MgSO_4$. The solvent was evaporated to leave a residue, which was purified by chromatography on silica gel to afford the corresponding ester.

**Procedure 2: Removal of the PMB group by DDQ oxidation**: A mixture of the PMB ether (0.2 mmol) and DDQ (0.25 mmol) in $CH_2Cl_2/H_2O$ (18:1, 2 mL) was stirred at room temperature for 1 h. The precipitate

formed was removed by filtration, and the filtrate was concentrated to furnish a gummy mass, which was purified by chromatography on silica gel to give the corresponding alcohol.

**Procedure 3: Macrocyclization by RCM**: The Grubbs ruthenium catalyst (second generation) (0.01 mmol) was added to a solution of the ω-diene compound (0.1 mmol) in $CH_2Cl_2$ (100 mL) under Ar atmosphere. After continuous stirring of the mixture for 24 h at room temperature, the solvent was evaporated to afford a residue, which was purified by chromatography on silica gel to give the cyclization product.

**Procedure 4-a: Conversion of alcohol to ketone by PDC oxidation**: PDC (1 mmol) was added portionwise to a stirred solution of the alcohol (0.25 mmol) and 4 Å molecular sieves (350 mg) in $CH_2Cl_2$ (10 mL) at 0 °C under an Ar atmosphere. After continuous stirring of the mixture for several hours at room temperature (monitored by TLC), the reaction mixture was diluted with diethyl ether and filtered through celite. The filtrate was evaporated to leave a residue, which was purified by chromatography on silica gel to give the corresponding ketone.

**Procedure 4-b: Conversion of alcohol to ketone by DMP oxidation**: DMP (0.2 mmol) was added to a solution of the alcohol (0.1 mmol) in $CH_2Cl_2$ (2 mL), and the mixture was stirred for several hours at room temperature (monitored by TLC). The reaction was quenched with saturated $NaHCO_3$, and the mixture was extracted with $CH_2Cl_2$. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel to afford the corresponding ketone.

**Procedure 5-a: Removal of the MEM group by TFA**: TFA (1 mL) was added to a solution of the MEM ether (0.1 mmol) in $CH_2Cl_2$ (1 mL) at 0 °C under an Ar atmosphere. After continuous stirring of the mixture for 24 h at room temperature, the solvent was evaporated to afford a residue, which was purified by chromatography on silica gel to give the corresponding alcohol.

**Procedure 5-b: Removal of the MEM group by $ZnBr_2$**: Zinc bromide (1 mmol) was added to a solution of the MEM ether (0.2 mmol) in $CH_2Cl_2$ (5 mL) at room temperature under an Ar atmosphere. After stirring of the mixture for 24 h at 50 °C, the solvent was evaporated. The residue was purified by chromatography on silica gel to afford the corresponding alcohol.

**Procedure 6-a: Removal of the TBS group by TBAF**: A 1 M solution of TBAF in THF (2 mL, 2 mmol) was added to a stirred solution of the TBS ether (1 mmol) in THF (2 mL) at room temperature under an Ar atmosphere, and the mixture was stirred for several hours at room temperature (monitored by TLC). The solvent was evaporated to leave a residue, which was dissolved in diethyl ether. The resulting organic layer was washed with water and brine, then dried over $MgSO_4$. Evaporation of the solvent left a residue, which was purified by chromatography on silica gel to give the corresponding alcohol.

**Procedure 6-b: Removal of the TBS group by TBAF–AcOH**: A 1 M solution of TBAF in THF (1.3 mL, 1.3 mmol) was added to a stirred solution of the TBS ether (1 mmol) and acetic acid (1.5 mmol) in THF (3 mL) at room temperature under an Ar atmosphere, and the mixture was stirred for 1 or 2 days at room temperature. The ethereal solution of the residue resulting from the evaporation of the solvent was washed with water, saturated $NaHCO_3$, and brine, then dried over $MgSO_4$. Evaporation of the solvent left a residue, which was purified by chromatography on silica gel to give the corresponding alcohol.

**Procedure 6-c: Removal of the TBS group by AcOH**: A solution of the TBS ether (1 mmol) in AcOH/THF/$H_2O$ (3:1:1, 4 mL) was stirred for 1 or 2 days at 50 °C. The reaction mixture was diluted with $Et_2O$, washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting oil was purified by column chromatography on silica gel to afford the corresponding alcohol.

**Procedure 7: Acryloylation of alcohol**: Acryloyl chloride (2 mmol) was added dropwise to a stirred solution of the alcohol (0.5 mmol) and *N,N*-diisopropylethylamine (2.5 mmol) in $CH_2Cl_2$ (3 mL) at 0 °C under an Ar atmosphere. After continuous stirring for 1 h at room temperature, the reaction mixture was diluted with $CH_2Cl_2$, washed successively with water, 10% HCl, saturated $NaHCO_3$, and brine, and dried over $MgSO_4$. Evaporation of the solvent afforded a residue, which was purified by chromatography on silica gel to give the corresponding ester.

**Synthesis of compound 8**: In accordance with procedure 1-a, alcohol **7** (100 mg, 0.19 mmol) gave ester **8** (114 mg, 99%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.22 (2H, d, $J$ = 8.4 Hz), 6.85 (2H, d, $J$ = 8.4 Hz), 6.78 (1H, dd, $J$ = 6.0, 16 Hz), 6.00 (1H, d, $J$ = 16 Hz), 5.86–5.66 (2H, m), 5.34–5.22 (3H, m), 5.09–4.96 (4H, m), 4.73 (1H, d, $J$ = 7.0 Hz), 4.67 (1H, d, $J$ = 7.0 Hz), 4.53 (1H, d, $J$ = 11 Hz), 4.31 (1H, d, $J$ = 11 Hz), 4.34–4.29 (1H, m), 3.78 (3H, s), 3.78–3.69 (2H, m), 3.65–3.58 (1H, m), 3.53–3.41 (2H, m), 3.36 (3H, s), 2.65 (1H, dd, $J$ = 15, 7.4 Hz), 2.53–2.33 (5H, m), 1.30 (3H, d, $J$ = 6.3 Hz), 1.18 (3H, d, $J$ = 6.3 Hz), 1.16 ppm (3H, d, $J$ = 5.8 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 172.2, 169.3, 164.8, 159.1, 143.5, 136.5, 136.4, 134.8, 130.3, 129.3, 124.3, 119.8, 115.6, 113.8, 93.9, 81.6, 72.2, 71.7, 71.3, 70.2, 67.8, 67.4, 59.2, 55.4, 41.3, 33.8, 33.3, 29.0, 28.8, 20.0, 15.8, 15.4 ppm; IR (neat): $\tilde{\nu}$ = 1734, 1656, 1613 cm$^{-1}$; MS (EI): $m/z$ 606 [$M^+$]; HRMS (EI): calcd for $C_{32}H_{46}O_{11}$: 606.3040 [$M^+$]; found: 606.3021; $[\alpha]_D^{25}$ = −43.8 ($c$ = 1.26 in $CHCl_3$).

**Synthesis of compound 9**: In accordance with procedure 2, PMB ether **8** (114 mg, 0.19 mmol) gave alcohol **9** (84.2 mg, 92%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 6.79 (1H, dd, $J$ = 6.3, 16 Hz), 6.01 (1H, dd, $J$ = 1.4, 16 Hz), 5.84–5.72 (2H, m), 5.38–5.24 (1H, m), 5.31 (1H, d, $J$ = 17 Hz), 5.20 (1H, dd, $J$ = 1.4, 11 Hz), 5.05–4.86 (4H, m), 4.72 (1H, d, $J$ = 7.0 Hz), 4.66 (1H, d, $J$ = 7.0 Hz), 4.32–4.28 (1H, m), 4.20–4.16 (1H, m), 3.79–3.72 (1H, m), 3.64–3.57 (1H, m), 3.52–3.48 (2H, m), 3.35 (3H, s), 2.67 (1H, dd, $J$ = 15, 7.8 Hz), 2.53 (1H, dd, $J$ = 15, 5.3 Hz), 2.38–2.31 (4H, m), 1.31 (3H, d, $J$ = 6.3 Hz), 1.17 (3H, d, $J$ = 6.6 Hz), 1.13 ppm (3H, d, $J$ = 6.6 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 172.3, 169.8, 165.0, 143.8, 136.5, 135.8, 124.1, 117.4, 115.6, 93.9, 74.6, 73.9, 71.7, 71.3, 67.8, 67.4, 59.2, 41.4, 33.8, 29.0, 28.8, 20.2, 15.3, 14.4 ppm; IR (neat): $\tilde{\nu}$ = 3471, 1730, 1654 cm$^{-1}$; MS (EI): $m/z$ 486 [$M^+$]; HRMS (EI): calcd for $C_{24}H_{38}O_{10}$: 486.2465 [$M^+$]; found: 486.2486; $[\alpha]_D^{25}$ = −33.1 ($c$ = 0.51 in $CHCl_3$).

**Synthesis of compound 10**: In accordance with procedure 3, compound **9** (84 mg, 0.17 mmol) gave **10** (62.1 mg, 78%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 6.78 (1H, dd, $J$ = 16, 8.6 Hz), 5.94 (1H, dd, $J$ = 16, 0.6 Hz), 5.67–5.62 (1H, m), 5.50–5.42 (1H, m), 5.32–5.25 (1H, m), 5.12–5.01 (2H, m), 4.67 (1H, d, $J$ = 7.1 Hz), 4.59 (1H, d, $J$ = 7.1 Hz), 4.12–4.02 (1H, m), 3.85–3.81 (1H, m), 3.70–3.63 (1H, m), 3.60–3.51 (1H, m), 3.49–3.45 (2H, m), 3.32 (3H, s), 2.88 (1H, br), 2.63–2.21 (6H, m), 1.31 (3H, d, $J$ = 6.3 Hz), 1.26 (3H, d, $J$ = 6.6 Hz), 1.10 ppm (3H, d, $J$ = 6.6 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 171.6, 170.4, 164.9, 143.5, 132.1, 128.0, 125.8, 93.0, 77.4, 75.6, 73.7, 71.6, 70.0, 68.8, 67.4, 59.1, 41.9, 33.4, 27.2, 20.7, 17.3, 17.3 ppm; IR (neat): $\tilde{\nu}$ = 3442, 1720 cm$^{-1}$; MS (EI): $m/z$ 458 [$M^+$]; HRMS (EI): calcd for $C_{22}H_{34}O_{10}$: 458.2152 [$M^+$]; found: 458.2115; $[\alpha]_D^{24}$ = −64.7 ($c$ = 0.85 in $CHCl_3$).

**Synthesis of 18MS-1**: In accordance with procedure 5-b, MEM ether **10** (84 mg, 0.18 mmol) gave **18MS-1** (21 mg, 30%) as a colorless solid: M.p. 122–124 °C (colorless powder from diethyl ether/hexane); $^1$H NMR ($CDCl_3$): $\delta$ = 6.95 (1H, dd, $J$ = 16, 8.5 Hz), 5.92 (1H, d, $J$ = 16 Hz), 5.79 (1H, dt, $J$ = 16, 5.1 Hz), 5.64 (1H, dd, $J$ = 16, 8.3 Hz), 5.32–5.25 (3H, m), 4.11 (1H, dd, $J$ = 9.0, 3.0 Hz), 4.00 (1H, dd, $J$ = 8.3, 2.3 Hz), 2.74–2.67 (2H, m), 2.61–2.49 (3H, m), 2.44–2.38 (1H, m), 1.41 (3H, d, $J$ = 6.4 Hz), 1.18 (3H, d, $J$ = 6.6 Hz), 1.15 ppm (3H, d, $J$ = 6.4 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 173.3, 171.5, 164.8, 143.6, 133.4, 126.7, 125.0, 76.6, 74.9, 73.3, 72.5, 69.1, 41.8, 32.6, 26.7, 20.2, 17.0, 16.7 ppm; IR (KBr): $\tilde{\nu}$ = 3455, 1730 cm$^{-1}$; MS (EI): $m/z$ 370 [$M^+$]; HRMS (EI): calcd for $C_{18}H_{26}O_8$: 370.1628 [$M^+$]; found: 370.1591; $[\alpha]_D^{24}$ = −43.3 ($c$ = 0.225 in $CHCl_3$).

**Synthesis of compound 11**: In accordance with procedure 4-a, alcohol **10** (100 mg, 0.22 mmol) gave corresponding ketone **11** (80 mg, 80%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 6.96–6.86 (1H, m), 6.70 (1H, dd, $J$ = 16, 7.3 Hz), 6.22 (1H, d, $J$ = 16 Hz), 5.99 (1H, d, $J$ = 16 Hz), 5.40–5.33 (1H, m), 5.13 (1H, dd, $J$ = 15, 8.5 Hz), 5.00–4.89 (1H, m), 4.65 (1H, s), 4.14–4.05 (1H, m), 3.75–3.68 (1H, m), 3.62–3.53 (1H, m), 3.50–3.47 (2H, m), 3.33 (3H, s), 2.72–2.37 (6H, m), 1.32 (3H, d, $J$ = 6.3 Hz), 1.29 (3H, d, $J$ = 6.3 Hz), 1.23 ppm (3H, d, $J$ = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 196.3, 170.7, 170.0, 164.5, 147.5, 143.8, 125.1, 124.8, 93.6, 77.6, 74.4, 71.7, 71.4, 68.2, 67.4, 59.1, 40.9, 33.2, 27.8, 20.3, 17.5, 16.5 ppm; IR (neat): $\tilde{\nu}$ = 1730, 1622 cm$^{-1}$; MS (EI): $m/z$ 456 [$M^+$]; HRMS (EI): calcd for $C_{22}H_{32}O_{10}$: 456.1996 [$M^+$]; found: 456.1992; $[\alpha]_D^{24}$ = −69.2 ($c$ = 0.92 in $CHCl_3$).

