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TITLE

Epothilone Analogues

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BACKGROUND OF THE INVENTION

[001] Microtubules are an essential component of the cytoskeleton. Agents that disrupt microtubule dynamics within the cell have the potential of arresting cell division and cell proliferation (anti-mitotic agents) and consequentially, acting as anticancer agents. Two types of such agents have been identified. One class inhibits the polymerization of α - and β -tubulin, to microtubules, and is exemplified by compounds such as colchicines **1** and vinca alkaloids **2** (Figure 26), some of which are clinically used anticancer drugs. In contrast, the second class of anti-mitotic agents accelerates the polymerization of tubulin to microtubules and stabilizes them, thus inhibiting their depolymerization, an essential process during cell division. This second class is commonly referred to as microtubule-stabilizing agents. Paclitaxel (Taxol®) **3** (Figure 26), initially isolated from the Pacific Yew tree, *Taxus bravifolia*, was the first of its kind reported and is already in clinical use.

[002] A number of limitations are encountered in the clinical use of paclitaxel. One major limitation is its susceptibility to multiple drug-resistance. Several other compounds possessing the same mechanism of action as paclitaxel have been reported since then. Epothilones **4** (Figure 27), originally isolated from the myxobacterium *Sorangium cellulosum*, constitute one such class. They are competitive inhibitors of paclitaxel binding and have been shown to compete for the same or overlapping binding sites on microtubules. From the point of view of anticancer properties, they possess a number of advantages over paclitaxel. Prominent among them is their activity against multiple drug resistant cell lines, which are resistant to paclitaxel.

[003] Extensive studies on structure-activity relationship (SAR) of epothilones have been reported. Many analogues have been synthesized with the aim of improving the pharmacological profile of epothilones. A few epothilone analogues are in various stages of clinical development. Based on SAR studies, the structure of epothilone molecule has been divided into three main sectors (Figure 28), namely: i) the acyl sector (sector 1); ii) the alkyl

sector (sector 2); and, iii) the aryl sector (sector 3). The acyl sector has been shown to be critical for biological activity and is not amenable to major chemical modification, whereas the alkyl and the aryl sectors can accommodate some degree of chemical modification without losing biological activity. Further, the macrolactone ring has been reported to be important for biological activity, as open-chain analogues synthesized were inactive.

[004] Despite the promising therapeutic utility of the epothilones, it would be desirable to investigate additional analogues as well as additional synthetic methodologies for the synthesis of existing epothilones, and analogues thereof, as well as novel analogues thereof.

[005] In particular, given the interest in the therapeutic utility of this class of compounds, it would also be desirable to develop methodologies capable of providing significant quantities of any epothilones, or those described herein, for clinical trials and for large-scale preparation.

[006] Due to the increasing interest in epothilones as anti-cancer agents, novel analogues of these compounds are needed and desired to more fully develop their therapeutic potential.

SUMMARY OF THE INVENTION

[007] Described herein is a method of incorporating a molecular scaffold to hold the key segments of epothilone in a predetermined orientation.

[008] The method includes incorporating a molecular scaffold to hold at least one segment of epothilone in cyclic epothilone analogues

[009] Also described herein is a method of rigidifying the region between the macrolactone ring and the aromatic side-chain in macrocyclic analogues for effective interaction with the tubulin receptor.

[0010] Also described herein is a method for assembling the two defined molecular segments into an epothilone analogue. In certain embodiments, the method includes synthesizing three fragments and coupling using a convergent strategy to generate the analogues. In certain embodiments, the method includes esterifying, then closing a macrolactone ring using an olefin metathesis approach.

[0011] In one aspect, the method includes synthesizing epothilone analogues:

[0012] by incorporating a molecular scaffold that holds at least one key component of epothilone in a favorable orientation for interaction with a tubulin receptor; and

[0013] structurally rigidifying a region between the macrolactone ring and the aromatic side-chain in epothilone by incorporating a single-carbon bridge between C14 and C17 carbon atoms in the form of a substituted cyclopentene ring in order to generate an epothilone analogue molecule having proper orientation of structural residues for enhanced interaction with the tubulin receptor.

[0014] Various objects and advantages of this invention will become apparent to those skilled in the art from the following detailed description of the preferred embodiment, when read in light of the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Fig. 1 shows the synthesis of 5a and 5b.

[0016] Fig. 2 shows the synthesis of alcohol fragment 9.

[0017] Fig. 3a shows the synthesis of carboxylic acid fragment 7a and 7b.

[0018] Fig. 3b shows the continued synthesis of carboxylic acid fragment 7a and 7b.

[0019] Fig. 4 shows the synthesis of 5a and 5b.

[0020] Fig. 5 shows the retrosynthetic strategy for the preparation of cyclic analogues.

[0021] Fig. 6 shows the synthesis of key aldehyde fragment.

[0022] Fig. 7 shows the synthesis of key ketone fragment 26.

[0023] Fig. 8 shows diastereoselective formation of aldol 40a.

[0024] Fig. 9 shows the synthesis of 44.

[0025] Fig. 10 shows the synthesis of (+/-) 48a and (+/-) 48b.

[0026] Fig. 11 shows the synthesis of 46b.

[0027] Fig. 12 shows the zinc borohydride reduction of (+/-) 48a.

[0028] Fig. 13 shows lipase resolution of (+/-) 52a.

[0029] Fig. 14 shows the synthesis of 58.

[0030] Fig. 15 shows the synthesis of α -iodoethyl ylide 57.

[0031] Fig. 16 shows the synthesis of (+/-) 58.

[0032] Fig. 17 shows the Zuzuki coupling of 58 and 44.

[0033] Fig. 18 shows the Troc-TBS approach (synthesis of target 6b).

[0034] Fig. 18 shows the olefin metathesis approach.

[0035] Fig. 20 shows the synthesis of 67.

- [0036] Fig. 21 shows the synthesis of 68.
- [0037] Fig. 22 shows the synthesis of 83.
- [0038] Fig. 23a shows the synthesis of 69.
- [0039] Fig. 23b shows the stereochemical assignment of (3S, 5S)-2-Methyl-3-phenyl-5-vinyl-cyclopent-2-enol (69) based on NMR spectroscopy (NOESY).
- [0040] Fig. 24 shows the synthesis of 6b (first olefin metathesis approach).
- [0041] Fig. 25 shows the synthesis of 6b (final olefin metathesis approach).
- [0042] Fig. 26 shows antimetabolic agents.
- [0043] Fig. 27 shows naturally occurring epothilones.
- [0044] Fig. 28 shows arbitrarily defined sectors of epothilone for definition of SAR.
- [0045] Fig. 29 shows open chain epothilone analogues.
- [0046] Fig. 30 shows designed epothilone analogues (6a-6e).
- [0047] Fig. 31 shows the nonstereoselective reduction of 88/89 and 90/91.
- [0048] Fig. 32 shows the synthesis of 89 and 92.
- [0049] Fig. 33 shows the synthesis of 96.
- [0050] Fig. 34 shows compounds 23 and 25/26.
- [0051] Fig. 35 shows the synthesis of 100, 101 and 102.

DETAILED DESCRIPTION OF THE INVENTION

- [0052] A method for synthesizing epothilone analogues includes incorporating a molecular scaffold to hold at least one segment of the epothilone analogue in a predetermined orientation. In certain embodiments, the epothilone analogue is adapted to interact with at least one tubulin receptor in a cell.
- [0053] A method for synthesizing an epothilone analogue having a macrolactone ring and an aromatic side-chain, the method includes: i) incorporating a molecular scaffold to hold at least one segment of the epothilone analogue in a predetermined orientation; and, ii) rigidifying a region between the macrolactone ring and the aromatic side-chain.
- [0054] A method for synthesizing an epothilone analogue having a macrolactone ring and an aromatic side-chain includes: i) incorporating a molecular scaffold that holds at least one sector of epothilone in a predetermined orientation for interaction with at least one tubulin receptor; and, ii) structurally rigidifying a region between the macrolactone ring and the

aromatic side-chain in epothilone by incorporating a single-carbon bridge between C14 and C17 carbon atoms in epothilone in the form of a substituted cyclopentene ring.

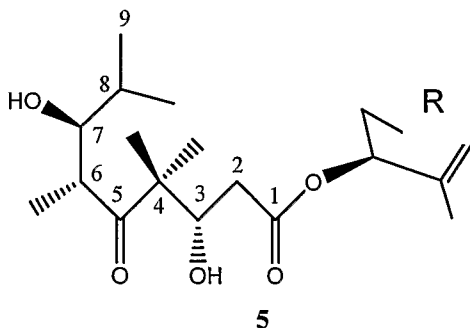
[0055] In certain embodiments, the epothilone analogue has a predetermined orientation of structural residues that allows for enhanced interaction with a tubulin receptor. Also, in certain embodiments, the epothilone analogue comprises an open chain epothilone.

[0056] The method for synthesizing epothilone analogue can include coupling a suitable aldehyde fragment, a suitable ketone fragment and a suitable alcohol fragment using a convergent strategy.

[0057] The method is also useful to establish whether the conformational relationship of the aromatic side chain to the macrolactone ring contributes to the bioactivity of the epothilone molecule and offers an opportunity to synthesize active epothilone analogues. Also, the method is applicable to the synthesis of other important related analogues of the epothilone series.

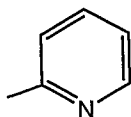
[0058] In another aspect, an epothilone analogue composition includes a non-naturally occurring molecular scaffold. The molecular scaffold extends between a macrolactone ring and an aromatic side-chain in an analogue of an epothilone. In certain embodiments, the molecular scaffold comprises a single-carbon bridge between C14 and C17 carbon atoms in an epothilone analogue in the form of a substituted cyclopentene ring.

[0059] The epothilone analogue, or a salt thereof, can comprise:

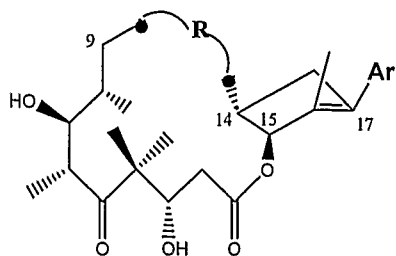


[0060]

[0061] wherein R comprises phenyl, 2-pyridyl or other heteroaromatic, including



[0062] The epothilone analogue, or a salt thereof, can comprise:



[0063] where Ar comprises phenyl, 2-pyridyl or other heteroaromatic, and wherein R a connecting link of variable hydrophobicity, length containing double bonds, or other heteroatom (such as N, O, S) functionality, and other combinations thereof.

[0064] In another aspect, pharmaceutical preparations can contain at least one epothilone analogue as well as a pharmaceutically compatible vehicle. In certain embodiments, the pharmaceutical compositions are useful for the treatment of a disease or condition characterized by cellular hyperproliferation. A method for treating a disease or condition characterized by cellular hyperproliferation in a subject suffering therefrom, includes administering a therapeutically effective amount an epothilone analogue.

[0065] In another aspect, epothilone analogues are useful for their anticancer activity are described, including, for example, the epothilone analogues,

[0066] Described herein are epothilone compounds that are useful for the treatment of cancer and other conditions characterized by undesirable cellular proliferation. Also described herein are open-chain analogues of epothilones and cyclic analogues of epothilones.

[0067] In another aspect, methods for preparing the compounds are provided. In one embodiment, certain of the compounds are prepared by total synthesis.

[0068] In another aspect, formulations comprising one or more of these compounds are provided. In one embodiment, the compounds constitute the active principle of the formulation. In another embodiment, the compounds are combined with other active compounds, such as cytotoxic agents and synergists.

[0069] In another aspect, methods for treating a disease or condition with the compounds are provided. In one embodiment, the compounds are used for treating a disease or condition characterized by cellular hyperproliferation in a subject. In one embodiment, the disease is cancer, including but not limited to cancers of the head and neck, liver or biliary tract, intestine, ovary, lung, central nervous system, lymphatic system, or sarcomas. In another embodiment, the condition includes cellular hyperproliferative disorders

[0070] Statements regarding the definitions of terms used herein are listed below. The definitions apply to the terms as they are used throughout this specification, unless otherwise limited in specific instances, either individually or as part of a larger group.

[0071] Unless stereochemistry is specifically indicated, all stereoisomers of the compounds are included, as pure compounds as well as mixtures thereof.

[0072] Some of the crystalline forms for the compounds may exist as polymorphs and as such are included. In addition, some of the compounds may form solvates with water (i.e., hydrates) or common organic solvents.

[0073] Protected forms of the compounds are included. A variety of protecting groups are disclosed; for example, a hydroxy protected form of the compounds are those where at least one of the hydroxyl groups is protected by a hydroxy protecting group.

[0074] In another aspect, prodrugs of the compounds are included. In general, such prodrugs are functional derivatives of the compounds that are readily convertible in vivo into the required compound. Thus, in the methods of treatment, the term "administering" includes the treatment of the various disorders described with the compound specifically disclosed or with a compound which may not be specifically disclosed, but which converts to the specified compound in vivo after administration to a subject in need thereof. The term "therapeutically effective amount" as used herein, means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

[0075] The term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product that results, directly or indirectly, from combinations of the specified ingredients in the specified amounts.

[0076] The term "pharmaceutically acceptable salt" is a salt of a compound. Suitable pharmaceutically acceptable salts of the compounds include acid addition salts which may, for example, be formed by mixing a solution of the compound with a solution of a pharmaceutically acceptable acid.

[0077] The term "pharmaceutically acceptable carrier" is a medium that is used to prepare a desired dosage form of the compound. A pharmaceutically acceptable carrier includes solvents, diluents, or other liquid vehicle; dispersion or suspension aids; surface active agents;

isotonic agents; thickening or emulsifying agents, preservatives; solid binders; lubricants and the like.

[0078] The term "purified," as used in reference to a compound means that the compound is in a preparation in which the compound forms a major component of the composition, such as constituting about 50%, about 60%, about 70%, about 80%, about 90%, about 95% or more by weight of the components in the composition.

[0079] Pharmaceutical preparations can include at least one of the compounds as described above and herein, or a pharmaceutically acceptable derivative thereof, which compounds are capable of inhibiting the growth of or killing cancer cells, and, in certain embodiments, are capable of inhibiting the growth of or killing multidrug resistant cancer cells. In certain embodiments, the pharmaceutical preparation also comprises as solubilizing or emulsifying agent.

[0080] In yet another aspect, methods for inhibiting tumor growth and/or tumor metastasis are provided. In certain embodiments, the method includes treating cancers by inhibiting tumor growth and/or tumor metastasis for tumors of multidrug resistant cancer cells. The method involves the administration of a therapeutically effective amount of the compound or a pharmaceutically acceptable derivative thereof to a subject (including, but not limited to a human or animal) in need of it. In certain embodiments, specifically for treating cancers comprising multidrug resistant cancer cells, the therapeutically effective amount is an amount sufficient to kill or inhibit the growth of multidrug resistant cancer cell lines. In certain embodiments, the compounds are useful for the treatment of solid tumors.

[0081] It will be appreciated by one of ordinary skill in the art that asymmetric centers may exist in the compounds. Thus, the compounds and pharmaceutical compositions thereof may be in the form of an individual enantiomer, diastereomer or geometric isomer, or may be in the form of a mixture of stereoisomers. In certain embodiments, the compounds are enantiopure compounds. In certain other embodiments, mixtures of stereoisomers or diastereomers are provided. Additionally, the compounds encompass both (Z) and (E) double bond isomers (or cis and trans isomers) unless otherwise specifically designated. Thus, compounds generally depicted in structures described herein encompass those structures in which double bonds are (Z) or (E).

[0082] It will be appreciated that the compounds, as described herein, may be substituted

with any number of substituents or functional moieties. In general, the term "substituted" whether preceded by the term "optionally" or not, and substituents contained in formulas refer to the replacement of hydrogen atoms in a given structure with a specified substituent. When more than one position in any given structure may be substituted with more than one substituent selected from a specified group, the substituent may be either the same or different at every position.