**Synthesis of 18MS-2**: In accordance with procedure 5-b, MEM ether **11** (59 mg, 0.13 mmol) gave **18MS-2** (35.4 mg, 60%) as a colorless solid: M.p. 162–164°C (colorless powder from diethyl ether/hexane); $^1$H NMR ($CDCl_3$): $\delta$ = 7.05–6.98 (1H, m), 6.84 (1H, dd, $J$ = 15, 5.5 Hz), 6.29 (1H, d, $J$ = 15 Hz), 6.06 (1H, dd, $J$ = 16, 1.3 Hz), 5.43–5.31 (1H, m), 5.25 (1H, q, $J$ = 6.8 Hz), 4.98–4.92 (1H, m), 4.20 (1H, dd, $J$ = 5.1, 11 Hz), 2.72 (1H, dd, $J$ = 9.6, 16 Hz), 2.66 (1H, dd, $J$ = 2.8, 16 Hz), 2.61–2.45 (4H, m), 2.28 (1H, br), 1.38 (3H, d, $J$ = 6.8 Hz), 1.37 (3H, d, $J$ = 6.4 Hz), 1.31 ppm (3H, d, $J$ = 6.4 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 196.4, 171.6, 169.9, 164.7, 147.7, 144.7, 124.9, 123.5, 77.3, 77.0, 76.7, 74.1, 73.9, 73.6, 68.0, 40.7, 32.8, 27.5, 20.0, 17.2, 16.3 ppm; IR (KBr): $\tilde{\nu}$ = 3465, 1727, 1620 cm$^{-1}$; MS (EI): $m/z$ 368 [$M^+$]; HRMS (EI): calcd for $C_{18}H_{24}O_8$: 368.1471 [$M^+$]; found: 368.1451; $[\alpha]_D^{24} = -42.5$ ($c$ = 0.135 in $CHCl_3$).

**Synthesis of compound 12**: In accordance with procedure 1-b, alcohol **7** (100 mg, 0.19 mmol) gave ester **12** (114 mg, 92%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.26–7.16 (1H, m), 7.21 (2H, d, $J$ = 8.6 Hz), 6.84 (2H, d, $J$ = 8.6 Hz), 6.84–6.77 (1H, m), 6.16–6.04 (1H, m), 6.01 (1H, dd, $J$ = 16, 1.5 Hz), 5.75–5.65 (2H, m), 5.33–5.22 (3H, m), 5.09–5.05 (1H, m), 4.99–4.95 (1H, m), 4.73 (1H, d, $J$ = 6.9 Hz), 4.67 (1H, d, $J$ = 6.9 Hz), 4.52 (1H, d, $J$ = 12 Hz), 4.37–4.32 (1H, m), 4.30 (1H, d, $J$ = 12 Hz), 3.77 (3H, s), 3.77–3.66 (2H, m), 3.64–3.56 (1H, m), 3.50–3.47 (2H, m), 3.34 (3H, s), 2.64 (1H, dd, $J$ = 15, 7.1 Hz), 2.48 (1H, dd, $J$ = 15, 6.1 Hz), 1.82 (3H, d, $J$ = 5.0 Hz), 1.29 (3H, d, $J$ = 6.3 Hz), 1.18 (3H, d, $J$ = 6.6 Hz), 1.11 ppm (3H, d, $J$ = 6.6 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 169.2, 166.4, 164.8, 159.1, 145.5, 143.6, 139.8, 134.8, 130.2, 129.7, 129.3, 124.1, 119.8, 118.7, 113.7, 93.9, 81.5, 76.7, 72.2, 71.7, 71.1, 70.1, 67.7, 67.3, 59.1, 55.4, 41.3, 20.0, 18.9, 15.8, 15.2 ppm; IR (neat): $\tilde{\nu}$ = 1719, 1645, 1615 cm$^{-1}$; MS (EI): $m/z$ 618 [$M^+$]; HRMS (EI): calcd for $C_{33}H_{46}O_{11}$: 618.3040 [$M^+$]; found: 618.2993; $[\alpha]_D^{24} = -36.1$ ($c$ = 0.89 in $CHCl_3$).

**Synthesis of compound 13**: In accordance with procedure 2, the PMB ether **12** (95 mg, 0.15 mmol) gave the alcohol **13** (72 mg, 95%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.25–7.16 (1H, m), 6.82 (1H, dd, $J$ = 6.0, 16 Hz), 6.21–6.11 (2H, m), 6.02 (1H, dd, $J$ = 1.5, 16 Hz), 5.84–5.69 (2H, m), 5.38–5.27 (2H, m), 5.20 (1H, d, $J$ = 10 Hz), 5.09–5.02 (1H, m), 4.96–4.87 (1H, m), 4.73 (1H, d, $J$ = 6.9 Hz), 4.67 (1H, d, $J$ = 6.9 Hz), 4.39–4.34 (1H, m), 4.20–4.15 (1H, m), 3.78–3.71 (1H, m), 3.64–3.55 (1H, m), 3.50–3.46 (2H, m), 3.35 (3H, s), 2.67 (1H, dd, $J$ = 16, 7.4 Hz), 2.53 (1H, dd, $J$ = 16, 5.2 Hz), 2.45–2.30 (1H, br), 1.83 (3H, d, $J$ = 5.2 Hz), 1.33 (3H, d, $J$ = 6.3 Hz), 1.20 (3H, d, $J$ = 6.6 Hz), 1.15 ppm (3H, d, $J$ = 6.6 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 169.8, 166.4, 165.0, 145.5, 143.9, 139.8, 135.8, 129.7, 123.9, 118.7, 117.4, 93.9, 74.6, 73.8, 71.7, 71.1, 67.8, 67.3, 59.1, 41.4, 20.2, 18.9, 15.2, 14.4 ppm; IR (neat): $\tilde{\nu}$ = 3486, 1716, 1644, 1619 cm$^{-1}$; MS (EI): $m/z$ 498 [$M^+$]; HRMS (EI): Calcd for $C_{25}H_{38}O_{10}$: 498.2465 [$M^+$]; found: 498.2424; $[\alpha]_D^{25} = -20.9$ ($c$ = 1.04 in $CHCl_3$).

**Synthesis of compound 14**: In accordance with procedure 3, compound **13** (87 mg, 0.17 mmol) gave **14** (29.1 mg, 37%) as a colorless solid.: M.p. 170–172°C (colorless plates from $CH_2Cl_2$/hexane); $^1$H NMR ($CDCl_3$): $\delta$ = 7.04 (1H, dd, $J$ = 11, 15 Hz), 6.74 (1H, dd, $J$ = 16, 8.8 Hz), 6.44 (1H, dd, $J$ = 16, 1.1 Hz), 6.14 (1H, dd, $J$ = 16, 1.5 Hz), 6.05 (1H, d, $J$ = 16 Hz), 5.75 (1H, d, $J$ = 15 Hz), 5.48–5.41 (1H, m), 4.86–4.74 (2H, m), 4.75 (1H, d, $J$ = 7.1 Hz), 4.70 (1H, d, $J$ = 7.1 Hz), 4.19–4.08 (2H, m), 3.81–3.75 (1H, m), 3.67–3.61 (1H, m), 3.56–3.52 (2H, m), 3.38 (3H, s), 2.64 (1H, dd, $J$ = 17, 10 Hz), 2.49 (1H, dd, $J$ = 17, 2.2 Hz), 1.42 (3H, d, $J$ = 6.0 Hz), 1.34 (3H, d, $J$ = 6.3 Hz), 1.30 ppm (3H, d, $J$ = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 169.4, 165.2, 164.4, 146.0, 144.6, 142.4, 127.0, 126.0, 121.1, 93.7, 79.0, 73.7, 73.3, 71.7, 70.5, 67.9, 67.4, 59.2, 40.8, 20.3, 18.5, 18.1 ppm; IR (KBr): $\tilde{\nu}$ = 3478, 1744, 1708, 1641 cm$^{-1}$; MS (EI): $m/z$ 456 [$M^+$]; HRMS (EI): calcd for $C_{22}H_{32}O_{10}$: 456.1996 [$M^+$]; found: 456.2030; $[\alpha]_D^{28} = +39.3$ ($c$ = 0.10 in $CHCl_3$).

**Synthesis of 18MS-3**: In accordance with procedure 5-a, MEM ether **14** (21.5 mg, 0.05 mmol) gave **18MS-3** (16.2 mg, 95%) as a colorless solid: M.p. 194–196°C (colorless plates from $CHCl_3$); $^1$H NMR ([$D_6$]DMSO): $\delta$ = 7.02 (1H, dd, $J$ = 15, 11 Hz), 6.62 (1H, dd, $J$ = 16, 8.5 Hz), 6.42 (1H, dd, $J$ = 15, 12 Hz), 6.15–6.02 (2H, m), 5.79 (1H, d, $J$ = 15 Hz), 5.64 (1H, d, $J$ = 6.0 Hz), 5.59 (1H, d, $J$ = 5.8 Hz), 5.31–5.20 (1H, m), 4.70–4.60 (1H, m), 4.50–4.40 (1H, m), 4.07–3.99 (1H, m), 3.98–3.89 (1H, m), 2.74 (1H, dd, $J$ = 17, 1.8 Hz), 2.56 (1H, dd, $J$ = 17, 10 Hz), 1.31 (3H, d, $J$ = 6.0 Hz), 1.26 (3H, d, $J$ = 6.3 Hz), 1.19 ppm (3H, d, $J$ = 6.3 Hz); $^{13}$C NMR ([$D_6$]DMSO): $\delta$ = 169.1, 164.7, 164.4, 148.9, 145.0, 144.6, 125.9, 122.8, 119.9, 73.6, 72.6, 71.6, 71.4, 67.3, 19.6, 18.2, 17.4 ppm; IR (KBr): $\tilde{\nu}$ = 3450, 1729, 1656 cm$^{-1}$; MS (EI): $m/z$ 368 [$M^+$]; HRMS (EI): calcd for $C_{18}H_{24}O_8$: 368.1471 [$M^+$]; found: 368.1450; $[\alpha]_D^{25} = +204.9$ ($c$ = 0.10 in MeOH).

**Synthesis of compound 15**: In accordance with procedure 4-a, alcohol **14** (60 mg, 0.13 mmol) gave the corresponding ketone **15** (40 mg, 66%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.33–7.24 (1H, m), 7.08 (1H, dd, $J$ = 15, 12 Hz), 6.78 (1H, dd, $J$ = 16, 8.8 Hz), 6.55 (1H, d, $J$ = 15 Hz), 6.18 (1H, d, $J$ = 16 Hz), 6.09 (1H, d, $J$ = 15 Hz), 5.44–5.35 (1H, m), 4.90 (1H, q, $J$ = 5.5 Hz), 4.80–4.68 (3H, m), 4.25–4.19 (1H, t, $J$ = 8.5 Hz), 3.82–3.75 (1H, m), 3.68–3.58 (1H, m), 3.56–3.52 (2H, m), 3.39 (3H, s), 2.89 (1H, dd, $J$ = 16, 9.9 Hz), 2.56 (1H, dd, $J$ = 16, 1.9 Hz), 1.45 (3H, d, $J$ = 6.9 Hz), 1.44 (3H, d, $J$ = 6.0 Hz), 1.30 ppm (3H, d, $J$ = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 197.1, 170.8, 164.4, 164.0, 146.3, 142.5, 139.7, 129.1, 128.6, 126.1, 93.6, 78.9, 77.4, 71.7, 71.3, 69.4, 67.5, 59.3, 40.8, 20.4, 18.2, 16.9 ppm; IR (neat): $\tilde{\nu}$ = 1735, 1710, 1644, 1618 cm$^{-1}$; MS (EI): $m/z$ 454 [$M^+$]; HRMS (EI): calcd for $C_{22}H_{30}O_{10}$: 454.1839 [$M^+$]; found: 454.1814; $[\alpha]_D^{26} = -31.0$ ($c$ = 0.44 in $CHCl_3$).

**Synthesis of 18MS-4**: In accordance with procedure 5-a, MEM ether **15** (49 mg, 0.11 mmol) gave **18MS-4** (32 mg, 80%) as a colorless solid: M.p. 150–152°C (colorless powder from diethyl ether/hexane); $^1$H NMR ($CDCl_3$): $\delta$ = 7.32–7.27 (1H, m), 7.10 (1H, dd, $J$ = 15, 12 Hz), 6.88 (1H, dd, $J$ = 15, 6.1 Hz), 6.57 (1H, d, $J$ = 15 Hz), 6.17 (1H, d, $J$ = 15 Hz), 6.12 (1H, d, $J$ = 15 Hz), 5.43–5.37 (1H, m), 4.92 (1H, q, $J$ = 7.3 Hz), 4.76–4.71 (1H, m), 4.26 (1H, t, $J$ = 8.3 Hz), 2.85 (1H, dd, $J$ = 10, 16 Hz), 2.58 (1H, dd, $J$ = 11, 16 Hz), 1.48 (3H, d, $J$ = 6.0 Hz), 1.45 (3H, d, $J$ = 7.2 Hz), 1.39 ppm (3H, d, $J$ = 6.4 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 197.0, 170.7, 164.6, 164.2, 147.4, 142.6, 139.7, 129.0, 128.7, 124.6, 75.6, 72.7, 69.4, 53.7, 40.8, 20.3, 17.8, 16.8 ppm; IR (KBr): $\tilde{\nu}$ = 3468, 1708, 1618 cm$^{-1}$; MS (EI): $m/z$ 366 [$M^+$]; HRMS (EI): calcd for $C_{18}H_{22}O_8$: 366.1315 [$M^+$]; found: 366.1303; $[\alpha]_D^{25} = +63.0$ ($c$ = 0.26 in MeOH).

**Synthesis of compound 16**: In accordance with procedure 1-b, carboxylic acid **5** (117 mg, 0.34 mmol) and alcohol **4** (50 mg, 0.23 mmol) gave ester **16** (105 mg, 85%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.24 (2H, d, $J$ = 8.5 Hz), 6.86 (2H, d, $J$ = 8.5 Hz), 6.81 (1H, dd, $J$ = 6.3, 16 Hz), 5.99 (1H, d, $J$ = 16 Hz), 5.82–5.70 (1H, m), 5.31 (1H, d, $J$ = 10 Hz), 5.27 (1H, d, $J$ = 17 Hz), 5.07–5.02 (1H, m), 4.74 (1H, d, $J$ = 7.1 Hz), 4.71 (1H, d, $J$ = 7.1 Hz), 4.56 (1H, d, $J$ = 12 Hz), 4.36 (1H, d, $J$ = 12 Hz), 4.07–4.03 (1H, m), 3.80 (3H, m), 3.84–3.73 (3H, m), 3.67–3.60 (1H, m), 3.54–3.50 (1H, m), 3.37 (3H, m), 1.24 (3H, d, $J$ = 6.3 Hz), 1.17 (3H, d, $J$ = 6.3 Hz), 0.86 (9H, s), 0.04 (3H, s), 0.02 ppm (3H, s); $^{13}$C NMR ($CDCl_3$): $\delta$ = 165.2, 159.0, 145.6, 134.9, 130.3, 129.2, 123.9, 119.4, 113.7, 94.0, 81.7, 80.0, 72.1, 71.8, 70.7, 70.6, 70.2, 67.3, 59.1, 55.3, 26.0, 20.1, 18.2, 15.7, −4.4, −4.5 ppm; IR (neat): $\tilde{\nu}$ = 1719, 1646, 1610 cm$^{-1}$; MS (EI): $m/z$ 552 [$M^+$]; HRMS (EI): calcd for $C_{29}H_{48}O_8Si$: 552.3118 [$M^+$]; found: 552.3120; $[\alpha]_D^{24} = -31.4$ ($c$ = 4.42 in $CHCl_3$).