[0083] As used herein, the term "substituted" is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. For purposes of explanation herein, heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valencies of the heteroatoms.

[0084] Furthermore, there not any intention to be limited in any manner by the permissible substituents of organic compounds. Combinations of substituents and variables envisioned are preferably those that result in the formation of stable compounds useful in the treatment, for example, of proliferative disorders, including, but not limited to cancer.

[0085] The term "stable", as used herein, preferably refers to compounds which possess stability sufficient to allow manufacture and which maintain the integrity of the compound for a sufficient period of time to be detected and preferably for a sufficient period of time to be useful for the purposes detailed herein.

[0086] Also provided are pharmaceutical agents that are based on pharmaceutically compatible compounds, i.e., compounds that are nontoxic in the doses used, optionally together with commonly used adjuvants and vehicles.

[0087] A composition generally comprises a compound and a pharmaceutically acceptable carrier. The compound may be in free form or where appropriate as pharmaceutically acceptable derivatives such as prodrugs, and salts and esters of the compound.

[0088] The composition may be in any suitable form such as solid, semisolid, or liquid form. In general, the pharmaceutical preparation will contain one or more of the compounds as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for external, enteral, or parenteral application. The active ingredient may be compounded, for

example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, capsules, suppositories, pessaries, solutions, emulsions, suspensions, and any other form suitable for use. The carriers that can be used include water, glucose, lactose, gum acacia, gelatin, mannitol, starch paste, magnesium trisilicate, talc, cornstarch, keratin, colloidal silica, potato starch, urea, and other carriers suitable for use in manufacturing preparations, in solid, semi-solid, or liquefied form. In addition, auxiliary stabilizing, thickening, and coloring agents and perfumes may be used.

[0089] The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the subject treated and the particular mode of administration. For example, a formulation for intravenous use comprises an amount of the compound ranging from about 1 mg/mL to about 25 mg/mL, preferably from about 5 mg/mL to 15 mg/mL, and more preferably about 10 mg/mL. Intravenous formulations are typically diluted between about 2 fold and about 30 fold with normal saline or 5% dextrose solution prior to use.

[0090] Methods of Treatment

[0091] In one aspect, the compounds are used to treat cancer. In one embodiment, the compounds are used to treat cancers of the head and neck which include tumors of the head, neck, nasal cavity, paranasal sinuses, nasopharynx, oral cavity, oropharynx, larynx, hypopharynx, salivary glands, and paragangliomas.

[0092] In another embodiment, the compounds are used to treat cancers of the liver and biliary tract, particularly hepatocellular carcinoma. In another embodiment, the compounds are used to treat intestinal cancers, particularly colorectal cancer. In another embodiment, the compounds are used to treat ovarian cancer. In another embodiment, the compounds are used to treat small cell and non-small cell lung cancer.

[0093] In another embodiment, the compounds are used to treat breast cancer. In another embodiment, the compounds are used to treat sarcomas which include fibrosarcoma, malignant fibrous histiocytoma, embryonal rhabdomyosarcoma, leiomyosarcoma, neurofibrosarcoma, osteosarcoma, synovial sarcoma, liposarcoma, and alveolar soft part sarcoma. In another embodiment, the compounds are used to treat neoplasms of the central nervous systems, particularly brain cancer.

[0094] In another embodiment, the compounds are used to treat lymphomas that include

Hodgkin's lymphoma, lymphoplasmacytoid lymphoma, follicular lymphoma, mucosa-associated lymphoid tissue lymphoma, mantle cell lymphoma, B-lineage large cell lymphoma, Burkitt's lymphoma, and T-cell anaplastic large cell lymphoma.

[0095] The method comprises administering a therapeutically effective amount of a compound to a subject suffering from cancer. The method may be repeated as necessary either to mitigate (i.e. prevent further growth) or to eliminate the cancer. Clinically, practice of the method will result in a reduction in the size or number of the cancerous growths and/ or a reduction in associated symptoms (where applicable). Pathologically, practice of the method will produce at least one of the following: inhibition of cancer cell proliferation, reduction in the size of the cancer or tumor, prevention of further metastasis, and inhibition of tumor angiogenesis.

[0096] The compounds and compositions can be used in combination therapies. In other words, the compounds and compositions can be administered concurrently with, prior to, or subsequent to one or more other desired therapeutic or medical procedures. The particular combination of therapies and procedures in the combination regimen will take into account compatibility of the therapies and/or procedures and the desired therapeutic effect to be achieved. In another aspect the compounds are used to treat non-cancer disorders that are characterized by cellular hyperproliferation (e.g., an abnormally increased rate or amount of cellular proliferation).

[0097] The synthesis of epothilone analogues as anticancer agents is based on two methodologies:

[0098] Analogues incorporating a molecular scaffold that holds the key components of epothilone, critical for biological activity, in favourable orientation for interaction with the tubulin receptor to form compounds with significant biological activity (Figure 29). This is contrary to the present knowledge that ring-open epothilone analogues are not biologically active.

[0099] Structural simplification accompanying such chemical modification increases the therapeutic index of such molecules and thereby leads to molecules of higher pharmacologic profile.

[00100] Structural rigidification of the region between the macrolactone ring and the aromatic side-chain by incorporating a single-carbon bridge between the C14 and C17 carbon atoms in

the form of a substituted cyclopentene ring in order to generate molecules with proper orientation of structural residues for enhanced interaction with the tubulin receptor (Figure 30). Such molecules have improved pharmacologic profiles for development as potent anticancer agents. It is to be understood, that in other embodiments, the Ar can comprise phenyl, 2-pyridyl or other heteroaromatic, and R can comprise a connecting link of variable hydrophobicity, length (usually 2 or 3 carbons) containing double bonds, or other heteroatom (such as N, O, S) functionality, and other combinations thereof.

[00101] Using the above two methods two classes of compounds of the types as shown in Figures 29 and 30 were made. In designing sector 2 of structurally rigidified analogues (Figure 30), the lipophilicity factor was taken into consideration since it is proposed to play a role in some epothilone analogues with high tubulin-binding activity and low cytotoxicity. The log P values of several analogues were calculated and compared with the corresponding values for epothilones B **4b** & D **4d** (see table in Figure 30). The substituents in sector 2 were modulated to obtain analogues with a variable lipophilicity in order to study the effect of lipophilicity on ligand partitioning through cell membrane and ligand-receptor interaction. Compounds **6a**, **6b**, and **6e** have lipophilicities comparable to those of the active epothilones. A variety of functionalities with different lipophilicities were introduced to circumvent any potential difficulty associated with the compound's ability to penetrate the cell membrane of the tumor cell.

[00102] The overall molecular geometry of the designed analogues was similar to that of the natural epothilones as shown by preliminary molecular modeling studies. Further, the C9–C15 distance was maintained close to that of the natural epothilones so that the conformation of the macrolactone remained as close as possible to that of the natural epothilones. The C9–C15 distance across the macrolactone ring of **6a** and **6e** was found to be 4.40 Å and 4.46 Å, respectively, compared to 4.20 Å for epothilone B **4b**.

[00103] Docking of the analogue **6a** on to the taxane-binding site on tubulin²⁴ showed the following interactions within 3 Å; i. C12-13 epoxide oxygen and HIS-229, ii. C2-OH and ARG-278, iii. C4-Me and ARG-278 (carbonyl backbone) and GLN-281 (backbone), iv. C7-OH and LEU-371 side chain, v. pyridine ring with ASP-226 side chain and LEU-219 side chain. In a similar study with **30e**, the following interactions were observed: i. pyridine ring with ASP-226, ii. HIS-229 with LEU-219, iii. C7-OH with GLN-281, iv. C14 triple bond–

C11 segment was maintaining contacts with SER-277 and THR-276. The designed compounds were synthesized as described below.

[00104] **I. Synthesis of Open-Chain Epothilone Analogues:**

[00105] The open-chain analogues (Fig. 29) were synthesized by esterifying an alcohol fragment **9** (Fig. 1) incorporating the molecular scaffold and the aromatic side chain of epothilone with a carboxylic acid fragment resembling the acyl sector **8a/8b** (racemic at the *). The alcohol and the carboxylic acid fragments were separately synthesized (Figs. 2 and 3, respectively). Fig. 1 shows the synthesis of **5a** and **5b**.

[00106] **Synthesis of alcohol fragment 9**

[00107] The synthesis of alcohol **9** was accomplished as shown in Fig. 2. The thiazolium salt-catalyzed addition of 2-pyridinecarboxaldehyde **11** to the activated double bond of ethyl vinyl ketone furnished the diketone **12**,⁷⁶ which was cyclized by intramolecular aldol condensation to the cyclopentenone **13**. Enantioselective reduction of ketone **13** using (R)-2-methyl-CBS-oxazaborolodine catalyst (CBS; Corey, Bakshi, and Shibata)⁷⁴ gave the desired (S)-alcohol **9** in a very good yield (86%) and enantioselectivity (84% *ee*). The absolute stereochemistry and enantiomeric excess of alcohol **9** was confirmed by Mosher ester analysis.^{77,78}

[00108] **Synthesis of carboxylic acid fragment 7**

[00109] The synthesis of carboxylic acid **7** was undertaken in a nine-step sequence as shown in Fig. 3. Prenyl chloride **16** and its isomer **17** were prepared as mixture from the commercially available alcohol **15** by reaction with concentrated hydrochloric acid.⁷⁹ Compounds **16** and **17** were obtained in a 6:1 ratio. The reaction was thermodynamically controlled (25°C) and favored the more stable product **16** over **17**. The prenyl chloride mixture was then converted to the corresponding Grignard reagent. Subsequent reaction with propionyl chloride gave a crude product which was purified by fractional distillation to give the unsaturated ketone **18** as a colorless oil.⁷⁵ The formation of **18** and not the tertiary alcohol was favored by slow addition of the Grignard reagent to an excess (2 equivalents) of propionyl chloride at -78 °C. The carbonyl group of compound **18** was also blocked from a rapid second addition because of steric hindrance.

[00110] By kinetically controlling the mixed aldol reaction between ketone **18** and isobutyraldehyde through formation of the *Z* enolate of **18** using a bulky base (LDA) at -78 °C, a racemic mixture of the desired *syn* aldol (+/-) **19a** was formed without formation of the

anti product.^{75,80} The steric hindrance in the transition state, due to 1,3-diaxial interaction between the isopropyl group of isobutyraldehyde and the bulky group of ketone **18**, prevented the formation of the racemic *anti* product (+/-) **19b** (Fig.3). No attempt was made to separate the racemic *syn* aldols (+/-) **19a** at this stage. The secondary alcohol functional group of compound (+/-) **19a** was protected using tert-butyldimethylsilyl chloride to give (+/-) **20**. Aldehyde (+/-) **21** was produced by ozonolysis of olefin (+/-) **20** under reducing conditions using Ph₃P. The crude oily product was purified by silica gel column chromatography to give compound (+/-) **21** in excellent yield.

[00111] Compound (+/-) **21** was enantioselectively converted to the homoallylic alcohols **22a** and **22b** by reaction with (+)-allyldiisopinocampheylborane (Fig. 3b). The (S) stereochemistry at homoallylic alcohol attached carbon was confirmed by Mosher ester analysis.^{77,78} Since compound (+/-) **21** was a racemic mixture, the products (**22a** and **22b**) obtained by allylation represented a pair of diastereomers. However, the two diastereomers were not separated at this stage. The secondary hydroxyl groups of **22a/22b** were protected using tert-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and 2,6-lutidine to give **23a** and **23b** in excellent yield. Ozonolysis of the terminal olefin function of the **23a/23b** mixture under reducing conditions (Ph₃P) gave the corresponding aldehydes **24a** and **24b**. The aldehydes **24a/24b** were then converted to the corresponding diastereomeric acids **7a** and **7b** by Pinnick oxidation.⁸¹ At this stage, the diastereomeric acids **7a** and **7b** were separated by column chromatography.

[00112] **Coupling between the carboxylic acids 7a/7b and alcohol 9**

[00113] Treating fragments **7a/7b** with 20% trifluoroacetic acid in methylene chloride resulted in the formation of the fully deprotected intermediates **8a/8b** (Fig. 4). Esterification between **8a/8b** and alcohol **9** resulted in the formation of the target molecules **5a/5b** as the sole esterification products in good yield (64% over two steps).

[00114] **II. Synthesis of Macrocyclic Epothilone Analogues**

[00115] The synthesis of analogues with a rigidified skeleton of the macrocyclic structure involved separate synthesis of three key fragments **25**, **26** and **27**, which were then coupled by a convergent strategy to generate the final product (Fig. 5). Aldehyde **25** and ketone **26** can be coupled by stereoselective aldol reaction. Depending on the target molecule, the northern segment (C10–C14) can then be inserted using one of several different synthetic strategies.

Finally, Yamaguchi macrolactonization furnishes the final target.

[00116] The syntheses of the three key fragments **25**, **26** and **27** are shown in Fig. 6, Fig. 7, and Fig. 10, respectively.

[00117] **Synthesis of the aldehyde 25**

[00118] Synthesis of the aldehyde **25** was approached as shown in Fig. 6 via Evans asymmetric alkylation protocol. The acyl chloride **30** was obtained from commercially available 5-benzyloxypentanol **28** by Jones oxidation followed by treatment with oxalyl chloride.⁸³ Coupling between acid chloride and the commercially available chiral auxiliary (*S*)-(-)-4-isopropyl-2-oxazolidinone gave the imide **31**.⁸⁴ Enolization of imide **31** using sodium hexamethyldisilazane (NaHMDS) in THF at -78°C, followed by reaction with excess methyl iodide gave the stereoselectively alkylated product **32** (11:1 ratio of diastereomers by ¹H NMR spectroscopy of the crude product). The diastereoselectivity was attributed to the formation of the *Z*-enolate of imide **31** followed by alkylation from the side opposite to the bulky isopropyl group (Fig. 6).

[00119] Reductive removal of the chiral auxiliary in **32** using LiAlH₄ gave alcohol **34** in 89% yield. While this approach gave the desired product, it was accompanied by loss of most of the chiral ligand. In an alternative procedure, hydrolysis of **32** using LiOOH gave the carboxylic acid **33** along with 98 % recovery of the chiral ligand.⁸⁵ LiAlH₄ reduction of acid **33** gave the alcohol **34** in 92% yield over two steps. This approach furnished the alcohol **34** in 71% overall yield and proved to be superior to what was reported earlier for the same fragment.⁸⁶ Dess-Martin periodinane oxidation of alcohol **34** gave the key aldehyde intermediate **25**.

[00120] **Synthesis of ketone 26**

[00121] The ketone **26** was synthesized as reported earlier (Fig. 7).^{86,87} The ketoaldehyde **38** was synthesized by addition of propionyl chloride to the 1-*N*-morpholinoisobutene **37**, which was prepared from condensation between isobutyraldehyde **35** and morpholine **36**.⁸⁸ The enantiomerically enriched alcohol derivative **39** was prepared by Brown's allylation of aldehyde **38** using (+)-allyldiisopinocampheylborane (+)-Ipc₂B-(allyl) in ether at -100 °C.⁷³ The stereochemistry of the chiral center in **39** was determined and confirmed to be (*S*) using Mosher ester analysis.⁷⁷ Protection of the hydroxyl group of **39** using tert-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and 2,6-lutidine gave the ketone **26** in 96 % yield.

[00122] **Coupling between fragments 25 and 26**

[00123] Having already made the aldehyde **25** and ketone **26**, the important diastereoselective aldol

reaction to construct the C6-C7 bond and establish the absolute stereochemistry at these two positions was performed (Fig. 8). Ketone-derived lithium enolate aldol reactions have a highly reversible nature.⁸⁹ The retro-aldol reaction can cause scrambling of enolate geometry which will affect the stereochemical outcome of the product. Nicolaou *et al.* overcame this problem by using a large excess of the ketone enolate (2.3 equivalents) which ensured that the initially formed *Z*-enolate remained predominant in the course of the reaction.⁹⁰ The *Z*-enolate of ketone **26** (2.3 equivalents) was further favored kinetically by using a bulky base (LDA) at -78 °C. The reaction time was kept as short as possible to minimize aldol equilibration. Thus, the desired *syn* aldol **40a** was formed together with the other *syn* product **40b** (**40a**: **40b**, 11:1) without detectable formation of the *anti* product (Fig. 8). Excess ketone **26** was easily recovered and separated by flash chromatography from the *syn* aldol **40a**. It was also possible to separate the two *syn* aldols **40a/40b** (74% yield for **40a** and 6.7% yield for **40b**). The stereochemistry at the C7 was confirmed to be (*S*) by Mosher ester analysis.⁷⁷

[00124] Protection of the alcohol function of **40a** with Troc-chloride and pyridine gave **41** (Fig. 9). Ozonolysis of **41** under reducing conditions (Ph₃P), followed by Pinnick oxidation gave the corresponding acid **42**. 4-(Dimethylamino)pyridine (DMAP)-catalyzed esterification of **42** with dicyclohexylcarbodiimide (DCC) to give the methyl ester, followed by debenzoylation furnished the key alcohol intermediate **43**. Selenylation of **43** using 2-nitrophenyl selenocyanate gave the corresponding 2-nitrophenyl selenocyanate intermediate, which was subjected to *in situ* alkaline hydrogen peroxide oxidation and elimination to give the corresponding olefin **44**.

[00125] **Synthesis of cyclic fragment 27**

[00126] The next challenge was to synthesize the aryl cyclopentenyl fragment that will be coupled to fragment **44** by Suzuki coupling reaction. The diketoesters **47a** and **47b** were synthesized by alkylation of the commercially available ethyl propionylacetate **45** with substituted α -bromoacetoaromatic derivatives **46a** and **46b** (Fig. 10). The diketoesters **47a** and **47b** were cyclized directly into the cyclopentenones (+/-) **48a** and (+/-) **48b** by an intramolecular aldol condensation reaction.

[00127] The synthesis of 2-bromo-1-(5-methylpyridin-2-yl)ethanone **46b** was performed as shown in Fig. 11. The facile lithium-bromine exchange reaction was used between the commercially available 2-bromo-5-methylpyridine **49** and butyllithium at low temperature to produce the 2-lithio-methylpyridine intermediate **50**, which was reacted in a one-pot reaction

with *N,N*-dimethylacetamide to form 1-(5-methylpyridin-2-yl)ethanone (**51**) in 72% yield over two steps.^{92a} We were able to make compound **46b** by bromination of **51** using a commercially available polymer supported tribromide (Amberlyst A26-Br₃).^{92b} This was a clean reaction and a simple filtration of the resin followed by flash chromatography gave the desired product **46b** in 91% yield (Fig. 11).

[00128] The next step was to stereoselectively reduce the ketone group of (+/-) **48a** and (+/-) **48b** to the corresponding alcohols. Since **48a** and **48b** are racemic mixtures, non stereoselective reduction will give a mixture of four isomers (two *cis* and two *trans*). The target was to convert the racemic β -keto esters **48a** and **48b** to the corresponding racemic *trans* products, and preferably the enantiomerically pure *trans*- β -hydroxyesters.

[00129] This was achieved by reduction of the racemic β -keto ester (+/-) **48a** using zinc borohydride Zn(BH₄)₂ (Fig. 12)^{96,97} to obtain **52a** as a racemic mixture. The *trans* diastereoselectivity was consistent with the coordination (chelation) of the zinc with the carbonyl oxygens of both ketone and ester, forming the cyclic chelated species **53** (Fig. 12). Hydride from the borohydride is delivered to the carbonyl carbon (*Re*) face from the same side of the ester group.

[00130] The mixture of *trans* racemate (+/-)-**52a** was resolved by enzyme-mediated chiral resolution using Amano PSD Lipase enzyme to form the desired product in the acetylated form (compound (-) **54**, Fig. 13). No hydrolysis of the ester group of (+/-) **52a** was observed since the reaction was performed under anhydrous conditions. The stereochemistry at the secondary hydroxyl carbon of the other *trans* isomer (-) **52a** and its enantiomeric purity were determined by Mosher ester analysis (*R*, 99 % ee).⁷⁷

[00131] Selective saponification of the secondary ester functionality of ester **54** gave the desired alcohol (+) **52a** in 92 % yield and 98 % ee as determined by Mosher ester analysis.⁷⁷ Protection of the secondary hydroxyl group of (+) **52a** with chlorotriethylsilane (TESCl) gave the protected cyclic ester (-) **55** in 93 % yield (Fig. 19). The ester group of compound **55** was reduced using diisobutylaluminum hydride (DIBAL-H) to give the corresponding aldehyde **56**, which was converted directly to the vinyl iodide **58** using the α -iodoethyl ylide **57** prepared *in situ* as shown in Fig. 15.⁹⁸

[00132] These 1-iodoalkyl ylides are reported to form mainly the (*Z*)-iodoalkenes upon reaction with aldehydes (>20: 1, *Z*: *E*).⁹⁸ The (*Z*) stereochemistry at the double bond of **58** was confirmed

by NOESY (2D NMR) experiment. The NMR study showed a strong NOESY interaction between the protons of the methyl group on the double bond with the vinylic proton of the (*Z*) configuration. This interaction would not appear in the (*E*) isomer. In a similar manner, the racemic mixture of vinyl iodide (+/-) **58** was made starting from the racemic trans β -hydroxy ester (+/-) **52a** (Fig. 16).

[00133] **Coupling between fragments 44 and (+/-) 58**

[00134] Suzuki coupling reaction was the next step after making the two necessary fragments (olefin **44** and the (*Z*)-vinyl iodide **58**). *Borane*-alkyl Suzuki coupling of the enantiomerically pure olefin **44** with the enantiomerically pure (*Z*)-vinyl iodide **58** gave the desired *Z*-olefin as a single isomer (Fig. 17).

[00135] The next step was the conversion of the methyl ester of **61** to the corresponding carboxylic acid **62** (Fig. 18). This was achieved by DIBAL-H reduction, followed by Pinnick's oxidation, though the yields were low. Successful Yamaguchi macrolactonization of hydroxyacid **63** furnished the macrolactone **64**. Subjecting **64** to zinc dust in slightly acidic ethanol (using anhydrous ammonium chloride) removed the Troc protecting group to give compound **65**. The crude product of **65** was treated with tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F) in DMF to give the first target analogue **6b**. TAS-F is a mild reagent that is usually used for the deprotection of silyl protecting groups in compounds that are sensitive to both acidic and basic conditions.¹⁰³ The first target molecule was synthesized, though in a low yield, due in part to the incompatibility of the Troc protecting group with the reduction step (conversion of **61** to **62** as shown in Fig. 18).

[00136] In view of the low yields obtained, at this stage, strategy was changed by proceeding with the esterification first, and then closing the macrolactone ring using olefin metathesis approach. A convergent synthetic approach was adapted as before using three key fragments **67**, **68**, and **69** (Fig. 19). The metathesis approach necessitated synthesis of compound **66**. The aldol product, formed by coupling between aldehyde **67** and ketone **68**, was converted to the corresponding carboxylic acid fragment and then coupled to alcohol **69** to give **66**. This intermediate was then subjected to olefin metathesis to yield the desired product.

[00137] **Synthesis of aldehyde 67**

[00138] Aldehyde **67** was made using the Evans asymmetric alkylation protocol⁸⁴ as described earlier for similar fragment (Fig. 20). Wittig olefination of the ketone in

commercially available 6-oxoheptanoic acid **70** gave compound **71**. The carboxylic acid group of **71** was then converted to the acid chloride **72** using oxalyl chloride. Coupling between **72** and the commercially available chiral auxiliary (*S*)-(-)-4-isopropyl-2-oxazolidinone gave the imide **73** in 81.6% yield over three steps starting from commercially available material. The method furnished imide **73** in a much simpler way and in higher yield compared to the approach reported by Schinzer et al. (39.6% yield over three steps).¹⁰⁴ Imide **73** was then converted to the aldehyde **67** following Schinzer's method (Fig. 20). Enolization of imide **73** using sodium hexamethyldisilazane (NaHMDS) in THF at -78°C, followed by reaction with excess methyl iodide gave the stereoselectively alkylated product **74** (10:1 ratio of diastereomers by ¹H NMR spectroscopy of the crude product). Reductive removal of the chiral auxiliary using LiAlH₄ gave alcohol **75** that was subjected to Dess-Martin periodinane oxidation to give aldehyde **67** (same spectral data as reported by Schinzer).¹⁰⁴

[00139] **Synthesis of ketone 68**

[00140] The bis(silyl ether) ketone **68**, with which **67** would be coupled, was made as shown in Fig. 21. Ozonolysis of the terminal double bond of compound **26** under reducing conditions (Ph₃P) gave aldehyde **76**. Selective reduction of the aldehyde group of **76** in the presence of the ketone group was accomplished by using NaBH₄ in methylene chloride/methanol solution to give the primary alcohol **77** as an equilibrium mixture with its hemiacetal **78**. The crude mixture was subjected to TBSCl and imidazole to give the bis-TBS ketone **68** in 81 % yield over two steps.

[00141] **2.3.3 Aldol coupling between aldehyde 67 and ketone 68**

[00142] Highly diastereoselective aldol reaction between the aldehyde **67** and ketone **68** under kinetic control using LDA at -78 °C generated the aldol **79** (Fig. 22). The desired *syn* aldol **79** was formed together with the other *syn* product (10:1) without any detectable formation of the *anti* product. The (*S*)-stereochemistry at the C7 position was confirmed by Mosher ester analysis.⁷⁷ The hydroxyl group of aldol **79** was protected with Troc group to give compound **80**. The TBS group attached to the primary hydroxyl was selectively removed using a catalytic amount of camphorsulfonic acid in methanol/methylene chloride at 0 °C to give compound **81**. Oxidation of the primary hydroxyl group of **81** using Dess-Martin periodinane reagent gave the corresponding aldehyde **82**. Pinnick's oxidation of aldehyde **82** gave carboxylic acid **83**.

[00143] The alcohol **69** was synthesized as shown in Fig. 23a. Wittig olefination of enantiomerically pure aldehyde **56** gave the corresponding olefin **84** which was treated with tetrabutylammonium fluoride (TBAF) to give the desired alcohol **69**. At this stage, the relative *trans* stereochemistry of the protons H5 and H3 in the cyclopentene moiety were confirmed on the basis of relevant correlations observed in the NOSEY experiment. The assignment was on the basis of strong NOESY correlations observed for H2/H1, H2/H4 α , H2/H5, and H3/H4 β and for a little weaker correlations observed for H1/H3 and H5/4 α (Figure 29). Since the absolute stereochemistry was already assigned at the secondary hydroxyl carbon using Mosher ester analysis (see compound (+) **52a**, Fig. 13), compound **69** depicted in Fig. 23b represents the absolute stereochemistry of this fragment.

[00144] **Coupling between acid 83 and alcohol 69**

[00145] The carboxylic acid **83** was coupled with alcohol **69** using DCC/DMAP in methylene chloride to give ester **85** (Fig. 24). Ring closure to form the sixteen-membered ring target molecule was then achieved by an intramolecular olefin metathesis approach using a second generation Grubb's catalyst (0.2 equivalents) under reflux for 7 hours to obtain the macrolactone **64** as a mixture of *E:Z* isomers. The crude mixture of **86** was purified by flash column chromatography. It was difficult to remove traces of the catalyst from the metathesis product **64**; therefore, this material was used directly in the next step. Treating the macrolactone **64** mixture with zinc dust and ammonium chloride in dry ethanol removed the Troc protecting group. The crude product was treated with TAS-F in DMF to give the first target analogue **6b** in 40% yield over two steps from **85**. The *E* and *Z* isomers were separated by preparative TLC. The stereochemistry of the formed double bond in the two isomers was determined by a NOESY experiment.

[00146] The low yield of the last two deprotection steps was attributed to the instability of the olefin metathesis product **64**. These last few steps were therefore modified, where the full deprotection was performed before metathesis (Fig. 25). Treating compound **85** with zinc dust and ammonium chloride in dry ethanol resulted in the removal of the Troc protecting group to give **86** that was then treated directly with TAS-F to give intermediate **66** in 69% yield over two steps. Finally, ring closure of **66** using the second generation Grubb's catalyst gave the desired target molecule **6b** as a *Z/E* mixture. The *Z/E* isomers were separated by preparative TLC. The formation of desired *Z* isomer was slightly more favored over the *E*

isomer.

[00147] Three novel conformationally restrained epothilones **5a**, **5b** and **6b** were synthesized. The results of these methodologies help establish whether the conformational relationship of the aromatic side chain to the macrolactone ring contributes to the bioactivity of the epothilone molecule and offers an opportunity to synthesize active epothilone analogues.

[00148] Stereoselective Reduction of the ketone group of (+/-) 87

[00149] The next step was to stereoselectively reduce the ketone group of (+/-) **87** to the corresponding alcohol. **87** is a racemic mixture. Therefore, a non stereoselective reduction gives a mixture of four isomers (two *cis* and two *trans*) (Figure 31). The racemic beta-keto esters **87** are then converted to the corresponding enantiomerically pure *trans*-beta-hydroxyesters **88** or to the racemic *trans* products.

[00150] Different conditions for stereoselective reduction were attempted without success.

Zinc borohydride $Zn(BH_4)_2$ which gave *trans* diastereoselectivity in the synthesis of phenyl analogue failed in the case of the pyridine analogue (+/-) **87**, which may be due to the coordination of the zinc ion with the pyridine nitrogen. Surprisingly, treating (+/-) **87** with excess of sodium borohydride failed to reduce it. This may have been due to the increased stabilization of the enolate because of the high electron density of the pyridine ring and hence delocalization of the negative charge through olefinic bond. This extended conjugated system may lower the electrophilicity of the carbonyl carbon making it resistant to reduction. To remove this extended conjugation, the beta-keto ester (+/-) **87** was treated with trifluoroacetic acid to convert it to the corresponding salt. Treatment of this trifluoroacetate salt with sodium borohydride rapidly reduced the β -keto ester (+/-) **87** to a mixture of all the four diastereomers (Figure 31). The *cis* and the *trans* diastereomers were separated using column chromatography.

[00151] The *trans* stereochemistry of 88/89

[00152] The *trans* stereochemistry of **88/89** was confirmed by NOESY experiment. The *trans* mixture **88/89** was subjected to enzyme mediated chiral resolution using Amano PSD Lipase enzyme and vinyl acetate in pentane as for phenyl analogue (Figure 32). The desired enantiomer **88** was acetylated to give compound **92** while the other *trans* enantiomer **89** remains unchanged.

[00153] Synthesis of alcohol 96

[00154] Saponification of the secondary ester functionality of ester **92** gave the desired alcohol **88** in 94 % yield and 95 % ee as determined by Mosher ester analysis (Figure 33).⁵⁶⁻⁵⁷ The NOESY experiment was performed to confirm the *trans* configuration of **88**. The *cis* isomer **90/91** showed a strong NOE between the two protons at the two stereogenic centers and no such NOE was observed between the two corresponding protons in **88a** and **88b/88c** (Figure 34). Protection of the secondary hydroxyl group of **88** with chlorotriethylsilane (TESCl) gave **93** in 94 % yield (Figure 33). Reduction of the ester group of compound **93** using diisobutylaluminum hydride (DIBAL-H) gave the corresponding aldehyde **94**. Wittig olefination of enantiomerically pure aldehyde **94** using methyl triphenylphosphonium bromide and *n*-butyl lithium gave the corresponding olefin **95**. Deprotection of **95** using tetrabutylammonium fluoride (TBAF) gave the desired alcohol **96**.