**Synthesis of compound 17**: In accordance with procedure 6-a, TBS ether **16** (1.60 g, 2.9 mmol) gave alcohol **17** (1.20 g, 95%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.23 (2H, d, $J$ = 8.8 Hz), 6.85 (2H, d, $J$ = 8.8 Hz), 6.81 (1H, dd, $J$ = 6.0, 16 Hz), 6.03 (1H, dd, $J$ = 1.5, 16 Hz), 5.81–5.69 (1H, m), 5.32 (1H, d, $J$ = 10 Hz), 5.28 (1H, d, $J$ = 17 Hz), 5.08–4.99 (1H, m), 4.78 (1H, d, $J$ = 7.1 Hz), 4.71 (1H, d, $J$ = 7.1 Hz), 4.56 (1H, d, $J$ = 11 Hz), 4.35 (1H, d, $J$ = 11 Hz), 4.24–4.20 (1H, m), 3.79 (3H, m), 3.96–3.73 (3H, m), 3.71–3.63 (1H, m), 3.58–3.52 (1H, m), 3.38 (3H, m), 1.22 (3H, d, $J$ = 6.3 Hz), 1.15 ppm (3H, d, $J$ = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 165.2, 159.1, 143.8, 134.9, 130.4, 129.3, 124.9, 119.6, 113.8, 94.6, 81.6, 81.0, 72.3, 71.8, 70.3, 69.2, 67.7, 59.2, 55.5, 17.9, 15.7 ppm; IR (neat): $\tilde{\nu}$ = 3456, 1710, 1646, 1611 cm$^{-1}$; MS (EI): $m/z$ 438 [$M^+$]; HRMS (EI): calcd for $C_{23}H_{34}O_8$: 438.2254 [$M^+$]; found: 438.2281; $[\alpha]_D^{25} = -52.7$ ($c$ = 1.73 in $CHCl_3$).

**Synthesis of compound 18**: In accordance with procedure 1-a, carboxylic acid **6** (1.07 g, 5.0 mmol) and alcohol **17** (1.1 g, 2.5 mmol) gave ester **18** (1.43 g, 90%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.24 (2H, d, $J$ = 8.5 Hz), 6.87 (2H, d, $J$ = 8.5 Hz), 6.79 (1H, dd, $J$ = 6.3, 16 Hz), 6.06 (1H, dd, $J$ = 16, 1.4 Hz), 5.82–5.70 (1H, m), 5.31 (1H, d, $J$ = 10 Hz), 5.29 (1H, d, $J$ = 16 Hz), 5.07–4.99 (2H, m), 4.76 (1H, d, $J$ = 7.1 Hz), 4.70 (1H, d, $J$ = 7.1 Hz), 4.57 (1H, d, $J$ = 12 Hz), 4.36 (1H, d, $J$ = 12 Hz), 4.34–4.21 (2H, m), 3.83–3.76 (1H, m), 3.80 (3H, s), 3.68–3.60 (1H, m), 3.55–3.51 (2H,

m), 3.38 (3H, s), 2.48 (1H, dd, $J=15$, 6.6 Hz), 2.46 (1H, dd, $J=16$, 6.6 Hz), 1.26 (3H, d, $J=6.3$ Hz), 1.21 (3H, d, $J=6.9$ Hz), 1.19 (3H, d, $J=6.0$ Hz), 0.86 (9H, s), 0.06 (3H, s), 0.05 ppm (3H, s); $^{13}$C NMR ($CDCl_3$): $\delta=170.7$, 165.1, 159.1, 143.3, 135.0, 130.3, 129.3, 124.6, 119.7, 113.8, 94.0, 81.6, 72.4, 71.8, 71.4, 70.3, 67.4, 65.8, 59.2, 55.4, 45.1, 26.0, 24.0, 18.3, 15.8, 15.3, −4.2, −4.6 ppm; IR (neat): $\tilde{\nu}=1718$, 1613 $cm^{-1}$; MS (EI): $m/z$ 638 [$M^+$]; HRMS (EI): calcd for $C_{33}H_{54}O_{10}Si$: 638.3486 [$M^+$]; found: 638.3459; $[\alpha]_D^{26}=-33.3$ ($c=1.77$ in $CHCl_3$).

**Synthesis of compound 19**: In accordance with procedure 6-b, the TBS ether **18** (100 mg, 0.156 mmol) gave the alcohol **19** (82 mg, 69%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta=7.24$ (2H, d, $J=8.4$ Hz), 6.86 (2H, d, $J=8.6$ Hz), 6.79 (1H, dd, $J=6.4$, 16 Hz), 6.05 (1H, dd, $J=1.4$, 16 Hz), 5.80–5.72 (1H, m), 5.33 (1H, d, $J=10$ Hz), 5.29 (1H, d, $J=17$ Hz), 5.13–5.02 (2H, m), 4.75 (1H, d, $J=7.0$ Hz), 4.70 (1H, d, $J=7.0$ Hz), 4.57 (1H, d, $J=12$ Hz), 4.36 (1H, d, $J=12$ Hz), 4.35–4.31 (1H, m), 4.19–4.13 (1H, m), 3.84–3.77 (1H, m), 3.80 (3H, s), 3.65–3.60 (1H, m), 3.57–3.52 (2H, m), 3.38 (3H, s), 2.48–2.38 (2H, m), 1.26 (3H, d, $J=6.3$ Hz), 1.25 (3H, d, $J=6.0$ Hz), 1.21 ppm (3H, d, $J=6.0$ Hz); $^{13}$C NMR ($CDCl_3$): $\delta=172.0$, 165.0, 159.1, 142.9, 134.8, 130.2, 129.3, 124.8, 119.7, 113.8, 93.9, 81.6, 72.4, 71.8, 71.6, 70.2, 67.4, 64.5, 59.2, 55.4, 43.4, 22.8, 15.7, 15.4 ppm; IR (neat): $\tilde{\nu}=$ 3458, 1718, 1613 $cm^{-1}$; MS (EI): $m/z$ 524 [$M^+$]; HRMS (EI): calcd for $C_{27}H_{40}O_{10}$: 524.2622 [$M^+$]; found: 524.2621; $[\alpha]_D^{26}=-40.1$ ($c=2.81$ in $CHCl_3$).

**Synthesis of compound 20**: In accordance with procedure 1-b, alcohol **19** (473 mg, 0.9 mmol) gave ester **20** (430 mg, 79%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta=7.24$–7.16 (1H, m), 7.21 (2H, d, $J=8.5$ Hz), 6.83 (2H, d, $J=8.5$ Hz), 6.75 (1H, dd, $J=16$, 6.3 Hz), 6.19–5.99 (3H, m), 5.79–5.67 (1H, m), 5.71 (1H, d, $J=15$ Hz), 5.31–5.23 (3H, m), 5.05–5.00 (2H, m), 4.72 (1H, d, $J=7.1$ Hz), 4.66 (1H, d, $J=7.1$ Hz), 4.54 (1H, d, $J=12$ Hz), 4.33 (1H, d, $J=12$ Hz), 4.31–4.27 (1H, m), 3.76 (3H, s), 3.80–3.72 (2H, m), 3.64–3.56 (1H, m), 3.52–3.48 (2H, m), 3.34 (3H, s), 2.64 (1H, dd, $J=15$, 7.5 Hz), 2.50 (1H, dd, $J=15$, 5.8 Hz), 1.81 (3H, d, $J=5.5$ Hz), 1.29 (3H, d, $J=6.3$ Hz), 1.23 (3H, d, $J=6.3$ Hz), 1.16 ppm (3H, d, $J=6.6$ Hz); $^{13}$C NMR ($CDCl_3$): $\delta=169.4$, 166.2, 165.0, 159.1, 145.2, 143.1, 139.4, 134.9, 130.2, 129.7, 129.2, 124.6, 119.5, 118.9, 113.7, 93.9, 81.5, 76.7, 72.3, 71.7, 71.5, 70.2, 67.4, 67.1, 59.1, 55.3, 41.2, 20.1, 18.8, 15.6, 15.2 ppm; IR (neat): $\tilde{\nu}=1713$, 1648, 1608 $cm^{-1}$; MS (EI): $m/z$ 618 [$M^+$]; HRMS (EI): calcd for $C_{33}H_{46}O_{11}$: 618.3040 [$M^+$]; found: 618.3058; $[\alpha]_D^{26}=$ −41.8 ($c=1.17$ in $CHCl_3$).

**Synthesis of compound 21**: In accordance with procedure 2, PMB ether **20** (430 mg, 0.71 mmol) gave alcohol **21** (270 mg, 78%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta=7.26$–7.17 (1H, m), 6.80 (1H, dd, $J=6.4$, 16 Hz), 6.16–6.03 (3H, m), 5.90–5.78 (1H, m), 5.71 (1H, d, $J=15$ Hz), 5.35 (1H, d, $J=17$ Hz), 5.33–5.26 (1H, m), 5.27 (1H, d, $J=10$ Hz), 5.06–4.97 (1H, m), 4.72 (1H, d, $J=7.1$ Hz), 4.67 (1H, d, $J=7.1$ Hz), 4.30–4.24 (2H, m), 3.79–3.72 (1H, m), 3.66–3.59 (1H, m), 3.54–3.50 (2H, m), 3.36 (3H, s), 2.66 (1H, dd, $J=15$, 7.6 Hz), 2.53 (1H, dd, $J=15$, 5.8 Hz), 1.83 (3H, d, $J=5.3$ Hz), 1.29 (3H, d, $J=6.3$ Hz), 1.24 (3H, d, $J=6.3$ Hz), 1.19 ppm (3H, d, $J=4.7$ Hz); $^{13}$C NMR ($CDCl_3$): $\delta=169.4$, 166.5, 165.3, 145.4, 143.4, 139.7, 135.9, 129.8, 124.6, 118.8, 117.3, 94.0, 77.0, 74.6, 74.0, 71.8, 71.5, 67.5, 67.2, 59.2, 41.4, 20.2, 18.9, 15.7, 14.4 ppm; IR (neat): $\tilde{\nu}=3490$, 1706, 1640, 1612 $cm^{-1}$; MS (EI): $m/z$ 498 [$M^+$]; HRMS (EI): calcd for $C_{25}H_{38}O_{10}$: 498.2465 [$M^+$]; found: 498.2420; $[\alpha]_D^{26}=-20.0$ ($c=1.26$ in $CHCl_3$).

**Synthesis of compound 22**: In accordance with procedure 3, compound **21** (270 mg, 0.56 mmol) gave compound **22** (100 mg, *E*/*Z* 3/1, 40%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta=7.21$ (1H, dd, $J=10$, 15 Hz), 6.51 (1H, dd, $J=16$, 9.0 Hz), 6.17–6.09 (1H, m), 6.01 (1H, dd, $J=15$, 7.9 Hz), 5.86 (1H, d, $J=16$ Hz), 5.68 (1H, d, $J=15$ Hz), 5.28–5.19 (2H, m), 4.94–4.88 (1H, m), 4.65–4.62 (2H, m), 4.06–4.00 (1H, m), 3.94–3.84 (1H, m), 3.74–3.61 (1H, m), 3.59–3.47 (3H, m), 3.35 (3H, s), 2.92 (1H, dd, $J=13$, 5.3 Hz), 2.22 (1H, dd, $J=13$, 2.2 Hz), 1.41 (3H, d, $J=6.3$ Hz), 1.38 (3H, d, $J=6.8$ Hz), 1.09 ppm (3H, d, $J=6.6$ Hz); $^{13}$C NMR ($CDCl_3$): $\delta=169.8$, 165.9, 165.0, 144.2, 142.6, 142.3, 128.8, 126.1, 121.4, 93.4, 77.7, 76.8, 72.0, 71.9, 71.7, 67.3, 67.2, 59.1, 39.4, 18.6, 17.5, 17.0 ppm; MS (EI): $m/z$ 456 [$M^+$]; HRMS (EI): calcd for $C_{22}H_{32}O_{10}$: 456.1996 [$M^+$]; found: 456.1986.

**Synthesis of 18MS-5**: In accordance with procedure 5-a, MEM ether **22** (180 mg, 0.39 mmol) gave **18MS-5** (55 mg, 38%) as a colorless solid: M.p. 163–164°C (colorless powder from $CH_2Cl_2$/hexane); $^1$H NMR ($CDCl_3$): $\delta=7.46$–7.22 (1H, m), 6.57 (1H, dd, $J=16$, 8.1 Hz), 6.21 (1H, dd, $J=15$, 11 Hz), 6.05 (1H, dd, $J=15$, 7.1 Hz), 5.89 (1H, d, $J=16$ Hz), 5.74 (1H, d, $J=15$ Hz), 5.33–5.29 (1H, m), 5.18 (1H, ddd, $J=13$, 6.4, 3.0 Hz), 4.97 (1H, dt, $J=14$, 6.4 Hz), 4.09 (1H, dd, $J=9.0$, 3.0 Hz), 2.93 (1H, dd, $J=13$, 5.2 Hz), 2.31 (1H, dd, $J=13$, 3.2 Hz), 1.44 (3H, d, $J=6.8$ Hz), 1.41 (3H, d, $J=6.9$ Hz), 1.14 ppm (3H, d, $J=6.8$ Hz); $^{13}$C NMR ($CDCl_3$): $\delta=$ 170.2, 165.9, 165.5, 144.2, 143.7, 142.2, 128.8, 124.5, 121.4, 100.7, 73.3, 72.4, 67.1, 39.3, 18.4, 17.3, 16.7 ppm; IR (KBr): $\tilde{\nu}=3460$, 1715, 1614 $cm^{-1}$; MS (EI): $m/z$ 368 [$M^+$]; HRMS (EI): calcd for $C_{18}H_{24}O_8$: 368.1471 [$M^+$]; found: 368.1434; $[\alpha]_D^{26}=-73.4$ ($c=0.91$ in $CHCl_3$).