[00155] **Coupling between acid 83 and alcohol 96**

[00156] The carboxylic acid **83** was coupled with alcohol **96** using DCC/DMAP in methylene chloride to give ester **97** (Figure 35). The TBS protecting group was removed by treating **97** with TAS-F to give **98** which was then treated directly with zinc dust and ammonium chloride in dry ethanol to give intermediate **99** in 67% yield over two steps. Finally, ring closure of **99** using the second generation Grubb's catalyst gave the desired target molecule **100** (The *Z* configuration of the double bond was confirmed by NOESY) along with the phenyl analogue **101** and the dimer **102**.

[00157] **Examples**

[00158] The examples below are used for a more detailed explanation, without intending that it be limited to these examples.

[00159] **Materials and Methods**

[00160] **General Techniques.** All reactions were carried out under an argon or nitrogen atmosphere using dry solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether were distilled under nitrogen from sodium-benzophenone. The solvents used were ACS grade from Fisher. Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous materials, unless otherwise noted. Reagents were purchased from Aldrich and Across, and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.20 mm POLYGRAM[®] SIL silica gel plates (Art.-Nr. 805 023) with fluorescent

indicator UV₂₅₄ using UV light and 15% sulfuric acid in ethanol solution and heat as visualizing agents. Normal phase flash column chromatography was carried out using Davisil[®] silica gel (100-200 mesh, Fisher). Preparative thin-layer chromatography (PTLC) separations were carried out on 1 mm, or 2mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on INOVA 600, Varian VXRS-400, or Bruker AC-F 300 MHz instruments and calibrated using residual undeuterated solvent as an internal reference. Coupling constants (*J*) were expressed in Hertz. Attached proton tests (APT) were performed to distinguish between different carbons in the ¹³C NMR spectra. The following abbreviations were used to explain the multiplicities: s = singlet, t = triplet, q = quartet, m = multiplet, and b = broad. Optical rotations were recorded on an AUTOPOL[®] III 589/546 polarimeter. High-resolution mass spectra (HRMS) were recorded on a Micromass LCT Electrospray mass spectrometer performed at the Mass Spectrometry & Proteomics Facility (The Ohio State University). Ozone was generated by passing 100% oxygen through commercial ozone generator (Model T-408; Welsbach Corp.).

(+)Allyldiisopinocampheylborane solution in pentane was prepared by an adaptation of a procedure reported by Brown *et al.*⁷³ Allylmagnesium bromide (5.82 ml of 1 M solution in ether, 5.82 mmol) was added dropwise to a well-stirred solution of (-)-*B*-methoxydiisopinocampheylborane (1.92 g, 6.062 mmol) in ether (35 ml) at 0 °C. After addition was complete, the reaction mixture was stirred at room temperature for 1h, and the solvents were pumped off under reduced pressure. The residue was extracted with dry pentane (3 x 13 ml) under nitrogen, and the stirring was discontinued to allow the precipitation of the MgBr(OMe) salt. The clear pentane supernatant was cannulated into another flask through a filtering funnel, and used without further purification.

[00161] Jones reagent was prepared by dissolving chromium trioxide (26.72 g) in concentrated sulfuric acid (23 ml) diluted with water to a volume of 100 ml.

[00162] Zinc borohydride (0.3M solution in dry ether) was prepared by addition of saturated solution of anhydrous zinc chloride (12 g, 88.05 mmol, oven dried at 130 °C for 8 h under vacuum) in ether (50 ml) to NaBH₄ (8.1 g) in ether (150 ml).^{96,97}

[00163] **1-Pyridin-2-yl-hexane-1,4-dione (12) 76**

[00164] To a solution of 2-pyridinecarboxaldehyde (**11**) (1 g, 9.35 mmol), ethyl vinyl ketone (0.78 g, 9.35 mmol, 1 equiv), and triethylamine (0.65 ml, 4.68 mmol, 0.5 equiv) was added 3-

ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (0.118 g, 0.468 mmol, 0.05 equiv). After stirring the reaction mixture for 12 hours at room temperature, methylene chloride (50 ml) was added. The organic phase was washed with 1N aqueous HCl (20 ml), brine (20 ml) and then dried over anhydrous sodium sulfate. The solvents were evaporated *in vacuo* and the residue was subjected to flash column chromatography (EtOAc / hexanes, 1:10) to give the pure product **12** (1.214 g, 68%) as a yellow oil: TLC R_f = 0.47 (silica gel, 33 % EtOAc / hexanes); ^1H NMR (600 MHz, CDCl_3) δ 8.67-8.66 (m, 1H), 8.0-7.98 (m, 1H), 7.82-7.79 (m, 1H), 7.46-7.43 (m, 1H), 3.52-3.49 (t, 3J = 6 Hz, 2H), 2.86-2.83 (t, 3J = 6 Hz, 2H), 2.56-2.52 (q, 3J = 7.2 Hz, 2H), 1.09-1.06 (t, 3J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 210.163, 200.727, 153.441, 149.187, 137.003, 127.320, 121.952, 36.170, 32.098, 8.069; HRMS calcd for $\text{C}_{11}\text{H}_{13}\text{NO}_2 + \text{Na}^+$ 214.0844; found 214.0839 [M + Na^+].

[00165] **2-Methyl-3-pyridin-2-yl-cyclopent-2-enone (13)**

[00166] A solution of the diketone **12** (1.2 g, 6.28 mmol) in dry ethanol (20 ml) was added dropwise to a solution of sodium hydroxide (0.251 g, 6.28mmol, 1 equiv) in dry ethanol (10 ml). The solution was stirred overnight at room temperature. Saturated aqueous ammonium chloride (30 ml) was added and the mixture was concentrated *in vacuo* to remove most of the ethanol. The resultant crude was extracted with ethyl acetate (3 x 30 ml) and the combined organic extracts were dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give an oil that was purified by flash column chromatography (EtOAc-hexane, 1:10) to give the cyclic ketone **13** (0.87 g, 80%) as a light brown solid: TLC R_f = 0.55 (silica gel, 25% hexanes / EtOAc); ^1H NMR (600 MHz, CDCl_3) δ 8.74-8.72 (m, 1H), 7.79-7.76 (m, 1H), 7.56-7.55 (d, 3J = 7.8 Hz, 1H), 7.30-7.27 (m, 1H), 3.04-3.0 (m, 2H), 2.08-2.06 (m, 2H), 2.08-2.07 (m, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 210.667, 164.865, 155.046, 150.082, 139.103, 136.529, 123.854, 123.577, 34.161, 28.344, 10.334; HRMS calcd for $\text{C}_{11}\text{H}_{11}\text{NO} + \text{H}^+$ 174.0919; found 174.0936 [M + H^+].

[00167] **(1S)-2-Methyl-3-pyridin-2-yl-cyclopent-2-enol (9)**

[00168] To a solution of ketone **13** (0.2 g, 1.16 mmol) in THF (2 ml) was added (*R*)-2-methyl-CBS-oxazaborolidine (0.35 ml of 1.0 M solution in toluene, 0.35 mmol, 0.3 equiv) at room temperature. To this solution was added borane-THF (0.755 ml of 1.0 M solution in THF, 0.755 mmol 0.65 equiv) dropwise. The reaction mixture was stirred at room temperature for 30 min after which time another portion of borane-THF (0.8 ml) was added and the mixture

was stirred for an additional 3 hours. It was then cooled to 0 °C and quenched carefully by slow addition of water (2 ml). The mixture was extracted with ethyl acetate (3 x 4 ml). The organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give a yellow color oil that was purified by flash column chromatography (EtOAc-hexanes, 1:7) to give the alcohol **9** (0.174 g, 86%) as a light yellow solid: $[\alpha]_D^{22} = -16.2$ (c=0.9, CHCl₃); TLC R_f= 0.47 (silica gel, 25% hexanes / EtOAc); ¹H NMR (600 MHz, CDCl₃) δ 8.6-8.59 (d, ³J= 4.8 Hz, 1H), 7.66-7.62 (m, 1H), 7.28-7.26 (d, ³J= 7.8 Hz, 1H), 7.13-7.10 (m, 1H), 4.75-4.74 (m, 1H), 2.89-2.83 (m, 1H), 2.73-2.67 (m, 1H), 2.42-2.36 (m, 1H), 2.05 (s, 3H), 2.01-1.99 (d, ³J= 7.8 Hz, 1H), 1.77-1.71 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 156.750, 149.405, 140.980, 137.494, 136.153, 122.930, 121.717, 82.459, 32.923, 32.771, 13.301; HRMS calcd for C₁₁H₁₃NO + H⁺ 176.1075; found 176.1080 [M + H⁺].

[00169] **1-Chloro-3-methyl-but-2-ene (16) and 3-chloro-3-methyl-but-1-ene (17)** ⁷⁹

[00170] Concentrated HCl (12.0 M) (300 ml) was added to 2-methyl-but-3-en-2-ol (**15**) (100 ml, 82.4 g, 0.957 mmol). The solution was stirred at room temperature for 50 min. The upper organic layer was separated after addition of water and dried over anhydrous potassium carbonate. Removal of solvent under reduced pressure gave an oily material. It was purified by fractional distillation at atmospheric pressure using a fractionating column with a nichrome wire to give a mixture of **16** and **17** (50 g, 55%) as a colorless oil: bp 111-113 °C. ¹H NMR (300 MHz, CDCl₃) δ 6.05-6.15 (dd, ³J= 10.6 Hz, ²J= 17.2 Hz, 1H, **17**), 5.4-5.5 (m, 1H, **16**), 5.2 (d, ³J= 17.2 Hz, 1H, **17**), 5.0 (d, ³J= 10.6 Hz, 1H, **17**), 4.0-4.1 (d, ³J= 8.0 Hz, 2H, **16**), 1.8 (s, 6H, **17**), (s, 6H, **17**).

[00171] **4,4-Dimethyl-hex-5-en-3-one (18)** ⁷⁵

[00172] Magnesium turnings (11 g, 0.452 mol) were placed in a three-necked round-bottomed flask equipped with a dropping funnel, reflux condenser, and a magnetic stirrer and charged with dry THF (50 ml) under nitrogen. A small crystal of iodine and a few drops of prenyl chloride mixture (**16** and **17**) were added. After stirring at room temperature for 5-10 min, during which time the iodine color disappeared, the reaction mixture was cooled to -10 to -15 °C and diluted with dry THF (30 ml). A solution of prenyl chloride mixture (**16** and **17**) (15.53 g, 0.15 mol) in dry THF (100 ml) was added dropwise through the dropping funnel over 1.5 h. The reaction mixture was allowed to warm to room temperature and stirred for 45 min. The resulting solution was transferred dropwise over a period of 30 min via a cannula,

into a three-necked round -bottomed flask containing propionyl chloride (26.25 g, 0.3 mol) in dry THF (100 ml) maintained at -78 °C under N₂. The resulting mixture was allowed to warm to room temperature, stirred for two hours, and poured into water (300 ml). The upper organic layer was removed and the aqueous layer was extracted with two 50 ml portions of ether. The combined organic layers were washed with 2.0 M sodium hydroxide (500 ml) and brine (250 ml). It was dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give an oil which was distilled at reduced pressure to give ketone **18** (11.5 g, 61%) as colorless oil: bp 72-74 °C /40 Torr. ¹H NMR (300 MHz, CDCl₃) δ 5.9-6.0 (dd, ³J = 10.6 Hz, ²J = 17.2 Hz, 1H), 5.14 (dd, ³J = 0.7 Hz, ²J = 17.2 Hz, 1H), 5.14 (dd, ³J = 0.7 Hz, ²J = 10.5 Hz, 1H), 2.45-2.55 (q, ³J = 7.2 Hz, 2H), 1.3 (s, 6H), 0.95-1.05 (t, ³J = 7.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 213.784, 142.783, 113.967, 51.657, 30.542, 23.593, 8.210.

[00173] **(5R*,6S*)-6-Hydroxy-3,3,5,7-tetramethyl-oct-1-en-4-one [(+/-) 19a]**

[00174] A solution of LDA (44 ml, 88mmol, 1.1equiv) in dry THF (100 ml) was cooled to -78 °C under N₂. To this solution was added dropwise ketone **18** (10 g, 80 mmol, 1 equiv). After stirring at -78 °C for 45 min, isobutyraldehyde (8.72 ml, 96 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred at -78 °C for 45 min. Water was added and the lower aqueous layer was extracted with ether. The ether extract was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The oily crude material was distilled at reduced pressure to give compound (+/-) **19a** (12.72 g, 81%) as a colorless oil: TLC R_f = 0.78 (silica gel, 33% EtOAc / hexanes); ¹H NMR (600 MHz, CDCl₃) δ ¹H NMR (600 MHz, CDCl₃) δ 5.9-5.85 (dd, ³J = 10.8 Hz, ²J = 18 Hz, 1H), 5.22 (s, 1H), 5.2-5.19 (d, ³J = 4.8 Hz, 1H), 3.33 (s, 1H), 3.22-3.19 (m, 2H), 1.69-1.61 (m, 1H), 1.24 (s, 3H), 1.22 (s, 3H), 1.01-0.97 (dd, ³J = 6.6 Hz, ²J = 13.2 Hz, 6H), 0.82-0.81 (d, ³J = 7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 219.620, 141.525, 115.660, 76.934, 51.993, 40.812, 30.864, 23.430, 23.278, 19.593, 19.147, 10.842; HRMS calcd for C₁₂H₂₂O₂ + Na⁺ 221.1517; found 221.1517 [M + Na⁺].

[00175] **(5R*,6S*)-6-(tert-Butyl-dimethyl-silanyloxy)-3,3,5,7-tetramethyl-1-oct-1-en-4-one [(+/-)20]**

[00176] In a three-necked round-bottomed flask equipped with a stirrer were placed *tert*-butyldimethylsilyl chloride (TBSCl) (25.670 g, 0.17 mol, 2 equiv) and imidazole (17.4 g, 0.255 mol, 3eq) under N₂. Anhydrous DMF (50 ml) was added followed by compound (+/-)

19a (16.908 g, 0.0852, 1 equiv). The reaction mixture was stirred at 38 °C under N₂ for 72 h. Water (50 ml) was added and the mixture was then extracted with ether (3 x 80 ml). The organic extract was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give an oily residue that was applied to a silica gel column and eluted with (hexanes:CH₂Cl₂, 5:1) to obtain (+/-) **20** (22.64 g, 85%) as a colorless oil: TLC R_f = 0.58 (silica gel, 25% EtOAc / hexanes); ¹H NMR (600 MHz, CDCl₃) δ 5.95-5.90 (dd, ³J = 10.2 Hz, ²J = 17.4 Hz, 1H), 5.18-5.13 (dd, ³J = 10.2 Hz, ²J = 16.8 Hz, 2H), 3.74-3.71 (dd, ³J = 1.8 Hz, ²J = 8.4 Hz, 1H), 3.1-3.05 (m, 1H), 1.45-1.40 (m, 1H), 1.22 (s, 3H), 1.20 (s, 3H), 1.02-1.0 (d, ³J = 6.6 Hz, 3H), 0.89 (s, 9H), 0.88-0.86 (d, ³J = 6.6 Hz, 3H), 0.80-0.78 (d, ³J = 7.2 Hz, 3H), 0.04 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 216.604, 142.598, 114.492, 78.0, 51.754, 45.383, 33.04, 26.458, 24.135, 23.921, 21.156, 18.767, 16.948, 16.164, -3.253, -3.488; HRMS calcd for C₁₈H₃₆O₂Si + Na⁺ 335.2382; found 335.2385 [M + Na⁺].

[00177] (**5R**^{*}, **6S**^{*})-5-(tert-Butyl-dimethyl-silanyloxy)-2,2,4,6-tetramethyl-3-oxo-heptenal (+/-)**21**

[00178] Ozonized oxygen was bubbled through a solution of (+/-) **20** (12 g, 38.462 mmol, 1 equiv) in dry CH₂Cl₂ (40 ml) at -78 °C. The ozone was detected by starch-iodine paper and the reaction was monitored by TLC. The end of ozonolysis was indicated by the blue color appearance in the reaction mixture. The ozone stream was then stopped and the solution was flushed with N₂ for 10-15 min to remove excess ozone. Triphenylphosphine (12.1 g, 46.15 mmol, 1.2 equiv) was then added at -78 °C and the reaction mixture was allowed to reach room temperature and stirred for an additional 1h. The solvent was removed under reduced pressure, and the mixture was purified by flash column chromatography (hexanes:CH₂Cl₂, 3:1) to give aldehyde (+/-) **21** (10.62 g, 88%) as a colorless oil: TLC R_f = 0.67 (silica gel, 33% CH₂Cl₂ / hexane); ¹H NMR (600 MHz, CDCl₃) δ 9.61 (s, 1H), 3.77-3.75 (dd, ³J = 2.4 Hz, ²J = 7.8 Hz, 1H), 3.02-2.96 (m, 1H), 1.48-1.42 (m, 1H), 1.33 (s, 3H), 1.32 (s, 3H), 1.02-1.01 (d, ³J = 7.2 Hz, 3H), 0.88 (s, 12H), 0.79-0.78 (d, ³J = 7.2 Hz, 3H), 0.047 (s, 3H), 0.032 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 212.627, 200.773, 77.173, 61.367, 46.423, 33.468, 26.400, 26.338, 20.517, 19.956, 19.935, 18.660, 16.535, 15.595, -3.463, -3.636; HRMS calcd for C₁₇H₃₄O₃Si + Na⁺ 337.2175; found 337.2171 [M + Na⁺].

[00179] (**3S**^{*}, **4R**^{*}, **7S**)-3-(tert-Butyl-dimethyl-silanyloxy)-7-hydroxy-2,4,6,6-tetramethyl-

dec-9-en-5-one (22a and 22b)

[00180] A solution of (+)-allyldiisopinocampheylborane (5.82 mmol, 1.1 equiv) in pentane (40 ml) ⁷³ was cannulated dropwise to a solution of aldehyde (+/-) **21** (1.661 g, 5.29 mmol, 1 equiv) in ether (20 ml) at -100 °C (ether/dry ice bath). After the addition was complete, the mixture was stirred at the same temperature for 30 min before methanol (1 ml) was added. The mixture was brought to room temperature and saturated aqueous sodium bicarbonate solution (10 ml) was added, followed by H₂O₂ (4 ml of 50% solution in water). The reaction mixture was stirred at room temperature for 12 h and then extracted with ethyl acetate (3 x 15 ml). The combined organic extracts were washed with saturated aqueous ammonium chloride (8 ml), and dried over anhydrous sodium sulfate. The solvents were removed *in vacuo* and the crude oily product was subjected to flash column chromatography (5% EtOAc/hexanes) to give the inseparable diastereomeric mixture (**22a** and **22b**) (1.205 g, 64%) as a clear oil: TLC R_f = 0.59 (silica gel, 33% CH₂Cl₂ / hexane); ¹H NMR (600 MHz, CDCl₃) δ 5.9-5.8 (m, 1H), 5.13-5.08 (m, 2H), 3.79-3.72 (m, 2H), 3.12-3.08 (m, 1H), 2.24-2.2 (m, 1H), 2.04-1.99 (m, 1H), 1.52-1.48 (m, 1H), 1.21 (s, 1H), 1.17-1.15 (m, 4H), 1.11 (s, 1H), 1.08-1.05 (m, 3H), 0.9 (s, 12H), 0.85-0.83 (d, ³J = 7.2 Hz, 3H), 0.1-0.2 (s, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 220.858, 194.799, 136.265, 136.170, 117.739, 117, 471, 78.127, 78.003, 75.705, 75.503, 52.492, 52.402, 45.681, 45.499, 36.447, 36.410, 33.154, 32.915, 26.475, 22.600, 22.419, 21.416, 21.321, 19.745, 19.654, 18.805, 16.808, 16.519, 16.143, 16.048, -3.211, -3.475; HRMS calcd for C₂₀H₄₀O₃Si + Na⁺ 379.2644; found 379.2631 [M + Na⁺].

[00181] **(3S*,4R*,7S)-3,7-Bis-(tert-butyl-dimethyl-silanyloxy)-2,4,6,6-tetramethyl-dec-9-en-5-one (23a and 23b)**

[00182] Alcohols **22a** and **22b** mixture (100 mg, 0.281 mmol) was dissolved in CH₂Cl₂ (1 ml), the solution was cooled at 0 °C, and 2,6-lutidine (82 µL, 0.702 mmol, 2.5 equiv) was added. After being stirred for 5 min at that temperature, *tert*-butyldimethylsilyltrifluoromethane sulfonate (97 µL, 0.422 mmol, 1.5 equiv) was added dropwise and the reaction mixture was stirred at 0 °C for 10 min, after which time no starting material was detected by TLC. Saturated aqueous ammonium chloride (1 ml) was added. The organic phase was separated, and the aqueous layer was extracted with ether (3 x 2 ml). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and the solvents were removed under reduced pressure. Purification by flash column chromatography (silica gel, hexanes / CH₂Cl₂,

4:1) gave pure **23a** and **23b** mixture (123 mg, 93%) as a clear oil: TLC R_f = 0.43 (silica gel, 20% CH_2Cl_2 / hexanes); ^1H NMR (600 MHz, CDCl_3) δ 5.87-5.75 (m, 1H), 5.0-4.95 (m, 2H), 4.07-3.9 (two dd, 1H), 3.76-3.73 (m, 1H), 3.09-3.03 (m, 1H), 2.17-2.03 (m, 2H), 1.50-1.45 (m, 1H), 1.89-1.16 (two s, 3H), 1.05-1.02 (m, 6H), 0.92-0.82 (m, 24H), 0.06-0.007 (m, 12H); ^{13}C NMR (75 MHz, CDCl_3) δ 212.290, 211.717, 137.051, 116.501, 76.806, 76.331, 75.438, 54.285, 45.989, 45.440, 39.810, 39.327, 33.291, 32.980, 26.486, 26.313, 24.946, 21.442, 21.271, 19.532, 18.821, 18.572, 16.316, 16.123, 15.994, 0.205, -3.236, -3.487, -3.758; HRMS calcd for $\text{C}_{26}\text{H}_{54}\text{O}_3\text{Si}_2 + \text{Na}^+$ 493.3509; found 493.3546 $[\text{M} + \text{Na}^+]$.

[00183] **(3S,6R*,7S*)-3,7-Bis-(tert-butyl-dimethyl-silanyloxy)-4,4,6,8-tetramethyl-5-oxo-nonanal (24a and 24b)**

[00184] Ozonized oxygen was bubbled through a solution of **23a/23b** mixture (769 mg, 1.69 mmol) in dry CH_2Cl_2 (4ml) previously cooled at -78°C until the appearance of blue color in the solution. The ozone stream was then stopped and the solution was flushed with N_2 gas for 10 min after which time triphenylphosphine (516 mg, 1.2 eq) was added. The cooling bath was removed and the reaction mixture was allowed to reach room temperature and stirred for an additional 1h. The solvent was removed under reduced pressure, and the mixture was purified by flash column chromatography (silica gel, hexanes / CH_2Cl_2 , 5:1) to give a mixture of the two aldehyde diastereomers **24a** and **24b** (710 mg, 92%) as a colorless oil: TLC R_f = 0.76 (33% CH_2Cl_2 / hexanes); ^1H NMR (600 MHz, CDCl_3) δ 9.8-9.74 (two dd, 1H), 4.60-4.47 (two m, 1H), 3.73-3.70 (m, 1H), 3.09-3.03 (m, 1H), 2.52-2.37 (m, 2H), 1.45-1.40 (m, 1H), 1.22-1.19 (two s, 3H), 1.10-1.0 (m, 6H), 0.90-0.84 (m, 24H), 0.08-0.01 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ 218.931, 218.229, 201.623, 201.416, 194.799, 134.061, 128.751, 128.681, 125.525, 77.887, 71.311, 70.502, 53.969, 53.813, 49.798, 49.295, 46.060, 45.595, 33.307, 32.932, 26.470, 26.161, 26.128, 24.131, 22.782, 21.495, 21.325, 19.485, 18.809, 18.359, 18.334, 16.638, 16.086, 15.900, 0.226, -3.446, -3.847, -3.946, -4.177, -4.259; HRMS calcd for $\text{C}_{25}\text{H}_{52}\text{O}_4\text{Si}_2 + \text{Na}^+$ 495.3302; found 495.3303 $[\text{M} + \text{Na}^+]$.

[00185] **(3S,6R*,7S*)-3,7-Bis-(tert-butyl-dimethyl-silanyloxy)-4,4,6,8-tetramethyl-5-oxo-nonanoic acid (7a and 7b)**

[00186] Aldehyde **24a/24b** mixture (830 mg, 1.76 mmol), *t*-butanol (37 ml), and 2-methyl-2-butene (8.9 ml) were mixed together. A solution of sodium chlorite (1.46 g, 9.17 equiv) and sodium dihydrogen phosphate (1.46 g, 6.92 equiv) in water (10 ml) was added to the aldehyde

mixture dropwise. The reaction mixture was stirred at room temperature for 30 min after which time it was concentrated under reduced pressure. The residue was subjected to flash column chromatography (silica gel, hexanes / methylene chloride, 3:1) to give the first carboxylic acid diastereomer (310 mg), followed by a mixture of the two acid diastereomers (171 mg), and finally the second acid diastereomer (282 mg) (763 mg, 89% overall yield) as colorless sticky liquids:

[00187] data for the first (higher R_f) acid **7a**: $[\alpha]_D^{22} = +6.91$ ($c = 0.6$, CHCl_3); TLC $R_f = 0.70$ (33% EtOAc / hexanes); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 4.52-4.50 (dd, $^3J = 3$ Hz, $^2J = 6.6$ Hz, 1H), 3.74-3.72 (dd, $^3J = 1.8$ Hz, $^2J = 7.8$ Hz, 1H), 3.08-3.03 (m, 1H), 2.47-2.43 (dd, $^3J = 3.6$ Hz, $^2J = 16.8$ Hz, 1H), 2.34-2.30 (dd, $^3J = 7.2$ Hz, $^2J = 16.8$ Hz, 1H), 1.45-1.40 (m, 1H), 1.19 (s, 3H), 1.03-1.02 (m, 6H), 0.90-0.88 (m, 12H), 0.84-0.82 (m, 12H), 0.04-0.03 (m, 12H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 217.821, 178.328, 78.019, 72.367, 54.097, 45.511, 40.007, 33.229, 26.475, 26.223, 22.336, 21.363, 19.300, 18.796, 18.400, 16.511, 16.090, -3.207, -3.479, -4.201, -4.321; HRMS calcd for $\text{C}_{25}\text{H}_{52}\text{O}_5\text{Si}_2 + \text{Na}^+$ 511.3251; found 511.3251 [$\text{M} + \text{Na}^+$].

[00188] data for the second (lower R_f) acid **7b**: $[\alpha]_D^{22} = -10.72$ ($c = 0.6$, CHCl_3); TLC $R_f = 0.68$ (33% EtOAc / hexanes); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 4.4-4.38 (dd, $^3J = 3$ Hz, $^2J = 6.6$ Hz, 1H), 3.74-3.72 (dd, $^3J = 1.8$ Hz, $^2J = 7.8$ Hz, 1H), 3.1-3.05 (m, 1H), 2.47-2.44 (dd, $^3J = 3$ Hz, $^2J = 16.2$ Hz, 1H), 2.31-2.27 (dd, $^3J = 6.6$ Hz, $^2J = 16.2$ Hz, 1H), 1.46-1.41 (m, 1H), 1.2 (s, 3H), 1.09 (s, 3H), 10.4-1.02 (m, 3H), 0.92-0.83 (m, 24H), 0.04-0.03 (m, 12H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 218.642, 178.113, 77.896, 73.431, 53.854, 46.089, 40.379, 32.960, 26.483, 26.223, 23.764, 21.523, 19.023, 18.809, 18.417, 16.193, 15.904, -3.149, -3.455, -4.053, -4.416; HRMS calcd for $\text{C}_{25}\text{H}_{52}\text{O}_5\text{Si}_2 + \text{Na}^+$ 511.3251; found 511.3247 [$\text{M} + \text{Na}^+$].

[00189] **(3S,6R,7S)-3,7-Dihydroxy-4,4,6,8-tetramethyl-5-oxo-nonanoic acid (1S,2E)-2-methyl-3-pyridin-2-yl-cyclopent-2-enyl ester (5) [Higher R_f isomer]**

[00190] To a solution of (higher R_f) carboxylic acid **7a** (7.5 mg, 15.4 μmol) in methylene chloride (0.5 ml), cooled to 0 °C, was added trifluoroacetic acid (75 μl) and the mixture was stirred at 4 °C for 12 h. The mixture was cooled back to 0 °C and pyridine (80 μl) was added dropwise. The solvents were removed *in vacuo* and the oily residue was passed through a plug of silica gel using (ethyl acetate / hexanes, 1:1) to give the fully deprotected acid **8** that was used directly in the next step. To a solution of acid **8** (*ca* 15.4 μmol) in methylene

chloride (0.4 ml) was added a solution of alcohol **9** (3.5 mg, 20 15.4 μmol mol, 1.3 equiv) in methylene chloride (0.5 ml) and DMAP (0.5 mg, 4 15.4 μmol , 0.26 equiv). The reaction mixture was cooled to 0 °C and DCC (20 μl of 1.0 M solution in methylene chloride, 20 μmol , 1.3 equiv) was added. The mixture was stirred at 0 °C for 20 min and at room temperature overnight. The white precipitate formed was removed by filtration and the filtrate was evaporated to dryness. The residue was then passed over flash column chromatography (20% EtOAc / hexanes) to give the target ester **5a** (4 mg, 64% yield over two steps): $[\alpha]_{\text{D}}^{22} = -25.2$ ($c = 0.25$, CHCl_3); TLC $R_f = 0.25$ (silica gel, 50% EtOAc / hexanes); ^1H NMR (600 MHz, CDCl_3) δ 8.63-8.61 (d, $^3J = 4.2$ Hz, 1H), 7.68-7.65 (m, 1H), 7.31-7.29 (d, $^3J = 7.8$ Hz, 1H), 7.16-7.14 (dd, $^3J = 4.8$ Hz, $^2J = 7.8$ Hz, 1H), 5.83 (m, 1H), 4.27-4.24 (m, 1H), 3.36-3.32 (m, 2H), 3.27-3.23 (m, 2H), 2.96-2.91 (m, 1H), 2.80-2.75 (m, 1H), 2.52-2.38 (m, 3H), 2.0 (s, 3H), 1.87-1.82 (m, 1H), 1.71-1.65 (m, 1H), 1.17 (s, 6H), 1.06-1.04 (d, $^3J = 6.6$ Hz, 3H), 1.01-1.0 (d, $^3J = 6.6$ Hz, 3H), 0.87-0.85 (d, $^3J = 6.6$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 222.360, 173.228, 156.073, 149.517, 140.568, 136.372, 136.223, 122.983, 122.067, 85.434, 76.645, 72.792, 52.389, 41.097, 37.123, 33.563, 30.778, 29.482, 21.660, 19.683, 19.316, 19.213, 13.519, 10.623; HRMS calcd for $\text{C}_{24}\text{H}_{35}\text{NO}_5 + \text{Na}^+$ 440.2413; found 440.2396 $[\text{M} + \text{Na}^+]$.