**Synthesis of compound 24**: In accordance with procedure 1-a, carboxylic acid **6** (328 mg, 1.5 mmol) and alcohol **23** (209 mg, 1.0 mmol) gave ester **24** (417 mg, quant.) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta=6.94$ (1H, s), 6.51 (1H, s), 5.79–5.66 (1H, m), 5.33 (1H, t, $J=6.9$ Hz), 5.09 (1H, dd, $J=1.9$, 17 Hz), 5.05 (1H, dd, $J=1.7$, 10 Hz), 4.31–4.23 (1H, m), 2.56–2.34 (4H, m), 2.07 (3H, s), 1.19 (3H, d, $J=6.0$ Hz), 0.83 (9H, s), 0.05 (3H, s), 0.02 ppm (3H, s); $^{13}$C NMR ($CDCl_3$): $\delta=170.1$, 164.0, 152.2, 136.5, 133.1, 120.8, 117.4, 116.0, 65.5, 44.7, 37.4, 25.7, 23.7, 19.1, 17.8, 14.5, −4.6, −5.0 ppm; IR (neat): $\tilde{\nu}=1737$, 1471 $cm^{-1}$; MS (EI): $m/z$ 409 [$M^+$]; HRMS (EI): calcd for $C_{21}H_{35}NO_3SSi$: 409.2107 [$M^+$]; found: 409.2059; $[\alpha]_D^{25}=-3.9$ ($c=1.27$ in $CHCl_3$).

**Synthesis of compound 25**: In accordance with procedure 6-a, TBS ether **24** (718 mg, 1.75 mmol) gave alcohol **25** (414 mg, 80%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta=6.95$ (1H, s), 6.51 (1H, s), 5.36 (1H, t, $J=6.9$ Hz), 5.14 (1H, dd, $J=1.7$, 17 Hz), 5.11 (1H, dd, $J=1.1$, 10 Hz), 4.24–4.16 (1H, m), 2.69 (3H, s), 2.56–2.39 (4H, m), 2.07 (3H, s), 1.21 ppm (3H, d, $J=6.3$ Hz); $^{13}$C NMR ($CDCl_3$): $\delta=171.5$, 164.4, 152.0, 136.4, 133.1, 120.6, 117.4, 116.2, 78.3, 64.1, 43.1, 37.5, 22.4, 19.1, 14.7 ppm; IR (neat): $\tilde{\nu}=$ 3406, 1732, 1643 $cm^{-1}$; MS (EI): $m/z$ 295 [$M^+$]; HRMS (EI): calcd for $C_{15}H_{21}NO_3S$: 295.1242 [$M^+$]; found: 295.1257; $[\alpha]_D^{26}=-18.2$ ($c=0.85$ in $CHCl_3$).

**Synthesis of compound 26**: In accordance with procedure 1-b, carboxylic acid **5** (273 mg, 0.80 mmol) and alcohol **25** (197 mg, 0.67 mmol) gave ester **26** (399 mg, 95%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta=6.95$ (1H, s), 6.83 (1H, dd, $J=6.5$, 16 Hz), 6.50 (1H, s), 5.96 (1H, d, $J=16$ Hz), 5.71–5.65 (1H, m), 5.37–5.31 (2H, m), 5.09 (1H, dd, $J=1.7$, 17 Hz), 5.03 (1H, dd, $J=1.7$, 10 Hz), 4.70 (1H, d, $J=6.9$ Hz), 4.69 (1H, d, $J=6.9$ Hz), 4.04 (1H, dd, $J=1.4$, 6.5 Hz), 3.83–3.51 (5H, m), 3.38 (3H, s), 2.70 (3H, s), 2.58–2.44 (4H, m), 2.06 (3H, s), 1.32 (3H, d, $J=6.3$ Hz), 1.15 (3H, d, $J=6.3$ Hz), 0.86 (9H, s), 0.04 (3H, s), 0.02 ppm (3H, s); $^{13}$C NMR ($CDCl_3$): $\delta=164.4$, 151.7, 136.0, 132.6, 122.8, 120.4, 117.3, 115.9, 93.4, 79.3, 76.1, 71.1, 70.1, 66.9, 66.7, 58.5, 53.0, 40.6, 37.1, 25.3, 19.5, 18.8, 17.6, 14.2, −5.0, −5.2 ppm; IR (neat): $\tilde{\nu}=1723$, 1658 $cm^{-1}$; MS (EI): $m/z$ 625 [$M^+$]; HRMS (EI): calcd for $C_{31}H_{51}NO_8SSi$: 625.3105 [$M^+$]; found: 625.3081; $[\alpha]_D^{24}=-27.0$ ($c=0.92$ in $CHCl_3$).

**Synthesis of compound 27**: In accordance with procedure 6-c, TBS ether **26** (100 mg, 0.16 mmol) gave alcohol **27** (52 mg, 64%) as a colorless oil (recovered starting material: 20 mg, 20%): $^1$H NMR ($CDCl_3$): $\delta=6.94$ (1H, s), 6.82 (1H, dd, $J=6.2$, 16 Hz), 6.49 (1H, s), 5.99 (1H, d, $J=16$ Hz), 5.75–5.61 (1H, m), 5.36–5.29 (2H, m), 5.07 (1H, dd, $J=1.1$, 17 Hz), 5.02 (1H, dd, $J=1.1$, 11 Hz), 4.71 (1H, d, $J=7.1$ Hz), 4.68 (1H, d, $J=7.1$ Hz), 4.18 (1H, dd, $J=1.4$, 6.0 Hz), 3.96–3.43 (5H, m), 3.37 (3H, s), 2.69 (3H, s), 2.67–2.42 (4H, m), 2.45 (3H, s), 1.32 (3H, d, $J=6.3$ Hz), 1.11 ppm (3H, d, $J=6.3$ Hz); $^{13}$C NMR ($CDCl_3$): $\delta=169.0$, 143.9, 136.5, 133.1, 123.7, 120.9, 117.8, 116.4, 94.4, 80.8, 78.5, 71.6, 68.9, 67.6, 67.5, 59.9, 59.0, 53.4, 41.1, 37.6, 20.0, 19.3, 17.7, 15.3, 14.7 ppm; IR (neat): $\tilde{\nu}=3447$, 1720, 1656 $cm^{-1}$; MS (EI): $m/z$ 511 [$M^+$]; HRMS (EI): calcd for $C_{25}H_{37}NO_8S$: 511.2240 [$M^+$]; found: 511.2249; $[\alpha]_D^{28}=-34.8$ ($c=1.55$ in $CHCl_3$).

**Synthesis of compound 28**: In accordance with procedure 7, alcohol **27** (31 mg, 0.06 mmol) gave compound **28** (29 mg, 87%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta=6.92$ (1H, s), 6.78 (1H, dd, $J=6.0$, 16 Hz), 6.46 (1H, s), 6.36 (1H, dd, $J=1.3$, 17 Hz), 6.11–5.97 (2H, m), 5.79 (1H, dd, $J=1.3$, 10 Hz), 5.67–5.61 (1H, m), 5.32–5.28 (2H, m), 5.08–4.97 (3H, m), 4.67 (1H, d, $J=7.1$ Hz), 4.64 (1H, d, $J=7.1$ Hz), 4.34 (1H, dd, $J=1.4$, 6.0 Hz), 3.76–3.46 (4H, m), 3.33 (3H, s), 2.66 (3H, m), 2.57–2.39 (4H, m), 1.30 (3H, d, $J=6.3$ Hz), 1.19 ppm (3H, d, $J=6.6$ Hz); $^{13}$C NMR

($CDCl_3$): $\delta$ = 168.9, 165.2, 164.7, 143.2, 136.5, 133.0, 130.9, 128.3, 124.1, 120.9, 117.8, 116.4, 93.7, 78.5, 76.5, 71.6, 71.4, 67.7, 67.2, 59.0, 53.4, 41.1, 37.6, 29.7, 20.0, 19.3, 15.0, 14.7 ppm; IR (neat): $\tilde{\nu}$ = 1718, 1653 $cm^{-1}$; MS (EI): *m/z* 565 [$M^+$]; HRMS (EI): calcd for $C_{28}H_{39}NO_9S$: 565.2345 [$M^+$]; found: 565.2352; $[\alpha]_D^{28}$ = −31.2 (*c* = 1.45 in $CHCl_3$).

**Synthesis of compound 29**: In accordance with procedure 3, compound **28** (29 mg, 0.05 mmol) gave compound **29** (22.7 mg, 84%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 6.98 (1H, s), 6.85–6.66 (1H, m), 6.49 (1H, s), 6.01 (1H, d, *J* = 16 Hz), 5.79 (1H, d, *J* = 16 Hz), 5.36 (1H, t, *J* = 6.0 Hz), 5.30 (1H, m), 4.90 (1H, qd, *J* = 6.3, 7.7 Hz), 4.77–4.70 (2H, m), 4.14 (1H, dd, *J* = 7.7, 16 Hz), 3.81–3.53 (4H, m), 3.39 (3H, s), 2.70 (3H, s), 2.66–2.56 (4H, m), 2.07 (3H, s), 1.41 (3H, d, *J* = 6.3 Hz), 1.30 ppm (3H, d, *J* = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 164.5, 164.3, 152.0, 144.9, 143.4, 136.1, 124.7, 124.0, 120.1, 116.7, 93.9, 79.4, 71.5, 70.6, 67.3, 67.2, 59.0, 40.6, 35.8, 29.7, 19.6, 19.3, 18.0, 15.4, 11.0 ppm; IR (neat): $\tilde{\nu}$ = 1724, 1655 $cm^{-1}$; MS (EI): *m/z* 537 [$M^+$]; HRMS (EI): calcd for $C_{22}H_{29}NO_7S$: 537.2032 [$M^+$]; found: 537.2052; $[\alpha]_D^{28}$ = −25.8 (*c* = 1.135 in $CHCl_3$).

**Synthesis of MSt-1′**: In accordance with procedure 5-a, MEM ether **29** (38.1 mg, 0.07 mmol) gave **MSt-1′** (30 mg, 94%) as a colorless solid: M.p. 39–41 °C; $^1$H NMR ($CDCl_3$): $\delta$ = 6.97 (1H, s), 6.95–6.90 (1H, m), 6.79 (1H, dd, *J* = 8.5, 16 Hz), 6.47 (1H, s), 6.04 (1H, d, *J* = 16 Hz), 5.77 (1H, d, *J* = 16 Hz), 5.44 (1H, d, *J* = 6.0 Hz), 5.27–5.22 (1H, m), 4.94 (1H, qd, *J* = 4.7, 6.3 Hz), 4.22 (1H, dd, *J* = 4.7, 8.5 Hz), 2.69 (3H, s), 2.66–2.58 (4H, m), 2.04 (3H, s), 1.33 (3H, d, *J* = 6.3 Hz), 1.26 ppm (3H, d, *J* = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 169.0, 165.5, 164.8, 164.6, 151.8, 145.7, 144.2, 136.1, 123.7, 122.6, 120.3, 116.6, 75.3, 74.6, 67.6, 40.2, 35.6, 19.5, 19.2, 18.0, 15.4, 14.2 ppm; IR (KBr): $\tilde{\nu}$ = 3446, 1717, 1653 $cm^{-1}$; MS (EI): *m/z* 449 [$M^+$]; HRMS (EI): calcd for $C_{22}H_{27}NO_7S$: 449.1508 [$M^+$]; found: 449.1459; $[\alpha]_D^{26}$ = +24.8 (*c* = 1.50 in $CHCl_3$).

**Synthesis of MSt-2′**: In accordance with procedure 4-b, **MSt-1′** (10 mg, 0.02 mmol) gave **MSt-2′** (6.7 mg, 67%) as a pale yellow oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.19 (1H, d, *J* = 16 Hz), 7.05–6.95 (2H, m), 6.66 (1H, d, *J* = 16 Hz), 6.53 (1H, s), 5.94 (1H, d, *J* = 16 Hz), 5.60 (1H, t, *J* = 6.5 Hz), 5.30–5.24 (1H, m), 5.17 (1H, q, *J* = 7.1 Hz), 2.71 (3H, s), 2.59–2.52 (4H, m), 2.11 (3H, s), 1.53 (3H, d, *J* = 7.1 Hz), 1.35 ppm (3H, d, *J* = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 198.4, 168.8, 164.5, 163.6, 146.1, 145.4, 136.2, 133.9, 131.9, 123.5, 120.5, 116.9, 105.3, 75.5, 68.1, 39.0, 36.6, 19.4, 18.7, 16.9, 15.1 ppm; IR (neat): $\tilde{\nu}$ = 1724, 1653 $cm^{-1}$; MS (EI): *m/z* 447 [$M^+$]; HRMS (EI): calcd for $C_{22}H_{25}NO_7S$: 447.1352 [$M^+$]; found: 447.1373; $[\alpha]_D^{25}$ = −6.9 (*c* = 0.90 in $CHCl_3$).

**Synthesis of compound 30**: A mixture of pyridine-2-carbaldehyde (107 mg, 1.0 mmol) and 2-(triphenylphosphoranilidene)propionaldehyde (336 mg, 1.15 mmol) in benzene (2 mL) was heated to reflux for 15 h. The solvent was evaporated to leave a residue, which was purified by chromatography on silica gel to afford aldehyde **30** (146 mg, 99%) as a brownish oil: $^1$H NMR ($CDCl_3$): $\delta$ = 9.75 (1H, s), 8.85 (1H, d, *J* = 4.9 Hz), 7.89 (1H, dd, *J* = 7.4, 8.0 Hz), 7.63 (1H, d, *J* = 8.0 Hz), 7.39 (1H, dd, *J* = 4.9, 7.4 Hz), 7.38 (1H, s), 2.63 ppm (3H, s); $^{13}$C NMR ($CDCl_3$): $\delta$ = 195.5, 154.1, 149.7, 147.3, 141.1, 136.2, 125.8, 123.1, 11.0 ppm; IR (neat): $\tilde{\nu}$ = 1681, 1632 $cm^{-1}$; MS (EI): *m/z* 147 [$M^+$]; HRMS (EI): calcd for $C_9H_9NO$: 147.0684 [$M^+$]; found: 147.0722.

**Synthesis of compound 31**: (+)-$Ipc_2B$(allyl) (1.0 M pentane solution, 6.0 mL, 6 mmol) was added to a solution of aldehyde **30** (696 mg, 4 mmol) in $Et_2O$ (16 mL) at −100 °C, and the mixture was stirred for 1.5 h at −100 °C. After addition of MeOH (1.6 mL), the mixture was warmed to room temperature, then 2-aminoethanol (2.4 mL, 40 mmol) was added. After stirring for 24 h, the mixture was diluted with saturated $NH_4Cl$, extracted with AcOEt, and dried over $MgSO_4$, then the solvent was evaporated. The residue was purified by silica gel column chromatography to afford compound **31** (749 mg, 99%) as a colorless oil. The optical purity was determined by a standard Mosher's ester analysis (93% *ee*): $^1$H NMR ($CDCl_3$): $\delta$ = 8.59 (1H, d, *J* = 4.9 Hz), 7.65 (1H, dd, *J* = 7.4, 8.0 Hz), 7.26 (1H, d, *J* = 8.0 Hz), 7.12 (1H, dd, *J* = 4.9, 7.4 Hz), 6.62 (1H, s), 5.93–5.79 (1H, m), 5.18 (1H, dd, *J* = 1.9, 17 Hz), 5.16 (1H, dd, *J* = 1.9, 10 Hz), 4.25 (1H, dt, *J* = 1.9, 5.3 Hz), 2.65 (1H, br), 2.54–2.34 (2H, m), 2.07 ppm (3H, s); $^{13}$C NMR ($CDCl_3$): $\delta$ = 156.4, 148.9, 144.3, 135.9, 134.5, 124.7, 124.1, 120.9, 117.8, 76.3, 40.0, 14.2 ppm; IR (neat): $\tilde{\nu}$ = 3348, 1643 $cm^{-1}$; MS (EI): *m/z* 189 [$M^+$]; HRMS (EI): calcd for $C_{12}H_{15}NO$: 189.1154 [$M^+$]; found: 189.1150; $[\alpha]_D^{28}$ = +20.9 (*c* = 1.05 in $CHCl_3$).

**Synthesis of compound 32**: In accordance with procedure 1-a, alcohol **31** (95 mg, 0.5 mmol) and carboxylic acid **6** (200 mg, 0.92 mmol) gave ester **32** (168 mg, 94%) as a pale yellow oil: $^1$H NMR ($CDCl_3$): $\delta$ = 8.60 (1H, d, *J* = 4.9 Hz), 7.63 (1H, dd, *J* = 7.4, 8.8 Hz), 7.20 (1H, d, *J* = 8.8 Hz), 7.10 (1H, dd, *J* = 4.9, 7.4 Hz), 6.53 (1H, s), 5.80–5.71 (1H, m), 5.34 (1H, dt, *J* = 6.0, 20 Hz), 5.12 (1H, d, *J* = 18 Hz), 5.07 (1H, d, *J* = 12 Hz), 4.28 (1H, dd, *J* = 5.9, 12 Hz), 2.59–2.34 (2H, m), 2.10 (3H, s), 1.20 (3H, d, *J* = 6.0 Hz), 0.87 (9H, s), 0.07 (3H, s), 0.05 ppm (3H, s); $^{13}$C NMR ($CDCl_3$): $\delta$ = 170.4, 156.0, 148.9, 140.1, 135.9, 133.2, 126.4, 124.3, 121.2, 117.7, 78.3, 65.7, 51.4, 45.0, 37.6, 25.9, 23.9, 18.1, 14.5, −4.5, −4.8 ppm; IR (neat): $\tilde{\nu}$ = 1739 $cm^{-1}$; MS (EI): *m/z* 389 [$M^+$]; HRMS (EI): calcd for $C_{22}H_{35}NO_3Si$: 389.2386 [$M^+$]; found: 389.2367; $[\alpha]_D^{25}$ = −57.2 (*c* = 1.20 in $CHCl_3$).

**Synthesis of compound 33**: In accordance with procedure 6-a, TBS ether **32** (1.461 g, 3.75 mmol) gave alcohol **33** (744 mg, 72%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 8.54 (1H, d, *J* = 4.9 Hz), 7.59 (1H, dd, *J* = 7.7, 8.0 Hz), 7.18 (1H, d, *J* = 8.0 Hz), 7.07 (1H, d, *J* = 4.9, 7.7 Hz), 6.52 (1H, s), 5.73 (1H, ddt, *J* = 4.9, 10, 17 Hz), 5.37–5.32 (1H, m), 5.09 (1H, d, *J* = 17 Hz), 5.05 (1H, d, *J* = 10 Hz), 4.24–4.13 (1H, m), 3.28 (1H, br), 2.54–2.39 (4H, m), 2.05 (3H, s), 1.19 ppm (3H, d, *J* = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 171.8, 155.9, 149.0, 139.7, 135,9, 133.1, 126.7, 124.3, 121.2, 118.0, 78.4, 64.2, 43.0, 37.6, 22.5, 14.5 ppm; IR (neat): $\tilde{\nu}$ = 3418, 1731, 1645 $cm^{-1}$; MS (EI): *m/z* 275 [$M^+$]; HRMS (EI): calcd for $C_{16}H_{21}NO_3$: 275.1522 [$M^+$]; found: 275.1506; $[\alpha]_D^{26}$ = +59.7 (*c* = 1.00 in $CHCl_3$).

**Synthesis of compound 34**: In accordance with procedure 1-a, alcohol **33** (55 mg, 0.20 mol) and carboxylic acid **5** (146 mg, 0.41 mmol) gave ester **34** (90 mg, 74%) as a pale yellow oil: $^1$H NMR ($CDCl_3$): $\delta$ = 8.59 (1H, d, *J* = 4.7 Hz), 7.62 (1H, dd, *J* = 7.7, 8.0 Hz), 7.21 (1H, d, *J* = 8.0 Hz), 7.09 (1H, dd, *J* = 4.7, 7.7 Hz), 6.82 (1H, dd, *J* = 6.3, 16 Hz), 6.52 (1H, s), 5.96 (1H, d, *J* = 16 Hz), 5.76–5.67 (1H, m), 5.39–5.32 (1H, m), 5.38 (1H, dd, *J* = 6.3, 6.9 Hz), 5.12 (1H, d, *J* = 17 Hz), 5.07 (1H, d, *J* = 10 Hz), 4.70 (2H, d, *J* = 2.2 Hz), 4.04 (1H, t, *J* = 6.3 Hz), 3.78 (2H, t, *J* = 4.9 Hz), 3.62 (1H, dq, *J* = 6.3, 6.2 Hz), 3.52 (2H, t, *J* = 4.9 Hz), 3.38 (3H, s), 2.76 (1H, dd, *J* = 6.9, 16 Hz), 2.55 (1H, dd, *J* = 6.3, 16 Hz), 2.52 (1H, d, *J* = 6.6 Hz), 2.49 (1H, d, *J* = 7.7 Hz), 2.09 (3H, s), 1.33 (3H, d, *J* = 6.3 Hz), 1.14 (3H, d, *J* = 6.3 Hz), 0.86 (9H, s), 0.04 (3H, s), 0.02 ppm (3H, s); $^{13}$C NMR ($CDCl_3$): $\delta$ = 169.0, 164.9, 156.0, 148.9, 145.7, 139.7, 135.8, 133.1, 126.6, 124.3, 123.2, 121.1, 118.8, 93.9, 79.8, 78.4, 71.6, 70.5, 67.4, 67.2, 59.0, 41.0, 37.5, 25.8, 21.1, 19.9, 18.1, 14.4, 14.2, −4.5, −4.7 ppm; IR (neat): $\tilde{\nu}$ = 1723, 1659 $cm^{-1}$; MS (EI): *m/z* 605 [$M^+$]; HRMS (EI): calcd for $C_{32}H_{51}NO_8Si$: 605.3384 [$M^+$]; found: 605.3392; $[\alpha]_D^{26}$ = −7.14 (*c* = 1.00 in $CHCl_3$).

**Synthesis of compound 35**: In accordance with procedure 6-b, TBS ether **34** (98 mg, 0.16 mmol) gave alcohol **35** (66 mg, 84%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 8.56 (1H, d, *J* = 4.7 Hz), 7.64 (1H, dd, *J* = 7.7, 8.8 Hz), 7.20 (1H, d, *J* = 8.8 Hz), 7.09 (1H, dd, *J* = 4.7, 7.7 Hz), 6.79 (1H, dd, *J* = 6.0, 16 Hz), 6.50 (1H, s), 5.97 (1H, d, *J* = 16 Hz), 5.72 (1H, m), 5.35 (1H, dd, *J* = 5.8, 7.4 Hz), 5.34–5.31 (1H, m), 5.09 (1H, d, *J* = 17 Hz), 5.05 (1H, d, *J* = 10 Hz), 4.72 (1H, d, *J* = 7.1 Hz), 4.65 (1H, d, *J* = 7.1 Hz), 4.14 (1H, dd, *J* = 1.6, 6.0 Hz), 3.87–3.78 (2H, m), 3.66–3.60 (1H, m), 3.54–3.51 (2H, m), 3.36 (3H, s), 3.10–2.90 (1H, br), 2.72 (1H, dd, *J* = 7.4, 16 Hz), 2.56 (1H, dd, *J* = 5.8, 16 Hz), 2.49 (1H, d, *J* = 5.8 Hz), 2.47 (1H, d, *J* = 7.4 Hz), 2.05 (3H, s), 1.31 (3H, d, *J* = 6.3 Hz), 1.11 ppm (3H, d, *J* = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 168.9, 164.7, 155.7, 148.7, 144.0, 139.7, 135.8, 132.9, 126.3, 124.2, 123.5, 121.1, 117.7, 94.1, 80.6, 78.3, 71.5, 68.7, 67.3, 58.8, 41.0, 37.4, 29.6, 19.8, 17.8, 14.3 ppm; IR (neat): $\tilde{\nu}$ = 3449, 1719, 1656 $cm^{-1}$; MS (EI): *m/z* 491 [$M^+$]; HRMS (EI): calcd for $C_{26}H_{37}NO_8$: 491.2519 [$M^+$]; found: 491.2543; $[\alpha]_D^{28}$ = −17.7 (*c* = 1.00 in $CHCl_3$).

**Synthesis of compound 36**: In accordance with procedure 7, alcohol **35** (127 mg, 0.26 mmol) gave compound **36** (98 mg, 69%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 8.59 (1H, d, *J* = 4.0 Hz), 7.63 (1H, dd, *J* = 7.7, 8.0 Hz), 7.21 (1H, d, *J* = 8.0 Hz), 7.10 (1H, dd, *J* = 4.0, 7.7 Hz), 6.81 (1H, dd, *J* = 6.3, 14 Hz), 6.52 (1H, s), 6.40 (1H, dd, *J* = 1.4, 17 Hz), 6.10 (1H, dd, *J* = 10, 17 Hz), 6.04 (1H, d, *J* = 16 Hz), 5.83 (1H, dd, *J* = 1.4, 10 Hz), 5.76–5.72 (1H, m), 5.37 (1H, dd, *J* = 5.9, 7.3 Hz), 5.38–5.35 (1H, m), 5.12 (1H, d, *J* = 17 Hz), 5.07 (1H, d, *J* = 10 Hz), 4.75–4.67 (2H, m), 4.37 (1H, dd, *J* = 1.2, 6.3 Hz), 3.79–3.74 (2H, m), 3.66–3.55 (1H, m), 3.53–3.38 (2H, m), 3.37 (3H, s), 2.76 (1H, dd, *J* = 7.3, 16 Hz), 2.57 (1H, dd, *J* = 5.9,

16 Hz), 2.52 (1H, d, $J$=7.4 Hz), 2.30 (1H, d, $J$=8.2 Hz), 2.08 (3H, s), 1.34 (3H, d, $J$=6.0 Hz), 1.24 ppm (3H, d, $J$=6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$=169.0, 165.2, 164.7, 148.9, 143.3, 135.9, 133.1, 132.9, 130.9, 128.3, 126.6, 124.4, 124.1, 124.0, 121.2, 117.9, 93.8, 78.5, 71.6, 71.4, 67.7, 67.2, 59.0, 41.0, 37.6, 29.8, 20.0, 15.0, 14.5 ppm; IR (neat): $\tilde{\nu}$=1725, 1659 cm$^{-1}$; MS (EI): $m/z$ 545 [$M^+$]; HRMS (EI): calcd for $C_{29}H_{39}NO_9$: 545.2625 [$M^+$]; found: 545.2646; $[\alpha]_D^{28}=-6.16$ ($c$=0.75 in $CHCl_3$).

**Synthesis of compound 37**: In accordance with procedure 3, compound **36** (49 mg, 0.09 mmol) gave compound **37** (38 mg, 82%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$=8.59 (1H, d, $J$=4.7 Hz), 7.64 (1H, dd, $J$=7.4, 8.0 Hz), 7.20 (1H, d, $J$=8.0 Hz), 7.12 (1H, dd, $J$=4.7, 7.4 Hz), 6.88 (1H, dd, $J$=7.4, 15 Hz), 6.74 (1H, dd, $J$=7.1, 14 Hz), 6.59 (1H, s), 5.96 (1H, d, $J$=16 Hz), 5.84 (1H, d, $J$=15 Hz), 5.47 (1H, q, $J$=9.3 Hz), 5.44–5.30 (1H, m), 4.93 (1H, dq, $J$=6.3, 14 Hz), 4.73 (2H, dd, $J$=7.1, 12 Hz), 4.11 (1H, dd, $J$=7.1, 14 Hz), 3.82–3.62 (2H, m), 3.56–3.38 (2H, m), 3.38 (3H, s), 2.73–2.55 (2H, m), 2.63–2.50 (2H, m), 2.13 (3H, s), 1.39 (3H, d, $J$=6.0 Hz), 1.32 ppm (3H, d, $J$=6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$=169.4, 164.4, 164.1, 155.6, 148.8, 144.7, 144.4, 139.9, 136.1, 126.0, 124.3, 124.0, 123.7, 121.4, 93.9, 78.7, 71.5, 70.3, 67.8, 67.3, 58.9, 41.3, 36.9, 29.7, 20.0, 17.9, 14.6 ppm; IR (neat): $\tilde{\nu}$=1724, 1659 cm$^{-1}$; MS (EI): $m/z$ 517 [$M^+$]; HRMS (EI): calcd for $C_{27}H_{35}NO_9$: 517.2312 [$M^+$]; found: 517.2311; $[\alpha]_D^{25}=+29.6$ ($c$=0.75 in $CHCl_3$).