[00191] **(3S,6S,7R)-3,7-Dihydroxy-4,4,6,8-tetramethyl-5-oxo-nonanoic acid (1S,2E)-2-methyl-3-pyridin-2-yl-cyclopent-2-enyl ester (5) [Lower R_f isomer]**

[00192] To a solution of (lower R_f) carboxylic acid **7b** (10 mg, 20.5 μmol) in methylene chloride (0.5 ml), cooled to 0 °C, was added trifluoroacetic acid (75 μl) and the mixture was stirred at 4 °C for 12 h. The mixture was cooled back to 0 °C and pyridine (80 μl) was added dropwise. The solvents were removed *in vacuo* and the oily residue was passed through a plug of silica gel using (ethyl acetate / hexanes, 1:1) to give the fully deprotected acid **8** that was used directly in the next step. To a solution of acid **8** (*ca* 20.5 μmol) in methylene chloride (0.5 ml) was added a solution of alcohol **9** (4.7 mg, 26.6 μl , 1.3 equiv) in methylene chloride (0.5 ml) and DMAP (1 mg, 8 μmol , 0.4 equiv). The reaction mixture was cooled to 0 °C and DCC (27 μl of 1.0 M solution in methylene chloride, 27 μmol , 1.3 equiv) was added. The mixture was stirred at 0 °C for 20 min and at room temperature overnight. The white precipitate formed was removed by filtration and the filtrate was evaporated to dryness. The residue was then passed over flash column chromatography (20% EtOAc / hexanes) to give

the target ester **5b** (5.7 mg, 68% yield over two steps: $[\alpha]_D^{22} = -51.9$ ($c = 0.52$, CHCl_3); TLC $R_f = 0.25$ (silica gel, 50% EtOAc / hexanes); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 8.63-8.61 (dd, $^3J = 0.6$ Hz, $^2J = 4.2$ Hz, 1H), 7.68-7.65 (m, 1H), 7.31-7.29 (d, $^3J = 7.8$ Hz, 1H), 7.16-7.14 (dd, $^3J = 4.8$ Hz, $^2J = 7.8$ Hz, 1H), 5.82 (m, 1H), 4.30-4.25 (m, 1H), 3.32 (m, 1H), 3.30-3.24 (m, 3H), 2.96-2.91 (m, 1H), 2.80-2.75 (m, 1H), 2.51-2.48 (dd, $^3J = 2.4$ Hz, $^2J = 16.2$ Hz, 1H), 2.47-2.42 (m, 1H), 2.42-2.38 (dd, $^3J = 10.8$ Hz, $^2J = 16.2$ Hz, 1H), 2.0 (s, 3H), 1.87-1.82 (m, 1H), 1.71-1.65 (m, 1H), 1.19 (s, 3H), 1.14 (s, 3H), 1.06-1.05 (d, $^3J = 6.6$ Hz, 3H), 1.00-0.998 (d, $^3J = 6.6$ Hz, 3H), 0.86-0.85 (d, $^3J = 6.6$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 222.331, 173.270, 156.056, 149.521, 140.584, 136.355, 136.219, 122.983, 122.067, 85.462, 76.621, 72.685, 52.257, 41.286, 36.942, 33.563, 30.815, 29.486, 21.495, 19.737, 19.205, 19.163, 13.544, 10.421; HRMS calcd for $\text{C}_{24}\text{H}_{35}\text{NO}_5 + \text{H}^+$ 418.2593; found 418.2615 $[\text{M} + \text{H}^+]$.

[00193] **5-Benzyloxy-pentanoic acid (29)**

[00194] Jones reagent was added dropwise to an ice cooled solution of 5-benzyloxy-pentan-1-ol **28** (5 g, 25.74 mmol) in acetone (170 ml). Addition of the Jones reagent was stopped when the acetone solution acquired a persistent yellow color with the concurrent formation of green chromium salts. The mixture was filtered and concentrated *in vacuo* to give an oily crude product that was purified by a flash chromatography (EtOAc / hexanes, 1:3) to give compound **29** (4.98 g, 93%) as a colorless oil: TLC $R_f = 0.68$ (silica gel, 50% EtOAc / hexanes); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.35-7.31 (m, 5H), 4.502 (s, 2H), 3.51-3.47 (t, $^3J = 6$ Hz, 2H), 2.41-2.36 (t, $^3J = 6.8$ Hz, 2H), 1.79-1.64 (m, 4H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 179.713, 138.651, 128.609, 127.870, 127.795, 73.158, 69.968, 33.915, 29.243, 21.749; HRMS calcd for $\text{C}_{12}\text{H}_{16}\text{O}_3 + \text{Na}^+$ 231.0997; found 231.0992 $[\text{M} + \text{Na}^+]$.

[00195] **5-Benzyloxy-pentanoyl chloride (30)**

[00196] To a solution of the acid **29** (4.98 g, 24 mmol) in dry benzene (40 ml), was added oxalyl chloride (2.5 ml, 28.8 mmol, 1.2 equiv) dropwise. A drying tube was placed on the flask and the reaction was stirred for 90 min at room temperature. The reaction was concentrated *in vacuo* and used directly in the next step: $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.38-7.27 (m, 5H), 4.50 (s, 2H), 3.51-3.40 (t, $^3J = 6.4$ Hz, 2H), 2.95-2.90 (t, $^3J = 7.2$ Hz, 3H), 1.87-1.78 (m, 2H), 1.71-1.63 (m, 2H); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 173.958, 138.519, 128.949, 128.787, 128.630, 127.862, 73.197, 69.551, 47.032, 28.618, 22.329.

[00197] **3-(5-Benzyloxy-pentanoyl)-4S-isopropyl-oxazolidin-2-one (31)**

[00198] To a solution of (*S*)-4-isopropyl-2-oxazolidonone (1.0 g, 7.74 mmol, 1 equiv) in THF (25 ml) at -78 °C was added *n*-butyllithium (3.1 ml of a 2.5 M solution in hexanes, 7.74 mmol, 1 equiv). After 15 min 5-(benzyloxy)-pentanoyl chloride **30** (1.924 g, 8.514 mmol, 1.1 equiv) was added and the mixture was stirred for 30 min at -78 °C and for 15 min at 0 °C. Saturated aqueous ammonium chloride (7 ml) was added and the resulting slurry was concentrated under reduced pressure. The residue was diluted with ether and washed successively with saturated aqueous sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc/hexanes) gave imide **31** (2.35 g, 95%) as a yellow oil: $[\alpha]_D^{22} = +57.6$ (c=0.50, CHCl₃); TLC R_f = 0.22 (silica gel, 20% EtOAc / hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.30 (m, 5H), 4.50 (s, 2H), 4.45-4.39 (m, 1H), 4.26-4.17 (m, 2H), 3.53-3.48 (t, ³J = 6.4 Hz, 2H), 3.05-2.86 (m, 2H), 2.42-2.32 (m, 1H), 1.81-1.65 (m, 4H), 0.92-0.89 (d, ³J = 6.8 Hz, 3H), 0.88-0.85 (d, ³J = 6.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 173.294, 154.281, 138.798, 128.559, 127.816, 127.692, 73.086, 70.153, 63.535, 58.600, 35.436, 29.300, 28.591, 21.399, 18.173, 14.869; HRMS calcd for C₁₈H₂₅NO₄ + Na⁺ 342.1681; found 342.1669 [M + Na⁺].

[00199] **3-(5-Benzyloxy-2-methyl-pentanoyl)-4S-isopropyl-oxazolidin-2-one (32)**

[00200] Sodium hexamethyldisilazane (6.9 ml of 1.0 M in THF, 6.9 mmol, 1.1 equiv) was added dropwise to a solution of imide **31** (2.0 g, 6.27 mmol, 1 equiv) in THF (12 ml) at -78 °C. The reaction mixture was stirred for 30 min before a solution of iodomethane (1.950 ml, 31.35 mmol, 5 equiv) in THF (2 ml) was added dropwise. After stirring for 7 h at -78 °C, the reaction was quenched with saturated aqueous ammonium chloride (10 ml), and extracted with ether (4 x 50 ml). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give crude **32** (12:1 ratio of diastereomers by ¹H NMR). Purification by flash column chromatography (10% EtOAc/hexanes) afforded pure compound **32** (1.850 g, 89%) as a colorless oil: $[\alpha]_D^{22} = +86.8$ (c=1.60, CHCl₃); TLC R_f = 0.34 (silica gel, 20% EtOAc / hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.34-7.30 (m, 5H), 4.48 (s, 2H), 4.43-4.38 (m, 1H), 4.175-4.15 (d, ³J = 6 Hz, 2H), 3.81-3.72 (m, 2H), 3.49-3.42 (m, 2H), 2.38-2.30 (m, 1H), 1.86-1.76 (m, 1H), 1.69-1.58 (m, 2H), 1.54-1.44 (m, 1H), 1.23-1.20 (d, ³J = 6.8 Hz, 3H), 0.91-0.88 (d, ³J = 6.8 Hz, 3H), 0.87-0.84 (d, ³J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 177.209, 154.281, 138.798, 128.561, 127.794, 127.691, 73.043,

70.478, 63.378, 58.629, 37.729, 29.961, 28.635, 27.641, 18.214, 18.146, 14.901; HRMS calcd for $C_{19}H_{27}NO_4 + Na^+$ 356.1838; found 356.1844 $[M + Na^+]$.

[00201] **(2S)-5-Benzyloxy-2-methyl-pentan-1-ol (34)**

[00202] A solution of aqueous 30% H_2O_2 (2.88 ml, 26.2 mmol) and lithium hydroxide (0.3 g, 12.45 mmol), in distilled water (4 ml) was added to a solution of imide **32** (2.1 g, 6.3 mmol) in dry THF-distilled water (3:1, 40 ml) at $0^\circ C$. After 1h, excess peroxide was quenched by the addition of 1.5 M sodium sulfite solution (19 ml, 28.2 mmol) and the mixture was concentrated in vacuo. The resulting residue (pH \sim 9-10) was washed with methylene chloride (3 x 40 ml) to recover the chiral ligand. The aqueous phase was acidified to pH \sim 1-2 with 1M HCl and extracted with ether (3 x 40 ml). The combined ethereal extracts were dried over anhydrous sodium sulfate and concentrated to give crude acid **33**. A solution of $LiAlH_4$ (7.56 ml 1.0M solution in THF, 1.2 equiv) was added dropwise to a solution of crude acid **33** (ca. 6.3 mmol, 1 equiv) in ether at $-78^\circ C$. The reaction was stirred at $-78^\circ C$ for 20 min, warmed to $0^\circ C$ and stirred for additional 1.5 h. Excess hydride was quenched by dropwise addition of water (0.29 ml), 15% aqueous NaOH (0.29 ml), and water (0.86 ml). Anhydrous sodium sulfate was added, and the resulting suspension was stirred at room temperature for 4 h. The white precipitate formed was filtered through a plug of celite and washed with Et_2O . The filtrate and washings were concentrated under reduced pressure to give a crude oil that was purified by flash column chromatography (15% EtOAc/hexanes) to give alcohol **34** (1.2 g, 92% over two steps) as a colorless oil: $[\alpha]_D^{22} = -7.5$ (c=0.6, $CHCl_3$); TLC $R_f = 0.52$ (silica gel, 50% EtOAc / hexanes); 1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.28 (m, 5H), 4.50 (s, 2H), 3.54-3.40 (m, 4H), 1.76-1.45 (m, 4H), 1.40-1.36 (t, $^3J = 5.6$ Hz, 1H), 1.25-1.15 (m, 1H), 0.94-0.91 (d, $^3J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.798, 128.600, 127.885, 127.765, 73.184, 70.890, 68.406, 35.841, 29.830, 27.365, 16.120; HRMS calcd for $C_{13}H_{20}O_2 + Na^+$ 231.1361; found 231.1338 $[M + Na^+]$.

[00203] **(2S)-5-Benzyloxy-2-methyl-pentanal (25)**

[00204] Dess-Martin periodinane (5.19 g, 12.23 mmol, 1.2 equiv) was added to a solution of **34** (2.1 g) in methylene chloride (20 ml) at $0^\circ C$. The mixture was stirred at room temperature for 10 min, filtered through a plug of celite and concentrated. Flash column chromatography (10% EtOAc/hexanes) gave aldehyde **25** (1.7 g, 82%) as a colorless oil: $[\alpha]_D^{22} = +15.5$ (c=0.5, $CHCl_3$); TLC $R_f = 0.87$ (silica gel, 50% EtOAc / hexanes); 1H NMR

(400 MHz, CDCl₃) δ 9.6 (s, 1H), 7.37-7.26 (m, 5H), 4.5 (s, 2H), 3.51-3.46 (t, ³J = 6 Hz, 2H), 2.41-2.32 (m, 1H), 1.87-1.78 (m, 1H), 1.74-1.60 (m, 2H), 1.52-1.42 (m, 1H), 1.115-1.097 (d, ³J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 205.23, 136.678, 128.62, 127.863, 73.187, 70.171, 46.298, 27.397, 13.529; HRMS calcd for C₁₃H₁₈O₂ + Na⁺ 229.1204; found 229.1221 [M + Na⁺].

[00205] **2,2-dimethyl-3-oxopentanal (38)**

[00206] As reported earlier. ⁸⁶ Colorless liquid: ¹H NMR (400 MHz, CDCl₃) δ 9.61 (s, 1H), 2.52-2.46 (q, ³J = 7.2 Hz, 2H), 1.33 (s, 6H), 1.06-1.02 (t, ³J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 210.085, 201.417, 60.437, 32.549, 19.545, 7.791; HRMS calcd for C₇H₁₂O₂ + Na⁺ 151.0735; found 151.0723 [M + Na⁺].

[00207] **(5S)-5-hydroxy-4,4-dimethyloct-7en-3-one (39)**

[00208] As reported earlier. ⁸⁷ Colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 5.91-5.80 (m, 1H), 5.15-5.10 (m, 2H), 3.78-3.74 (m, 1H), 2.62-2.45 (m, 2H), 2.40-2.38 (d, ³J = 4.8 Hz, 1H), 2.29-2.22 (m, 1H), 2.07-1.98 (m, 1H), 1.17 (s, 3H), 1.14 (s, 3H), 1.05-1.0 (t, ³J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 213.271, 135.917, 117.967, 75.683, 51.462, 36.706, 31.549, 22.089, 19.734, 8.076; HRMS calcd for C₁₀H₁₈O₂ + Na⁺ 193.1204; found 193.1191 [M + Na⁺].

[00209] **(5S)-5-(tert-butyl-dimethyl-silanyloxy)-4,4-dimethyloct-7en-3-one (26)**

[00210] As reported earlier. ⁸⁷ Colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 5.80-5.70 (m, 1H), 5.03-4.96 (m, 2H), 4.0-3.97 (dd, ³J = 5.2 Hz, ²J = 6.4 Hz, 1H), 2.60-2.39 (m, 2H), 2.23-2.08 (m, 2H), 1.1 (s, 3H), 1.08 (s, 3H), 1.0-0.97 (³J = 7.2 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 214.608, 136.416, 116.770, 76.805, 53.127, 39.219, 32.167, 26.208, 22.668, 20.366, 7.923, -3.359, -4.167; HRMS calcd for C₁₆H₃₂O₂Si + Na⁺ 307.2069; found 307.2051 [M + Na⁺].