**Synthesis of MSp-1**: In accordance with procedure 5-a, MEM ether **37** (23 mg, 0.04 mmol) gave **MSp-1** (18 mg, 95%) as a pale yellow oil: $^1$H NMR ($CDCl_3$): $\delta$=8.59 (1H, d, $J$=3.6 Hz), 7.65 (1H, dd, $J$=7.7, 8.8 Hz), 7.21 (1H, d, $J$=8.8 Hz), 7.12 (1H, dd, $J$=3.6, 7.7 Hz), 6.87 (1H, dd, $J$=7.0, 10 Hz), 6.87 (1H, dd, $J$=4.9, 16 Hz), 6.58 (1H, s), 6.02 (1H, d, $J$=16 Hz), 5.86 (1H, d, $J$=10 Hz), 5.47 (1H, d, $J$=10 Hz), 5.50–5.42 (1H, m), 4.91–4.87 (1H, m), 4.18 (1H, dd, $J$=4.9, 5.2 Hz), 2.67 (2H, dd, $J$=7.0, 10 Hz), 2.54 (1H, d, $J$=16 Hz), 2.54 (1H, d, $J$=2.5 Hz), 2.11 (3H, s), 1.43 (3H, d, $J$=6.3 Hz), 1.32 ppm (3H, d, $J$=6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$=169.4, 165.5, 164.4, 155.7, 149.0, 145.3, 144.7, 139.8, 136.0, 126.4, 124.4, 123.7, 122.7, 121.4, 74.7, 74.1, 67.7, 41.2, 36.8, 29.8, 20.0, 18.1, 14.6 ppm; IR (neat): $\tilde{\nu}$=3448, 1720, 1659 cm$^{-1}$; MS (EI): $m/z$ 429 [$M^+$]; HRMS (EI): calcd for $C_{23}H_{27}NO_7$: 429.1788 [$M^+$]; found: 429.1741; $[\alpha]_D^{25}=+38.8$ ($c$=1.30 in $CHCl_3$).

**Synthesis of MSp-2**: In accordance with procedure 4-b, **MSp-1** (10 mg, 0.02 mmol) gave **MSp-2** (9 mg, 92%) as a pale yellow oil: $^1$H NMR ($CDCl_3$): $\delta$=8.61 (1H, d, $J$=4.7 Hz), 7.66 (1H, dd, $J$=7.7, 9.6 Hz), 7.23 (1H, d, $J$=16 Hz), 7.21 (1H, d, $J$=7.2 Hz), 7.13 (1H, dd, $J$=4.7, 7.7 Hz), 7.00 (1H, dd, $J$=8.7, 16 Hz), 6.68 (1H, d, $J$=16 Hz), 6.59 (1H, s), 6.03 (1H, d, $J$=16 Hz), 5.53 (1H, d, $J$=8.7 Hz), 5.39 (2H, tq, $J$=2.3, 6.3 Hz), 5.15 (1H, q, $J$=7.1 Hz), 2.84–2.65 (2H, m), 2.59 (2H, d, $J$=2.3 Hz), 2.13 (3H, s), 1.51 (3H, d, $J$=7.1 Hz), 1.35 ppm (3H, d, $J$=6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$=197.9, 169.0, 164.9, 163.4, 155.6, 149.0, 146.0, 139.5, 136.1, 132.7, 132.3, 126.7, 124.4, 123.1, 121.5, 75.5, 68.8, 40.8, 37.0, 29.8, 19.7, 16.9, 14.6 ppm; IR (neat): $\tilde{\nu}$=1725, 1656 cm$^{-1}$; MS (EI): $m/z$ 427 [$M^+$]; HRMS (EI): calcd for $C_{23}H_{25}NO_7$: 427.1631 [$M^+$]; found: 427.1654; $[\alpha]_D^{24}=+23.9$ ($c$=0.80 in $CHCl_3$).

**Synthesis of compound 39**: *tert*-Butylchlorodiphenylsilane (3.68 mL, 14.4 mmol) was added to a solution of alcohol **38** (2.60 g, 12.0 mmol), imidazole (1.23 g, 18.0 mmol), and DMAP (440 mg, 3.6 mmol) in anhydrous DMF (36 mL), and the reaction mixture was stirred at 50°C for 24 h. The mixture was diluted with $H_2O$, and the aqueous mixture was extracted with $Et_2O$. The organic layer was washed successively with 10% HCl, saturated $NaHCO_3$, and brine, then dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by chromatography on silica gel to afford TBDPS ether **39** (3.91 g, 72%) as a colorless oil (recovered starting material: 621 mg, 24%): $^1$H NMR ($CDCl_3$): $\delta$=7.70–7.62 (4H, m), 7.41–7.29 (6H, m), 5.73 (1H, ddd, $J$=7.6, 10, 17 Hz), 4.87 (1H, d, $J$=10 Hz), 4.71 (1H, dd, $J$=1.2, 17 Hz), 3.91–3.88 (1H, m), 3.76–3.71 (1H, m), 1.06 (3H, d, $J$=6.6 Hz), 1.04 (9H, s), 0.82 (9H, s), −0.01 ppm (6H, s); $^{13}$C NMR ($CDCl_3$): $\delta$=138.1, 136.2, 136.1, 134.4, 134.2, 129.4, 129.4, 127.2, 127.2, 116.2, 80.4, 72.5, 27.1, 25.9, 19.5, 19.4, 18.1, −4.5, −4.6 ppm; IR (neat): $\tilde{\nu}$=1590 cm$^{-1}$; MS (EI): $m/z$ 454 [$M^+$]; HRMS (EI): calcd for $C_{27}H_{42}O_2Si_2$: 454.2723 [$M^+$]; found: 454.2760; $[\alpha]_D^{25}=+2.17$ ($c$=1.15 in $CHCl_3$).

**Synthesis of compound 40**: In accordance with procedure 6-c, TBS ether **39** (1.59 g, 3.50 mmol) gave alcohol **40** (987 mg, 83%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$=7.69–7.63 (4H, m), 7.44–7.36 (6H, m), 5.81 (1H, ddd, $J$=7.3, 10, 17 Hz), 5.07 (1H, d, $J$=10 Hz), 4.94 (1H, dd, $J$=17, 1.0 Hz), 4.04–4.01 (1H, m), 3.78–3.70 (1H, m), 2.17 (1H, br), 1.07 (9H, s), 1.01 ppm (3H, d, $J$=6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$=136.0, 135.8, 134.8, 133.7, 133.5, 129.8, 129.7, 127.7, 127.5, 117.8, 79.0, 70.5, 27.1, 19.4, 17.5 ppm; IR (neat): $\tilde{\nu}$=3444, 1589 cm$^{-1}$; MS (EI): $m/z$ 283 [$M^+$−57]; HRMS (EI): calcd for $C_{17}H_{19}O_2Si$: 283.1154 [$M^+$−57]; found: 283.1144; $[\alpha]_D^{28}=+2.52$ ($c$=0.90 in $CHCl_3$).

**Synthesis of compound 42**: A mixture of olefin **41** (2.86 g, 7.6 mmol) and 10% Pd/C (456 mg) in THF (23 mL) was vigorously stirred under an $H_2$ atmosphere at room temperature for 3 h. The catalyst was removed by filtration through a celite pad, and the filtrate was concentrated in vacuo to afford almost pure compound **42** (2.85 g, 99%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$=4.79 (1H, d, $J$=6.9 Hz), 4.72 (1H, d, $J$=6.9 Hz), 4.09 (2H, q, $J$=7.1 Hz), 3.80–3.61 (3H, m), 3.67 (2H, t, $J$=4.8 Hz), 3.46–3.41 (1H, m), 3.35 (3H, s), 2.43–2.34 (2H, m), 1.81–1.72 (2H, m), 1.22 (3H, t, $J$=7.1 Hz), 1.09 (3H, d, $J$=6.6 Hz), 0.84 (9H, s), 0.01 ppm (6H, s); $^{13}$C NMR ($CDCl_3$): $\delta$=173.6, 95.3, 80.9, 71.7, 70.1, 67.3, 60.1, 58.9, 30.5, 25.7, 25.7, 19.0, 17.9, 14.2, −4.6, −4.9 ppm; IR (neat): $\tilde{\nu}$=1736 cm$^{-1}$; MS (EI): $m/z$ 333 [$M^+$−45]; HRMS (EI): calcd for $C_{16}H_{33}O_5Si$: 333.2097 [$M^+$−45]; found: 333.2081; $[\alpha]_D^{27}=+36.3$ ($c$=5.96 in EtOH).

**Synthesis of compound 43**: 1M NaOH (30 mL, 30 mmol) was added to a solution of ester **42** (2.84 g, 7.5 mmol) in MeOH/THF (3:1, 60 mL) at 0°C. The reaction mixture was stirred at room temperature for 2 h, and the organic solvents were evaporated off. The resulting aqueous mixture was acidified with 10% HCl (pH 4) and extracted with $CH_2Cl_2$. The organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent gave carboxylic acid **43** (2.61 g, 99%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$=4.83 (1H, d, $J$=6.9 Hz), 4.74 (1H, d, $J$=6.9 Hz), 3.83–3.77 (2H, m), 3.70–3.66 (1H, m), 3.56 (2H, t, $J$=4.5 Hz), 3.50–3.47 (1H, m), 3.39 (3H, s), 2.53–2.46 (2H, m), 1.83–1.76 (2H, m), 1.12 (3H, d, $J$=6.3 Hz), 0.87 (9H, s), 0.04 ppm (6H, s); $^{13}$C NMR ($CDCl_3$): $\delta$=179.2, 95.4, 81.0, 71.8, 70.1, 67.4, 59.0, 30.3, 25.8, 25.4, 19.1, 18.0, −4.5, −4.9 ppm; IR (neat): $\tilde{\nu}$=1712 cm$^{-1}$; MS (EI): $m/z$ 293 [$M^+$−57]; HRMS (EI): calcd for $C_{12}H_{25}O_6Si$: 293.1421 [$M^+$−57]; found: 293.1416; $[\alpha]_D^{26}=+37.8$ ($c$=2.065 in EtOH).

**Synthesis of compound 44**: In accordance with procedure 1-b, alcohol **40** (987 mg, 2.90 mmol) and carboxylic acid **43** (1.22 g, 3.48 mmol) gave ester **44** (1.82 g, 93%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$=7.71–7.62 (4H, m), 7.42–7.34 (6H, m), 5.76 (1H, ddd, $J$=7.3, 10, 17 Hz), 5.02–4.88 (1H, m), 4.99 (1H, dd, $J$=1.5, 10 Hz), 4.92 (1H, dd, $J$=1.5, 17 Hz), 4.83 (1H, d, $J$=6.9 Hz), 4.74 (1H, d, $J$=6.9 Hz), 4.18–4.14 (1H, m), 3.81–3.65 (3H, m), 3.53 (2H, t, $J$=4.3 Hz), 3.47–3.39 (1H, m), 3.37 (3H, s), 2.46–2.16 (2H, m), 1.79–1.71 (2H, m), 1.17 (3H, d, $J$=6.6 Hz), 1.12 (3H, d, $J$=6.3 Hz), 1.07 (9H, s), 0.88 (9H, s), 0.05 ppm (6H, s); $^{13}$C NMR ($CDCl_3$): $\delta$=173.0, 136.7, 136.0, 129.6, 129.5, 127.4, 127.3, 127.3, 117.3, 95.3, 80.9, 77.0, 73.2, 71.8, 70.2, 67.3, 59.0, 30.8, 27.0, 25.8, 25.7, 19.4, 19.1, 18.0, 14.7, −4.5, −4.8 ppm; IR (neat): $\tilde{\nu}$=1735 cm$^{-1}$; MS (EI): $m/z$ 615 [$M^+$−57]; HRMS (EI): calcd for $C_{33}H_{51}O_7Si_2$: 615.3173 [$M^+$−57]; found: 615.3136; $[\alpha]_D^{25}=+13.8$ ($c$=4.11 in $CHCl_3$).

**Synthesis of compound 45**: In accordance with procedure 6-c, TBS ether **44** (673 mg, 1.0 mmol) gave alcohol **45** (358 mg, 61%) as a colorless oil (recovered starting material: 92 mg, 14%): $^1$H NMR ($CDCl_3$): $\delta$=7.70–7.61 (4H, m), 7.45–7.31 (6H, m), 5.75 (1H, ddd, $J$=6.9, 10, 17 Hz), 5.04–4.99 (1H, m), 4.98–4.90 (1H, m), 4.93–4.82 (1H, m), 4.80 (1H, d, $J$=6.9 Hz), 4.68 (1H, d, $J$=6.9 Hz), 4.19–4.15 (1H, m), 3.87–3.63 (3H, m), 3.55 (2H, t, $J$=4.5 Hz), 3.52–3.43 (1H, m), 3.38 (3H, s), 2.41–2.10 (2H, m), 2.19–2.10 (1H, br), 1.79–1.65 (2H, m), 1.17 (3H, d, $J$=6.3 Hz), 1.13 (3H, d, $J$=6.6 Hz), 1.06 ppm (9H, s); $^{13}$C NMR ($CDCl_3$): $\delta$=172.7, 136.5, 135.8, 135.8, 133.6, 133.5, 129.5, 129.4, 127.3, 127.2, 117.2, 96.1, 83.7, 76.7, 73.1, 71.5, 68.3, 67.4, 58.7, 30.5, 26.8, 25.1, 19.3, 17.3, 14.4 ppm; IR (neat): $\tilde{\nu}$=3446, 1733, 1641 cm$^{-1}$; MS (EI): $m/z$ 501 [$M^+$−57]; HRMS (EI): calcd for $C_{27}H_{37}O_7Si$: 501.2309 [$M^+$−57]; found: 501.2304; $[\alpha]_D^{24}=-7.96$ ($c$=0.845 in $CHCl_3$).

**Synthesis of compound 46**: In accordance with procedure 1-b, alcohol **45** (808 mg, 1.45 mmol) and carboxylic acid ent-**6** (442 mg, 2.03 mmol) gave

ester **46** (1.06 g, 96%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.70–7.61 (4H, m), 7.45–7.31 (6H, m), 5.75 (1H, ddd, $J$ = 6.9, 10, 17 Hz), 5.02–4.88 (4H, m), 4.80 (1H, d, $J$ = 6.9 Hz), 4.69 (1H, d, $J$ = 6.9 Hz), 4.28–4.23 (1H, m), 4.19–4.15 (1H, m), 3.71–3.67 (2H, m), 3.64–3.58 (1H, m), 3.54–3.49 (2H, m), 3.37 (3H, s), 2.53–2.12 (4H, m), 1.79–1.73 (2H, m), 1.19 (3H, d, $J$ = 6.6 Hz), 1.19 (3H, d, $J$ = 5.9 Hz), 1.17 (3H, d, $J$ = 6.3 Hz), 1.07 (9H, s), 0.87 (9H, s), 0.08 (3H, s), 0.00 ppm (3H, s); $^{13}$C NMR ($CDCl_3$): $\delta$ = 172.5, 170.9, 136.6, 135.97, 135.95, 133.8, 133.6, 129.6, 129.5, 127.4, 127.3, 117.3, 95.0, 77.9, 77.2, 73.3, 71.6, 71.2, 67.3, 65.6, 58.9, 44.9, 30.5, 26.9, 25.7, 25.5, 23.8, 19.4, 17.9, 15.1, 14.5, −4.6, −5.0 ppm; IR (neat): $\tilde{\nu}$ = 1737 cm$^{-1}$; MS (EI): $m/z$ 701 [$M^+$−57]; HRMS (EI): calcd for $C_{37}H_{57}O_9Si_2$: 701.3541 [$M^+$−57]; found: 701.3494; $[\alpha]_D^{25}$ = +0.49 ($c$ = 0.75 in $CHCl_3$).