[00211] **(4S,7R,8S,9S)-12-Benzoyloxy-4-(tert-butyl-dimethyl-silanyloxy)-8-hydroxy-5,5,7,9-tetramethyl-dodec-1-en-6-one (40a)**

[00212] A solution of (5S)-5-(tert-butyl-dimethyl-silanyloxy)-4,4-dimethyl-oct-7-en-3-one **26** (1.268 g, 4.465 mmol, 2.3 equiv) in THF (6 ml) was added dropwise to a solution of freshly prepared LDA in THF [prepared by adding n-butyllithium (2.85 ml of 1.6 M solution in hexanes, 4.56 mmol) to diisopropylamine (0.64 ml, 4.56 mmol) in THF (5 ml) at -78 °C, then warming the solution to 0 °C for 20 min, and finally cooling back to -78 °C]. The reaction

mixture was stirred at -78 °C for 1 h, at -40 °C for 30 min and then cooled back to -78 °C. To this mixture was added, via cannula, a pre-cooled solution of aldehyde **25** (0.4 g, 1.94 mmol, 1 equiv) in THF (10 ml) over 1 min. The reaction mixture was stirred at -78 °C for 10 min and quenched rapidly by injection of a solution of acetic acid (0.53 ml) in THF (1.5 ml). The mixture was stirred at -78 °C for 5 min and then brought to room temperature. Saturated aqueous ammonium chloride (20 ml) and ether (25 ml) were added and the layers were separated. The aqueous layer was extracted with ether (3 x 25 ml) and the organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated. Flash column chromatography (4-20% ether/hexanes) gave recovered ketone **26** (0.5 g) followed by the diastereomerically pure aldol **40a** (0.78 g, 82%) along with other aldol diastereomer **40b** (66 mg, 7%) as colorless oils:

[00213] Data for **40a**: $[\alpha]_D^{22} = -26.1$ (c=1.0, CHCl₃); TLC R_f = 0.36 (silica gel, 25% ether / hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.28 (m, 5H), 5.85-5.7 (m, 1H), 5.05-4.98 (m, 2H), 4.502 (s, 2H), 3.95-3.913 (dd, ³J = 4.4 Hz, ²J = 6.4 Hz, 1H), 3.52-3.44 (m, 3H), 3.35-3.32 (d, ³J = 8.8 Hz, 1H), 3.29-3.22 (q, ³J = 6.4 Hz, 1H), 2.25-2.06 (m, 2H), 1.84-1.50 (m, 5H), 1.181 (s, 3H), 1.125 (s, 3H), 1.05-1.03 (d, ³J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.854-0.837 (d, ³J = 6.8 Hz, 3H), 0.078 (s, 3H), 0.064 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 208.042, 138.909, 136.502, 128.542, 127.853, 127.661, 116.955, 76.716, 75.097, 73.112, 71.168, 54.577, 41.382, 39.789, 35.568, 29.453, 27.123, 26.279, 23.644, 19.567, 18.457, 15.620, 10.020, -3.242, -3.804; HRMS calcd for C₂₉H₅₀O₄Si + Na⁺ 513.3376; found 513.3383 [M + Na⁺].

[00214] **3-Oxo-2-(2-oxo-2-phenyl-ethyl)-pentanoic acid ethyl ester (47a)**

[00215] Ethyl propionylacetate (**45**) (10 g, 69.4 mmol) was added slowly to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 3.33 g, 83.3 mmol, 1.2 equiv) in THF (100 ml) at 0 °C and the mixture was stirred for 30 min. 2-Bromoacetophenone **46a** (15.2 g, 76.34 mmol, 1.1 equiv) in THF (10 ml) was added dropwise and the reaction mixture was stirred at room temperature for 16 h. Saturated aqueous ammonium chloride (60 ml) was added and the mixture was subsequently extracted with diethyl ether (3 X 70 ml). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give a dark yellow oil that was purified by flash column chromatography (EtOAc-hexane, 1:10) to give the diketoester **47a** (14.8 g, 81%) as a yellow

oil: TLC R_f = 0.50 (silica gel, 25% EtOAc / hexanes); ^1H NMR (400 MHz, CDCl_3) δ 7.98 (d, 3J = 8.4 Hz, 2H), 7.58 (m, 1H), 7.46 (m, 2H), 4.18-4.25 (q, 3J = 7.2 Hz, 3H), 3.70-3.3.79 (dd, 3J = 8.4 Hz, 2J = 18.4 Hz, 1H), 3.49-3.57 (dd, 3J = 5.2 Hz, 2J = 18.4 Hz, 1H), 2.70-2.91 (m, 2H), 1.26-1.31 (t, 3J = 7.2 Hz, 3H), 1.10-1.15 (t, 3J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 205.42, 197.43, 169.26, 136.29, 133.63, 128.81, 128.31, 61.864, 53.20, 37.68, 36.55, 14.22, 7.84; HRMS calcd for $\text{C}_{15}\text{H}_{18}\text{O}_4 + \text{Na}^+$ 285.1103; found 285.1093 [$\text{M} + \text{Na}^+$].

[00216] **3-Methyl-2-oxo-4-phenyl-cyclopent-3-enecarboxylic acid ethyl ester (+/-48a)**

[00217] A solution of the diketoester **47a** (12 g, 45.8 mmol) in dry ethanol (150 ml) was added dropwise to a solution of sodium hydroxide (1.83 g, 45.8 mmol) in dry ethanol (75 ml) with vigorous stirring. The solution was heated to 50 °C and stirred overnight at that temperature. Ether (1.5 L) was added and the organic phase was washed with 2.0 M hydrochloric acid (3 x 300 ml) and dried over anhydrous sodium sulfate.

[00218] The solvent was removed *in vacuo* to give an oil that was purified by flash column chromatography (EtOAc-hexane, 1:15) to give the cyclic β -ketoester (+/-) **48a** (8.7 g, 78%) as a yellow oil: TLC R_f = 0.40 (silica gel, 25% EtOAc / hexane); ^1H NMR (400 MHz, CDCl_3) δ 7.56-7.52 (m, 2H), 7.50-7.42 (m, 3H), 4.29-4.22 (q, 3J = 7.2 Hz, 2H), 3.59-3.56 (dd, 3J = 3.2 Hz, 2J = 7.6 Hz, 1H), 3.38-3.31 (m, 1H), 3.15-3.07 (m, 1H), 1.99 (s, 3H), 1.35-1.30 (t, 3J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 202.593, 169.605, 166.477, 135.828, 134.955, 130.179, 128.936, 127.954, 61.900, 51.297, 33.671, 14.461, 10.486; HRMS calcd for $\text{C}_{15}\text{H}_{16}\text{O}_3 + \text{Na}^+$ 267.0997; found 267.0974 [$\text{M} + \text{Na}^+$].

[00219] **1-(5-methylpyridin-2-yl)-ethanone (51)**

[00220] To a solution of 2-bromo-5-methyl pyridine **49** (1.73 g, 10 mmol) in dry ether (20 ml), cooled to -78 °C, was added n-butyllithium (6.25 ml of 1.6M solution in hexanes, 10 mmol, 1 equiv) dropwise. The reaction mixture was allowed to warm to -40 °C for 15 min, then cooled back to -78 °C again. N,N-dimethylacetamide (1.023 ml, 11 mmol, 1.1 equiv) was added dropwise and the mixture was stirred at -78 °C for 2h. Saturated aqueous ammonium chloride (10 ml) was added and the organic layer was separated. The aqueous layer was extracted with ether (3 x 10 ml) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give an oily residue that was subjected to flash column chromatography using (5% methanol in methylene chloride) to give compound **51** (0.977 g, 72%) as a yellow oil: TLC R_f = 0.48 (silica gel, 25% EtOAc /

hexanes); ^1H NMR (400 MHz, CDCl_3) δ 8.5-8.48 (m, 1H), 7.96-7.93 (d, $^3J = 8$ Hz, 1H), 7.63-7.60 (m, 1H), 2.70 (s, 3H), 2.414 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 200.239, 151.741, 149.704, 137.786, 137.442, 121.663, 26.017, 18.969; HRMS calcd for $\text{C}_8\text{H}_9\text{NO} + \text{Na}^+$ 158.0582; found 158.0580 $[\text{M} + \text{Na}^+]$.

[00221] **2-bromo-1-(5-methylpyridin-2-yl)ethanone (46b)**

[00222] To a solution of compound **51** (0.9 g, 6.67 mmol) in THF (25 ml) was added Amberlyst A26- Br_3^- (Aldrich, 1.26 mmol Br_3^- / g) (4.76 g, 6 mmol, 0.9 equiv) in one portion. The mixture was stirred at 50 °C for 10 h and the decolorized resin was filtered off and washed with ethyl acetate. The organic solution was washed with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to give an oily residue that was chromatographed on silica gel with (10-30% methylene chloride in hexanes) to give compound **46b** (1.29 g, 91%) as a yellow oil: TLC $R_f = 0.62$ (silica gel, 20% EtOAc / hexane); ^1H NMR (400 MHz, CDCl_3) δ 8.50 (broad s, 1H), 8.02-7.99 (d, $^3J = 8$ Hz, 1H), 7.67-7.64 (dd, $^3J = 1.6$ Hz, $^2J = 8$ Hz, 1H), 4.84 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 192.476, 149.775, 149.317, 138.653, 137.601, 122.594, 32.492, 18.955; HRMS calcd for $\text{C}_8\text{H}_8\text{BrNO} + \text{Na}^+$ 235.9687; found 235.9676 $[\text{M} + \text{Na}^+]$.

[00223] **3-Oxo-2-(2-oxo-2-pyridin-2-yl-ethyl)-pentanoic acid ethyl ester (47b)**

[00224] Ethyl propionylacetate (**45**) (5 g, 34.7 mmol) was added slowly to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 1.665 g, 41.65 mmol, 1.2 equiv) in THF (50 ml) at 0 °C and the mixture was stirred for 30 min. Compound **46b** (8.092 g, 38.17 mmol, 1.1 equiv) in THF (5 ml) was added dropwise and the reaction mixture was stirred at room temperature for 16 h. Saturated aqueous ammonium chloride (30 ml) was added and the mixture was subsequently extracted with diethyl ether (3 X 30 ml). The combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give a dark yellow oil that was purified by flash column chromatography (EtOAc / hexanes, 1:10) to give the diketoester **47b** (7.3 g, 76%) as a yellow oil: TLC $R_f = 0.33$ (silica gel, 20% EtOAc / hexane); ^1H NMR (400 MHz, CDCl_3) δ 8.5 (broad s, 1H), 7.9-7.87 (d, $^3J = 8$ Hz, 1H), 7.67-7.64 (dd, $^3J = 1.6$ Hz, $^2J = 8$ Hz, 1H), 4.23-4.17 (q, $^3J = 7.2$ Hz, 2H), 4.17-4.13 (dd, $^3J = 6$ Hz, $^2J = 8$ Hz, 1H), 3.96-3.89 (dd, $^3J = 8.4$ Hz, $^2J = 18.8$ Hz, 1H), 3.78-3.71 (dd, $^3J = 6$ Hz, $^2J = 18.8$ Hz, 1H), 2.85-2.66 (m, 2H), 2.412 (s, 3H), 1.29-1.25 (t, $^3J = 7.2$ Hz, 3H), 1.27-1.09 ($^3J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 205.463,

198.902, 169.557, 150.697, 149.748, 138.125, 137.344, 121.709, 61.745, 53.460, 37.110, 36.191, 18.944, 14.249, 7.875; HRMS calcd for C₁₅H₁₉NO₄ + Na⁺ 300.1212; found 300.1200 [M + Na⁺].

[00225] **3-Methyl-2-oxo-4-pyridin-2-yl-cyclopent-3-enecarboxylic acid ethyl ester (+/-) 48b**

[00226] A solution of the diketoester 47b (3.1 g, 11.19 mmol) in dry ethanol (35 ml) was added dropwise to a solution of sodium hydroxide (0.447 g, 11.19 mmol) in dry ethanol (15 ml) with vigorous stirring. The solution was stirred at room temperature overnight. Ether (200 ml) was added and the organic phase was washed with 2.0 M hydrochloric acid (3 x 100 ml). The aqueous layer was cooled to 0 °C and made slightly basic by addition of sodium bicarbonate. The aqueous layer was then extracted with ethyl acetate (3 x 300 ml) and the organic phase was dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* to give an oil that was purified by flash column chromatography (EtOAc / hexanes, 1:10) to give the cyclic β-ketoester (+/-) 48b (2.115 g, 73%) as a yellow oil: TLC R_f = 0.35 (silica gel, 33% EtOAc / hexanes); ¹H NMR (400 MHz, CDCl₃) δ 8.59 (s, 1H), 7.62-7.60 (m, 1H), 7.54-7.52 (m, 1H), 4.27-4.21 (q, ³J = 7.2 Hz, 2H), 3.58-3.55 (dd, ³J = 2.8 Hz, ²J = 7.2 Hz, 1H), 3.42-3.25 (m, 2H), 2.41 (s, 3H), 2.12 (s, 3H), 1.33-1.29 (t, ³J = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 203.180, 169.521, 164.379, 151.379, 150.614, 136.787, 136.482, 134.188, 123.331, 61.688, 51.063, 32.495, 18.617, 14.322, 10.597; HRMS calcd for C₁₅H₁₇NO₃ + Na⁺ 282.1106; found 282.1109 [M + Na⁺].

[00227] **(1R*,2S*,3E)-2-Hydroxy-3-methyl-4-phenyl-cyclopent-3-enecarboxylic acid ethyl ester (+/-) 52a**

[00228] A solution of zinc borohydride (150ml of 0.3M solution in ether, 45 mmol, 4 equiv) was added dropwise at 0 °C to a stirred solution of β-ketoester (+/-) 48a (2.75 g, 11.25 mmol) in THF (5 ml). The mixture was stirred overnight at 4 °C, quenched by slow addition of water and stirred for about 1 hour. Anhydrous sodium sulfate was added and the resulting suspension was filtered and the filtrate was concentrated. The residue was dissolved in methylene chloride and filtered again and dried. Purification by flash column chromatography (EtOAc / hexanes, 1:12) gave recovered starting material (0.27 g, 10%) and racemic β-hydroxyester (+/-) 52a (2.1 g, 75%) as a yellow oil: TLC R_f = 0.17 (silica gel, 25% EtOAc / hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.24 (m, 5H), 4.98 (s, 1H), 4.25-4.20 (q, ³J = 7.2 Hz, 2H), 3.03-2.94 (m, 3H), 2.33-2.31 (d, ³J = 5.6 Hz, 1H), 1.90-1.89 (d, ³J = 1.2

Hz, 3H), 1.33-1.29 (t, $^3J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.878, 137.229, 135.744, 135.076, 128.425, 127.934, 127.336, 83.964, 61.102, 51.799, 37.077, 14.525, 12.825; HRMS calcd for $\text{C}_{15}\text{H}_{18}\text{O}_3 + \text{Na}^+$ 269.1154; found 269.1143 [M + Na^+].

[00229] **(1R,2S,3E)-2-Acetoxy-3-methyl-4-phenyl-cyclopent-3-enecarboxylic acid ethyl ester (-) 84 and (1R,2R,3E)-2-Hydroxy-3-methyl-4-phenyl-cyclopent-3-enecarboxylic acid ethyl ester (-) 52a**

[00230] Vinyl acetate (7.5 ml, 81.4 mmol) was added to a solution of (+/-) **52a** (2 g, 8.13 mmol) in anhydrous pentane (30 ml). Amano PS-D lipase (2.0 g) and 4 Å MS (2.0 g) were added and the suspension was stirred at room temperature. The reaction was monitored by TLC and ^1H NMR and after 4 days 48-50% conversion of (+/-) **52a** to the acetate (-) **54** was achieved. The sieves and lipase were filtered and washed with Et_2O . The solvent was removed and crude product was purified by flash column chromatography (ether / hexanes, 1:4) to give (-) **54** (1.15 g, 49%) as a slightly yellow oil along with (-) **52a** (0.96 g, 48%. 98% ee).