**Synthesis of compound 47**: In accordance with procedure 6-c, TBS ether **46** (228 mg, 0.30 mmol) gave alcohol **47** (179 mg, 93%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.69–7.60 (4H, m), 7.40–7.29 (6H, m), 5.75 (1H, ddd, $J$ = 6.9, 10, 17 Hz), 5.10–4.87 (4H, m), 4.80 (1H, d, $J$ = 6.9 Hz), 4.66 (1H, d, $J$ = 6.9 Hz), 4.21–4.15 (2H, m), 3.69–3.61 (3H, m), 3.54–3.49 (2H, m), 3.35 (3H, s), 3.05 (1H, br), 2.53–2.14 (4H, m), 1.81–1.73 (2H, m), 1.20 (3H, d, $J$ = 6.6 Hz), 1.20 (3H, d, $J$ = 6.6 Hz), 1.16 (3H, d, $J$ = 6.6 Hz), 1.05 ppm (9H, s); $^{13}$C NMR ($CDCl_3$): $\delta$ = 172.5, 171.7, 136.5, 135.9, 133.7, 129.6, 129.5, 127.3, 127.2, 117.2, 94.9, 77.8, 77.2, 73.3, 71.5, 71.4, 67.3, 64.1, 58.9, 43.4, 30.4, 26.9, 25.1, 22.3, 19.3, 15.0, 14.4 ppm; IR (neat): $\tilde{\nu}$ = 3482, 1733 cm$^{-1}$; MS (EI): $m/z$ 587 [$M^+$−57]; HRMS (EI): calcd for $C_{31}H_{43}O_9Si$: 587.2676 [$M^+$−57]; found: 587.2703; $[\alpha]_D^{24}$ = −2.68 ($c$ = 0.99 in $CHCl_3$).

**Synthesis of compound 48**: In accordance with procedure 7, alcohol **47** (387 mg, 0.60 mmol) gave compound **48** (385 mg, 92%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.70–7.61 (4H, m), 7.42–7.31 (6H, m), 6.38 (1H, dd, $J$ = 1.5, 17 Hz), 6.07 (1H, dd, $J$ = 10, 17 Hz), 5.80 (1H, dd, $J$ = 1.5, 10 Hz), 5.75 (1H, ddd, $J$ = 6.9, 10, 17 Hz), 5.35–5.30 (1H, m), 5.06–4.88 (4H, m), 4.78 (1H, d, $J$ = 6.9 Hz), 4.67 (1H, d, $J$ = 6.9 Hz), 4.18–4.14 (1H, m), 3.68 (2H, t, $J$ = 4.8 Hz), 3.62–3.50 (3H, m), 3.37 (3H, s), 2.73–2.13 (4H, m), 1.80–1.75 (2H, m), 1.33 (3H, d, $J$ = 6.3 Hz), 1.17 (3H, d, $J$ = 6.6 Hz), 1.17 (3H, d, $J$ = 6.3 Hz), 1.06 ppm (9H, s); $^{13}$C NMR ($CDCl_3$): $\delta$ = 172.5, 169.5, 165.1, 136.6, 135.9, 133.8, 133.6, 130.6, 129.6, 129.5, 128.5, 127.4, 127.3, 117.3, 95.0, 77.8, 76.8, 73.3, 71.6, 71.5, 67.5, 67.3, 58.9, 41.0, 30.4, 26.9, 25.2, 19.8, 19.4, 15.1, 14.5 ppm; IR (neat): $\tilde{\nu}$ = 1731 cm$^{-1}$; MS (EI): $m/z$ 641 [$M^+$−57]; HRMS (EI): calcd for $C_{34}H_{45}O_{10}Si$: 641.2782 [$M^+$−57]; found: 641.2758; $[\alpha]_D^{25}$ = +6.27 ($c$ = 0.765 in $CHCl_3$).

**Synthesis of compound 49**: In accordance with procedure 6-b, TBDPS ether **48** (1.57 g, 2.25 mmol) gave alcohol **49** (769 mg, 74%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 6.37 (1H, dd, $J$ = 1.5, 17 Hz), 6.06 (1H, dd, $J$ = 10, 17 Hz), 5.83 (1H, ddd, $J$ = 6.9, 11, 19 Hz), 5.80 (1H, dd, $J$ = 1.5, 10 Hz), 5.35–5.30 (1H, m), 5.34 (1H, dd, $J$ = 1.6, 19 Hz), 5.23 (1H, dd, $J$ = 1.6, 11 Hz), 5.08 (1H, dq, $J$ = 3.0, 6.6 Hz), 4.98 (1H, dq, $J$ = 3.0, 6.6 Hz), 4.77 (1H, d, $J$ = 7.3 Hz), 4.67 (1H, d, $J$ = 7.3 Hz), 4.24–4.21 (1H, m), 3.73–3.62 (3H, m), 3.54 (2H, t, $J$ = 4.5 Hz), 3.37 (3H, s), 2.69 (1H, dd, $J$ = 7.6, 16 Hz), 2.54 (1H, dd, $J$ = 5.6, 16 Hz), 2.43 (2H, t, $J$ = 7.4 Hz), 2.29 (1H, br), 1.85 (2H, q, $J$ = 6.8 Hz), 1.32 (3H, d, $J$ = 6.3 Hz), 1.18 (3H, d, $J$ = 6.6 Hz), 1.18 ppm (3H, d, $J$ = 7.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 172.9, 169.6, 165.3, 135.8, 130.7, 128.5, 117.1, 95.2, 78.1, 74.2, 73.4, 71.7, 71.4, 67.6, 67.6, 59.0, 40.1, 30.7, 25.1, 19.9, 15.3, 14.1 ppm; IR (neat): $\tilde{\nu}$ = 3475, 1730 cm$^{-1}$; MS (EI): $m/z$ 385 [$M^+$−75]; HRMS (EI): calcd for $C_{19}H_{29}O_8$: 385.1862 [$M^+$−75]; found: 385.1861; $[\alpha]_D^{27}$ = +15.4 ($c$ = 0.125 in EtOH).

**Synthesis of compound 50**: In accordance with procedure 3, compound **49** (368 mg, 0.80 mmol) gave compound **50** (336 mg, 97%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.08 (1H, dd, $J$ = 4.0, 16 Hz), 6.12 (1H, d, $J$ = 16 Hz), 5.35–5.25 (1H, m), 5.14–5.06 (2H, m), 4.78 (1H, d, $J$ = 6.9 Hz), 4.72 (1H, d, $J$ = 6.9 Hz), 4.30 (1H, br), 3.72 (2H, t, $J$ = 4.6 Hz), 3.68–3.52 (1H, m), 3.54 (2H, t, $J$ = 4.6 Hz), 3.38 (3H, s), 2.77–2.29 (4H, m), 1.78 (2H, q, $J$ = 6.8 Hz), 1.39 (3H, d, $J$ = 5.6 Hz), 1.37 (3H, d, $J$ = 6.6 Hz), 1.19 ppm (3H, d, $J$ = 6.6 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 175.2, 169.3, 165.3, 145.3, 122.7, 95.6, 80.1, 76.2, 75.4, 71.8, 71.7, 67.6, 67.2, 59.0, 40.8, 32.1, 26.4, 19.5, 17.8, 16.0 ppm; IR (neat): $\tilde{\nu}$ = 3421, 1716 cm$^{-1}$; MS (EI): $m/z$ 357 [$M^+$−75]; HRMS (EI): calcd for $C_{17}H_{25}O_8$: 357.1549 [$M^+$−75]; found: 357.1563; $[\alpha]_D^{27}$ = −0.11 ($c$ = 1.055 in $CHCl_3$).

**Synthesis of MSD-1 (macrosphelide I)**: In accordance with procedure 5-a, compound **50** (95 mg, 0.22 mmol) gave **MSD-1** (49 mg, 65%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.20 (1H, dd, $J$ = 3.0, 16 Hz), 6.21 (1H, dd, $J$ = 2.0, 16 Hz), 5.70–5.57 (1H, m), 4.87–4.80 (2H, m), 4.28 (1H, br), 3.92–3.60 (1H, br), 3.24 (1H, d, $J$ = 12 Hz), 2.74–2.52 (3H, m), 2.52–2.32 (1H, br), 2.34 (1H, dt, $J$ = 4.6, 15 Hz), 1.75–1.65 (2H, m), 1.44 (3H, d, $J$ = 6.6 Hz), 1.30 (3H, d, $J$ = 6.3 Hz), 1.17 ppm (3H, d, $J$ = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 175.1, 168.6, 166.8, 147.8, 121.8, 77.9, 74.7, 74.4, 71.2, 67.0, 41.7, 30.4, 27.6, 19.9, 18.5, 12.7 ppm; IR (neat): $\tilde{\nu}$ = 3487, 1716 cm$^{-1}$; $[\alpha]_D^{24}$ = +12.6 ($c$ = 0.205 in EtOH; literature value:[6d] $[\alpha]_D$ = +10.3 ($c$ = 0.310, EtOH)).

**Synthesis of MSD-2 (macrosphelide L)**: Trichloroacetyl chloride (42 μL, 0.375 mmol) was added to a solution of **50** (54 mg, 0.125 mmol) and $Et_3N$ (63 μL, 0.45 mmol) in $CH_2Cl_2$ (1.3 mL) at 0 °C. After stirring of the mixture at room temperature for 1 h, TFA (1.3 mL) was added, and the mixture was stirred for an additional 3 h. Evaporation of the solvent left a residue, which was purified by chromatography on silica gel to afford the 8-trichloroacetoxy-14-hydroxy derivative (51 mg, 83%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.10 (1H, dd, $J$ = 5.1, 16 Hz), 6.12 (1H, dd, $J$ = 1.3, 16 Hz), 5.75–5.67 (1H, m), 5.40 (1H, ddd, $J$ = 1.3, 5.1, 6.3 Hz), 5.10 (1H, dq, $J$ = 6.3, 8.2 Hz), 4.83 (1H, dq, $J$ = 2.1, 6.3 Hz), 3.19 (1H, dt, $J$ = 2.0, 11 Hz), 2.73–2.55 (3H, m), 2.43 (1H, br), 2.38 (1H, dt, $J$ = 4.6, 15 Hz), 1.79–1.68 (1H, m), 1.57–1.46 (1H, m), 1.40 (3H, d, $J$ = 6.3 Hz), 1.32 (3H, d, $J$ = 6.3 Hz), 1.16 ppm (3H, d, $J$ = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 172.3, 168.5, 166.0, 160.5, 142.2, 123.2, 78.3, 77.2, 74.6, 71.3, 71.1, 67.5, 41.7, 30.8, 28.3, 20.0, 18.2, 12.5 ppm; IR (neat): $\tilde{\nu}$ = 3523, 1732 cm$^{-1}$; MS (EI): $m/z$ 488 [$M^+$]; HRMS (EI): calcd for $C_{18}H_{23}Cl_3O_9$: 488.0408 [$M^+$]; found: 488.0427; $[\alpha]_D^{24}$ = −14.9 ($c$ = 0.66 in $CHCl_3$). This compound (49 mg, 0.1 mmol) was dissolved in $CH_2Cl_2$ (1 mL), and DMP (85 mg, 0.2 mmol) was added at room temperature. After stirring of the mixture for 2 h, MeOH/saturated $NaHCO_3$ (1:1, 10 mL) was added. The resulting mixture was stirred for an additional 1 h and extracted with $CH_2Cl_2$. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was purified by chromatography on silica gel to afford **MSD-2** (25 mg, 74%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 6.95 (1H, dd, $J$ = 4.3, 16 Hz), 6.10 (1H, dd, $J$ = 1.7, 16 Hz), 5.48–5.40 (1H, m), 5.17 (1H, q, $J$ = 7.3 Hz), 4.98 (1H, dq, $J$ = 2.7, 6.9 Hz), 4.29–4.24 (1H, br), 3.26 (1H, dt, $J$ = 2.0, 12 Hz), 2.81–2.35 (6H, m), 1.39 (3H, d, $J$ = 6.9 Hz), 1.38 (3H, d, $J$ = 6.3 Hz), 1.37 ppm (3H, d, $J$ = 7.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 205.2, 174.2, 169.2, 165.5, 144.9, 122.9, 76.2, 75.2, 75.0, 67.6, 41.2, 33.8, 28.5, 20.0, 17.9, 16.3 ppm; IR (neat): $\tilde{\nu}$ = 3453, 1729 cm$^{-1}$; $[\alpha]_D^{25}$ = −23.5 ($c$ = 0.05 in EtOH; literature value:[18] $[\alpha]_D^{21}$ = −24.2 ($c$ = 0.33 in EtOH)).

**Synthesis of MSD-3**: In accordance with procedure 4-b, **MSD-1** (14 mg, 0.04 mmol) gave **MSD-3** (11 mg, 81%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.14 (1H, d, $J$ = 16 Hz), 6.55 (1H, d, $J$ = 16 Hz), 5.44–5.33 (1H, m), 5.28 (1H, q, $J$ = 6.9 Hz), 5.23 (1H, q, $J$ = 7.3 Hz), 3.08–2.95 (1H, m), 2.77–2.54 (4H, m), 2.48–2.38 (1H, m), 1.43 (3H, d, $J$ = 6.9 Hz), 1.42 (3H, d, $J$ = 6.3 Hz), 1.40 ppm (3H, d, $J$ = 7.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 204.5, 197.6, 171.9, 169.0, 164.9, 136.0, 132.0, 74.3, 73.9, 69.3, 41.1, 33.8, 27.7, 19.9, 16.1, 15.3 ppm; IR (neat): $\tilde{\nu}$ = 1733 cm$^{-1}$; MS (EI): $m/z$ 340 [$M^+$]; HRMS (EI): calcd for $C_{16}H_{20}O_8$: 340.1158 [$M^+$]; found: 340.1192; $[\alpha]_D^{25}$ = −83.7 ($c$ = 0.55 in $CHCl_3$).

**Synthesis of MSD-4**: In accordance with procedure 4-a, compound **50** (26 mg, 0.059 mmol) gave the corresponding ketone (19 mg, 73%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.39 (1H, d, $J$ = 16 Hz), 6.66 (1H, d, $J$ = 16 Hz), 5.42–5.28 (1H, m), 5.23–5.14 (2H, m), 4.71 (2H, s), 3.70 (2H, t, $J$ = 4.6 Hz), 3.61–3.47 (2H, m), 3.44–3.38 (1H, m), 3.37 (3H, s), 2.77 (1H, dd, $J$ = 4.0, 14 Hz), 2.67–2.34 (3H, m), 1.96–1.88 (2H, m), 1.45 (3H, d, $J$ = 6.6 Hz), 1.40 (3H, d, $J$ = 6.6 Hz), 1.21 ppm (3H, d, $J$ = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 197.7, 172.4, 169.1, 164.4, 135.6, 131.9, 95.9, 80.6, 74.9, 72.2, 71.7, 68.4, 67.6, 59.0, 40.6, 32.0, 26.1, 18.8, 15.7, 15.6 ppm; IR (neat): $\tilde{\nu}$ = 1733 cm$^{-1}$; MS (EI): $m/z$ 355 [$M^+$−75]; HRMS (EI): calcd for $C_{17}H_{23}O_8$: 355.1393 [$M^+$−75]; found: 355.1380; $[\alpha]_D^{28}$ = −11.6 ($c$ = 0.925 in $CHCl_3$). This MEM ether (30 mg, 0.07 mmol) was allowed to react with TFA in accordance with procedure 5-a to afford **MSD-4** (16 mg, 68%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.55 (1H, d, $J$ = 16 Hz), 6.68 (1H, d, $J$ = 16 Hz), 5.84–5.72 (1H, m), 4.96 (1H, q, $J$ = 7.3 Hz), 4.83 (1H, dq, $J$ = 2.0, 6.6 Hz), 3.26 (1H, dt, $J$ = 2.0, 12 Hz), 2.90–2.78 (1H, m), 2.72–2.61 (2H, m), 2.41 (1H, dt, $J$ = 4.3, 16 Hz), 2.36 (1H, br), 1.84–1.72 (1H, m), 1.48 (3H, d, $J$ = 7.3 Hz), 1.33 (3H, d, $J$ = 6.3 Hz), 1.17 ppm (3H, d, $J$ =

6.6 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 198.1, 173.5, 167.9, 166.2, 136.3, 131.6, 76.0, 74.5, 70.7, 67.8, 41.7, 29.4, 27.1, 19.9, 16.0, 12.1 ppm; IR (neat): $\tilde{\nu}$ = 3539, 1738 cm$^{-1}$; MS (EI): *m/z* 342 [$M^+$]; HRMS (EI): calcd for $C_{16}H_{22}O_8$: 342.1315 [$M^+$]; found: 342.1314; $[\alpha]_D^{28} = -56.9$ ($c$ = 1.410 in $CHCl_3$).

**Synthesis of compound 56**: A mixture of compound **55** (75 mg, 0.14 mmol) and $Rh/Al_2O_3$ (37 mg) in EtOH (10 mL) was vigorously stirred under an $H_2$ atmosphere at room temperature for 9 h. The mixture was diluted with $Et_2O$ and filtered through a celite pad. The filtrate was concentrated in vacuo to leave a residue, which was purified by chromatography on silica gel to afford compound **56** (49 mg, 66%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 6.94 (1H, s), 6.74 (1H, dd, $J$ = 7.7, 16 Hz), 6.50 (1H, s), 5.97 (1H, d, $J$ = 16 Hz), 5.47–5.34 (2H, m), 4.83 (1H, qd, $J$ = 6.3, 8.2 Hz), 4.73 (1H, d, $J$ = 7.1 Hz), 4.68 (1H, d, $J$ = 7.1 Hz), 4.10 (1H, dd, $J$ = 7.7, 8.2 Hz), 3.81–3.52 (4H, m), 3.38 (3H, s), 2.69 (3H, s), 2.65–2.47 (4H, m), 2.25 (1H, d, $J$ = 3.3 Hz), 2.22 (1H, d, $J$ = 3.6 Hz), 2.05 (3H, s), 1.78–1.51 (2H, m), 1.34 (3H, d, $J$ = 6.0 Hz), 1.32 ppm (3H, d, $J$ = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 171.6, 169.7, 152.1, 144.7, 124.9, 120.3, 116.3, 93.6, 78.4, 77.8, 71.5, 70.5, 68.4, 67.3, 59.0, 53.4, 41.8, 35.4, 33.4, 22.7, 20.3, 19.2, 17.8, 14.9 ppm; IR (neat): $\tilde{\nu}$ = 1737, 1660 cm$^{-1}$; MS (EI): *m/z* 539 [$M^+$]; HRMS (EI): calcd for $C_{26}H_{37}NO_9S$: 539.2189 [$M^+$]; found: 539.2206; $[\alpha]_D^{38} = -7.5$ ($c$ = 0.795 in $CHCl_3$).

**Synthesis of compound 57**: With the reduction procedure described above, compound **29** (6.0 mg, 0.01 mmol) gave compound **57** (5.4 mg, 90%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 6.97 (1H, s), 6.74 (1H, dd, $J$ = 8.7, 16 Hz), 6.48 (1H, s), 5.99 (1H, d, $J$ = 16 Hz), 5.45–5.40 (1H, m), 5.20 (1H, t, $J$ = 6.9 Hz), 4.96 (1H, qd, $J$ = 6.3, 9.1 Hz), 4.73 (1H, d, $J$ = 7.4 Hz), 4.70 (1H, d, $J$ = 7.1 Hz), 4.03 (1H, dd, $J$ = 8.7, 9.1 Hz), 3.79–3.52 (4H, m), 3.38 (3H, s), 2.69 (3H, s), 2.26–2.23 (2H, m), 2.00 (3H, s), 1.67–1.42 (2H, m), 1.34 (3H, d, $J$ = 6.0 Hz), 1.32 ppm (3H, d, $J$ = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 168.7, 164.4, 152.0, 145.2, 136.4, 125.7, 121.7, 116.4, 93.4, 79.9, 71.6, 70.0, 67.3, 59.1, 53.4, 41.7, 34.7, 31.9, 29.7, 21.4, 20.0, 19.3, 17.9, 14.1 ppm; IR (neat): $\tilde{\nu}$ = 1732, 1658 cm$^{-1}$; MS (EI): *m/z* 539 [$M^+$]; HRMS (EI): calcd for $C_{26}H_{37}NO_9S$: 539.2189 [$M^+$]; found: 539.2191; $[\alpha]_D^{29} = -58.9$ ($c$ = 0.62 in $CHCl_3$).

**Synthesis of compound MSDt-1**: In accordance with procedure 5-a, MEM ether **56** (57 mg, 0.11 mmol) gave **MSDt-1** (24 mg, 51%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 6.94 (1H, s), 6.88 (1H, dd, $J$ = 5.5, 16 Hz), 6.50 (1H, s), 6.07 (1H, d, $J$ = 16 Hz), 5.49–5.35 (2H, m), 4.81 (1H, qd, $J$ = 6.3, 11 Hz), 4.18 (1H, dd, $J$ = 5.5, 11 Hz), 2.70 (3H, s), 2.69–2.48 (4H, m), 2.27 (2H, d, $J$ = 8.8 Hz), 2.24 (2H, d $J$ = 8.2 Hz), 2.05 (3H, s), 1.78–1.52 (2H, m), 1.40 (3H, d, $J$ = 6.3 Hz), 1.34 ppm (3H, d, $J$ = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 172.8, 169.7, 152.1, 137.1, 123.0, 120.3, 116.3, 78.3, 74.2, 68.5, 53.4, 41.6, 35.4, 33.4, 22.8, 20.3, 19.3, 17.9, 15.0 ppm; IR (neat): $\tilde{\nu}$ = 3447, 1732, 1660 cm$^{-1}$; MS (EI): *m/z* 451 [$M^+$]; HRMS (EI): calcd for $C_{22}H_{29}NO_7S$: 451.1665 [$M^+$]; found: 451.1665; $[\alpha]_D^{24} = +58.0$ ($c$ = 1.22 in $CHCl_3$).

**Synthesis of compound MSDt-2**: In accordance with procedure 4-b, **MSDt-1** (16.8 mg, 0.04 mmol) gave **MSDt-2** (16.4 mg, 98%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.19 (1H, d, $J$ = 16 Hz), 6.95 (1H, s), 6.74 (1H, d, $J$ = 16 Hz), 6.52 (1H, s), 5.47–5.42 (2H, m), 5.10 (1H, q, $J$ = 7.1 Hz), 2.71 (3H, s), 2.64–2.58 (4H, m), 2.42–2.34 (2H, m), 2.04 (3H, s), 1.86–1.63 (2H, m), 1.47 (3H, d, $J$ = 7.1 Hz), 1.38 ppm (3H, d, $J$ = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 197.4, 171.9, 169.4, 163.4, 152.1, 136.9, 132.9, 132.5, 120.4, 116.5, 78.1, 75.4, 69.4, 41.1, 35.0, 33.5, 23.1, 19.8, 19.3, 16.9, 15.1 ppm; IR (neat): $\tilde{\nu}$ = 1733, 1626 cm$^{-1}$; MS (EI): *m/z* 449 [$M^+$]; HRMS (EI): calcd for $C_{22}H_{27}NO_7S$: 449.1508 [$M^+$]; found: 449.1509; $[\alpha]_D^{26} = +37.6$ ($c$ = 1.215 in $CHCl_3$).

**Synthesis of compound MSDt-1′**: In accordance with procedure 5-a, MEM ether **57** (29.5 mg, 0.05 mmol) gave **MSDt-1′** (19.7 mg, 81%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 6.98 (1H, s), 6.89 (1H, dd, $J$ = 6.0, 16 Hz), 6.50 (1H, s), 6.05 (1H, d, $J$ = 16 Hz), 5.41–5.26 (2H, m), 4.92 (1H, qd, $J$ = 6.3, 13 Hz), 4.13 (1H, dd, $J$ = 6.0, 13 Hz), 2.70 (3H, s), 2.56–2.45 (4H, m), 2.35–2.17 (2H, m), 2.01 (3H, s), 1.63–1.43 (2H, m), 1.41 (3H, d, $J$ = 6.6 Hz), 1.35 ppm (3H, d, $J$ = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 173.1, 168.8, 164.6, 145.7, 136.3, 123.4, 121.7, 116.5, 79.6, 74.9, 74.0, 67.7, 41.6, 34.5, 31.9, 21.5, 20.0, 19.3, 17.9, 14.2 ppm; IR (neat): $\tilde{\nu}$ = 3447, 1731, 1660 cm$^{-1}$; MS (EI): *m/z* 451 [$M^+$]; HRMS (EI): calcd for $C_{22}H_{29}NO_7S$: 451.1665 [$M^+$]; found: 451.1623; $[\alpha]_D^{24} = -7.1$ ($c$ = 0.985 in $CHCl_3$).

**Synthesis of compound MSDt-2′**: In accordance with procedure 4-b, **MSDt-1′** (12.2 mg, 0.03 mmol) gave **MSDt-2′** (11.5 mg, 95%) as a colorless oil: $^1$H NMR ($CDCl_3$): $\delta$ = 7.17 (1H, d, $J$ = 16 Hz), 6.97 (1H, s), 6.72 (1H, d, $J$ = 16 Hz), 6.49 (1H, s), 5.40–5.34 (2H, m), 5.07 (1H, q, $J$ = 7.1 Hz), 2.70 (3H, s), 2.66–2.52 (4H, m), 2.32–2.27 (2H, m), 2.00 (3H, s), 1.72–1.69 (2H, m), 1.48 (3H, d, $J$ = 7.1 Hz), 1.46 ppm (3H, d, $J$ = 6.3 Hz); $^{13}$C NMR ($CDCl_3$): $\delta$ = 197.4, 172.2, 168.6, 163.6, 151.8, 136.3, 133.6, 132.2, 121.3, 116.5, 79.0, 75.5, 68.4, 40.4, 33.9, 32.3, 29.6, 21.7, 19.3, 19.2, 16.4, 14.2 ppm; IR (neat): $\tilde{\nu}$ = 1731, 1624 cm$^{-1}$; MS (EI): *m/z* 449 [$M^+$]; HRMS (EI): calcd for $C_{22}H_{27}NO_7S$: 449.1508 [$M^+$]; found: 449.1536; $[\alpha]_D^{24} = -40.1$ ($c$ = 0.725 in $CHCl_3$).

**Biological evaluation procedures**

Cell line and culture: A human lymphoma cell line, U937, was obtained from the Human Sciences Research Resource Bank (Japan Human Sciences Foundation, Tokyo, Japan) and was maintained in RPMI 1640 medium supplemented with 10% heat-inactivated fetal bovine serum (FBS) at 37°C in humidified air with 5% $CO_2$.

**Measurement of DNA fragmentation**: A quantitative DNA-fragmentation assay was carried out according to the previously reported method.[27] Briefly, cells were incubated with the test compounds at 37°C for 12 h at the indicated drug concentrations. The cells were lysed in a lysis buffer (10 mM tris(hydroxymethyl)aminomethane (Tris), 1 mM ethylenediaminetetraacetate (EDTA), and 0.2% Triton X-100; pH 7.5) and centrifuged at 13000 *g* for 10 min. Subsequently, each DNA sample in the supernatant was precipitated, and the resulting pellet was added to 12.5% trichloroacetic acid (TCA) at 4°C and quantified by using a diphenylamine reagent after hydrolysis in 5% TCA at 90°C for 20 min. "Percentage of DNA fragmentation" refers to the ratio of DNA in the supernatant ("fragmented") to the total DNA recovered in both the supernatant and pellet ("fragmented plus intact").

**Apoptosis assay by flow cytometry**: Flow cytometry was performed with PI and FITC-labeled annexin V (Immunotech, Marseille, France) to detect phosphatidylserine externalization (on the surface of the cell membrane) as an endpoint indicator of early apoptosis. After treatment of the cells with test compounds, the remaining intact cells were incubated at 37°C for 12 h, collected, washed with cold phosphate-buffered saline (PBS) at 4°C, and centrifuged at 500 *g* for 3 min. FITC-labeled annexin V (5 μL) and PI (5 μL) were added to the cell suspension (490 μL) and mixed in gently. After incubation at 4°C for 10 min in the dark, the cells were analyzed by flow cytometry (Epics XL, Beckman-Coulter, Miami, FL).

**Statistics**: The results are expressed as the mean ± the standard deviation. The significance of differences between means was tested by using Student's *t*-test and was assumed for $p$ values $< 0.05$. All experiments were performed in triplicate.

## Acknowledgements

This work was supported by The Fugaku Trust For Medicinal Research and by a Grant-in-Aid for Scientific Research (C) (grant no.: 19590098) from the Japan Society for the Promotion of Science (JSPS).

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Received: December 18, 2008
Revised: March 4, 2009
Published online: April 15, 2009

  