[00231] Data for (-) **54**; : $[\alpha]_{\text{D}}^{22} = -50.5$ (c=0.6, CHCl_3); TLC $R_f = 0.38$ (silica gel, 25% EtOAc / hexanes); ^1H NMR (600 MHz, CDCl_3) δ 7.40-7.25 (m, 5H), 6.06 (s, 1H), 4.22-4.18 (q, $^3J = 7.2$ Hz, 2H), 3.08-2.95 (m, 3H), 2.11 (s, 3H), 1.797 (s, 3H), 1.29-1.26 (t, $^3J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.227, 170.951, 138.398, 136.673, 131.751, 128.491, 128.004, 127.683, 85.90, 61.186, 48.68, 38.625, 21.301, 14.402, 12.867; HRMS calcd for $\text{C}_{17}\text{H}_{20}\text{O}_4 + \text{Na}^+$ 311.1259; found 311.1240 [M + Na^+].

[00232] Data for (-) **52a**; $[\alpha]_{\text{D}}^{22} = -15.2$ (c=0.6, CHCl_3); TLC $R_f = 0.17$ (silica gel, 25% EtOAc / hexane); ^1H NMR (400 MHz, CDCl_3) δ 7.36-7.22 (m, 5H), 5.0 (d, $^3J = 5.2$ Hz, 1H), 4.22-4.17 (q, $^3J = 7.2$ Hz, 2H), 3.06-2.93 (m, 3H), 2.34-2.32 (d, $^3J = 5.6$ Hz, 1H), 1.90 (s, 3H), 1.30-1.27 (t, $^3J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.887, 137.238, 135.753, 135.085, 128.714, 127.943, 127.365, 83.973, 61.111, 51.808, 37.086, 14.534, 12.834.

[00233] **(1R,2S,3E)-2-Hydroxy-3-methyl-4-phenyl-cyclopent-3-enecarboxylic acid ethyl ester (+) 52a**

[00234] Anhydrous potassium carbonate (240 mg, 1.74 mmol) was added at 0 °C to a solution of (-) **84** (500 mg, 1.74 mmol) in dry ethanol (15 ml) and the solution was stirred at room temperature for 12 hr. Ethanol was removed under reduced pressure and the residue was

dissolved in methylene chloride and washed with saturated aqueous solution of ammonium chloride. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography (EtOAc-hexane, 1:3) to give compound (+) **52a** (393 mg, 92%, 99% ee) as a slightly yellow oil: $[\alpha]_D^{22} = +14.8$ (c=0.8, CHCl₃); TLC R_f=0.17 (silica gel, 25% EtOAc / hexane); ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.25 (m, 5H), 4.99 (s, 1H), 4.26-4.20 (q, ³J=7.2 Hz, 2H), 3.05-2.94 (m, 3H), 2.34-2.32 (d, ³J=5.6 Hz, 1H), 1.91-1.89 (d, ³J=1.2 Hz, 3H), 1.34-1.29 (t, ³J=7.2 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 175.184, 137.308, 135.435, 135.419, 128.438, 127.955, 127.328, 83.862, 61.103, 51.680, 37.288, 14.522, 12.896; HRMS calcd for C₁₅H₁₈O₃ + Na⁺ 269.1154; found 269.1148 [M + Na⁺].

[00235] **(1R,2S,3E)-3-Methyl-4-phenyl-2-triethylsilyloxy-cyclopent-3-enecarboxylic acid ethyl ester (-) 55**

[00236] Triethylsilyl chloride (876 μL, 5.22 mmol, 1.5 equiv) was added dropwise to a solution of alcohol (+) **52a** (856 mg, 3.48 mmol) and imidazole (711 mg, 10.44 mmol, 3 equiv) in methylene chloride (25 ml) at 0 °C. After stirring at 0 °C for 2 hr, the reaction was quenched with water (15 ml), and extracted with ethyl acetate (3 x 30 ml). The organic extracts were washed with brine (20 ml), and dried over anhydrous sodium sulfate. Filtration and evaporation of the solvents *in vacuo* furnished an oily crude product which was purified by flash column chromatography (2% EtOAc / hexanes) to give TES ether (-) **55** (1.16 g, 93%) as a yellow oil: $[\alpha]_D^{22} = -34.2$ (c=0.6, CHCl₃); TLC R_f=0.53 (silica gel, 10% EtOAc / hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.22 (m, 5H), 5.11 (s, 1H), 4.24-4.18 (q, ³J=7.2 Hz, 2H), 3.08-2.82 (m, 3H), 1.83 (s, 3H), 1.34-1.29 (t, ³J=7.2 Hz, 3H), 1.02-0.97 (t, ³J=8 Hz, 9H), 0.71-0.64 (q, ³J=8 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 175.525, 137.491, 135.728, 134.988, 128.334, 128.028, 127.172, 84.518, 60.922, 51.813, 38.603, 14.482, 12.965, 7.065, 5.131, 0.179; HRMS calcd for C₂₁H₃₂O₃Si + Na⁺ 383.2018; found 383.2019 [M + Na⁺].

[00237] **(1R,2S,3E)-3-Methyl-4-phenyl-2-triethylsilyloxy-cyclopent-3-enecarbaldehyde (56)**

[00238] A solution of DIBAL-H (2.2 ml, 1.0 M in hexane, 2.2 mmol, 1.1 equiv) was added dropwise to a solution of silyl ether **55** (720 mg, 2 mmol) in toluene (10 ml) at -78 °C. The reaction was stirred at that temperature for 1h and quenched by dropwise addition of saturated

NH₄Cl (1.0 ml). The reaction was allowed to reach room temperature and a saturated solution of Rochelle salt (3.0 ml) and brine (2.0 ml) were added. The mixture was extracted with ethyl acetate (3 x 7 ml) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo* to give crude aldehyde **56** as a colorless liquid which was used in the next step without further purification; ¹H NMR (400 MHz, CDCl₃) δ 9.86-9.85 (d, ³J = 2 Hz, 1H), 7.38-7.25 (m, 5H), 5.08 (s, 1H), 3.12-2.98 (m, 2H), 2.90-2.84 (m, 1H), 1.84 (s, 3H), 1.02-0.98 (t, ³J = 8 Hz, 9H), 0.72-0.65 (q, ³J = 8 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 200.239, 135.465, 133.901, 133.698, 126.638, 126.267, 125.606, 79.549, 57.417, 33.140, 11.303, 5.298, 3.378.

[00239] **(1S,2E)-Triethyl-[5S-(2Z-iodo-propenyl)-2-methyl-3-phenyl-cyclopent-2-enyloxy]-silane (58)**

[00240] To a suspension of ethyl triphenylphosphonium iodide (1.746 g, 4.177 mmol, 3 equiv) in THF (10 ml) at 0 °C was added *n*-butyllithium (1.640 ml of 2.5 M solution in hexanes, 4.1 mmol, 2.95 equiv). The resulting red ylide solution was stirred at room temperature for 30 min before it was added dropwise to a vigorously stirred solution of iodine (1.028 g, 4.05 mmol, 2.90 eq) in THF (30 ml) in the presence of 4 Å MS (590 mg) at -78 °C [The iodine mixture was stirred at room temperature for 30 min before cooling to -78 °C]. The resulting yellow suspension was stirred vigorously for 10 min at -78 °C and for 30 min at -20 °C in an ethylene glycol and dry-ice cooling bath. A solution of sodium hexamethyldisilazane (3.91 ml of 1.0 M in THF, 3.91 mmol, 2.8 equiv) was added dropwise and the mixture was stirred at -20 °C for 15 min. A solution of aldehyde **56** (440 mg, 1.392 mmol, 1 equiv) in THF (2 ml) was added dropwise. After stirring for 45 min at -20 °C the reaction was quenched with saturated aqueous ammonium chloride (0.5 ml). A mixture of hexanes / ethylacetate (4:1, 20 ml) was added and the mixture was filtered through a small plug of silica and the filtrate was concentrated *in vacuo*. Purification by flash chromatography (2% EtOAc/hexanes) gave vinyl iodide **58** (380 mg, 60%) as a pale yellow oil: TLC R_f = (silica gel, % EtOAc / hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.33-7.25 (m, 5H), 5.56 (d, ³J = 8 Hz, 1H), 4.63 (s, 1H), 3.02-2.93 (m, 2H), 2.54 (s, 3H), 2.41-2.30 (m, 1H), 1.84 (s, 3H), 1.02-0.98 (t, ³J = 8 Hz, 9H), 0.69-0.63 (q, ³J = 8 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ; 138.447, 137.931, 136.611, 135.538, 128.310, 127.938, 126.994, 101.780, 86.548, 54.807, 39.558, 33.893, 13.152, 7.252, 5.399; HRMS calcd for C₂₁H₃₂O₃Si + Na⁺; found [M + Na⁺].

[00241] 6-Methyl-hept-6-enoic acid (71)

[00242] *n*-Butyllithium (10.8 ml of 2.5 M in hexanes, 27 mmol, 1.3 equiv) was added to a solution of methyltriphenylphosphonium bromide (9.7 g, 27 mmol, 1.3 equiv) in dimethyl sulfoxide (50 ml) at 0 °C, and the mixture was stirred at room temperature for 1 h. It was added to a solution of 6-oxo-heptanoic acid **70** (3 g, 20.82 mmol, 1 equiv) and *n*-butyllithium (8.33 ml of 2.5 M in hexanes, 20.82 mmol, 1 equiv) in THF (30 ml). The mixture was stirred at room temperature for 48 hr. Water was added and the mixture was acidified with 2 N HCl and extracted with methylene chloride (3 x 50 ml). The organic layer was washed with 10% sodium hydroxide solution. The aqueous layer was acidified with 2.0 N HCl and extracted with ethyl acetate (3 x 60 ml). The organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc / hexanes) gave pure acid **123** (2.32 g, 78%) as a colorless oil: TLC R_f = 0.47 (silica gel, 25% EtOAc / hexanes); ^1H NMR (600 MHz, CDCl_3) δ 4.688 (s, 1H), 4.653 (s, 1H), 2.36-2.33 (t, $^3J = 7.8$ Hz, 2H), 2.03-1.99 (t, $^3J = 7.8$ Hz, 2H), 1.687 (s, 3H), 1.64-1.58 (m, 2H), 1.50-1.44 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 180.696, 145.56, 110.362, 37.54, 34.182, 27.098, 24.436, 22.477; HRMS calcd for $\text{C}_{12}\text{H}_{20}\text{O}_2 + \text{Na}^+$; found $[\text{M} + \text{Na}^+]$.

[00243] 6-Methyl-hept-6-enoyl chloride (72)

[00244] To a solution of the carboxylic acid **71** (2.2 g, 15.5 mmol) in benzene (30 ml), was added oxalyl chloride (3 ml, 34.4 mmol, 2.22 equiv). A drying tube was placed on the flask and the reaction mixture was stirred for 90 min at room temperature before it was concentrated *in vacuo*. The crude acid chloride was used in the next step without further purification: TLC R_f = 0.37 (silica gel, 25 % EtOAc / hexanes); ^1H NMR (600 MHz, CDCl_3) δ 4.69 (s, 1H), 4.67 (s, 1H), 2.90-2.87 (t, $^3J = 7.8$ Hz, 2H), 2.03-2.00 (t, $^3J = 7.8$ Hz, 2H), 1.74-1.66 (m, 2H), 1.69 (s, 3H), 1.58-1.46 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.979, 145.086, 110.717, 46.663, 37.334, 26.421, 24.799, 22.431.

[00245] (4S)-4-Isopropyl-3-(6-methyl-hept-6-enoyl)-oxazolidin-2-one (73)

[00246] To a solution of (*S*)-4-isopropyl-2-oxazolidinone (1.56 g, 12.1 mmol, 1 equiv) in THF (40 ml) at -78 °C was added *n*-butyllithium (4.84 ml of a 2.5 M solution in hexanes, 12.1 mmol, 1 equiv). After 15 min acid chloride (2.14 g, 13.3 mmol, 1.1 equiv) was added and the mixture was stirred for 30 min at -78 °C and for 15 min at 0 °C. Saturated aqueous ammonium chloride (10 ml) was added and the resulting slurry was concentrated *in vacuo*.

The residue was diluted with ether and washed successively with saturated aqueous sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash chromatography (10% EtOAc/hexanes) gave imide **73** (2.94 g, 96%) as a colorless oil: $[\alpha]_D^{22} = +66.7$ ($c = 0.6$, CHCl_3); TLC $R_f = 0.40$ (silica gel, 25 % EtOAc / hexanes); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 4.682 (s, 1H), 4.656 (s, 1H), 4.428-4.40 (m, 1H), 4.263-4.230 (t, $^2J = 9\text{ Hz}$, 1H), 4.198-4.178 (dd, $^2J = 9\text{ Hz}$, $^3J = 3\text{ Hz}$, 1H), 3.01-2.83 (m, 2H), 2.381-2.32 (m, 1H), 2.04-2.01 (t, $^3J = 7.8\text{ Hz}$, 2H), 1.691 (s, 3H), 1.67-1.61 (m, 2H), 1.51-1.46 (m, 2H), 0.904-0.891 (d, $^3J = 7.2\text{ Hz}$, 3H), 0.86-0.848 (d, $^3J = 7.2\text{ Hz}$, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 173.488, 154.311, 145.775, 110.238, 63.546, 58.615, 37.697, 35.609, 28.603, 27.217, 24.275, 22.563, 18.206, 14.877; HRMS calcd for $\text{C}_{14}\text{H}_{23}\text{NO}_3 + \text{Na}^+$ 276.1576; found 276.1567 $[\text{M} + \text{Na}^+]$.

[00247] **(4S)-3-[(2S)-2,6-Dimethyl-hept-6-enoyl]-4-isopropyl-oxazolidin-2-one (74)**

[00248] As reported by Schinzer *et al.*¹⁰⁴ Sodium hexamethyldisilazane (13 ml of 1.0 M in THF, 13 mmol, 1.1 equiv) was added dropwise to a solution of imide **73** (3.0 g, 11.9 mmol, 1 equiv) in THF (15 ml) at $-78\text{ }^\circ\text{C}$. The reaction mixture was stirred for 30 min and a solution of iodomethane (3.74 ml, 60 mmol, 5 equiv) in THF (2 ml) was added dropwise. After stirring for 10 h at $-78\text{ }^\circ\text{C}$, the reaction was quenched with saturated aqueous ammonium chloride (10 ml), and extracted with ether (4 x 50 ml). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo* to give crude product **74** (12:1 ratio of diastereomers by $^1\text{H NMR}$). Purification by flash column chromatography (10% EtOAc/hexanes) afforded compound **74** (2.69 g, 85%) as a colorless oil: $[\alpha]_D^{22} = +87.2$ ($c = 0.5$, CHCl_3); TLC $R_f = 0.47$ (silica gel, 25 % EtOAc / hexanes); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 4.674 (s, 1H), 4.642 (s, 1H), 4.45-4.42 (m, 1H), 4.265-4.23 (t, $^2J = 9\text{ Hz}$, 1H), 4.2-4.17 (dd, $^2J = 9.6\text{ Hz}$, $^3J = 3\text{ Hz}$, 1H), 3.75-3.69 (m, 1H), 2.36-2.29 (m, 1H), 2.01-1.97 (t, $^2J = 7.2\text{ Hz}$, 2H), 1.68 (s, 3H), 1.57-1.30 (m, 4H), 1.195-1.183 (d, $^3J = 7.2\text{ Hz}$, 3H), 0.9-0.888 (d, $^3J = 7.2\text{ Hz}$, 3H), 0.861-0.85 (d, $^3J = 6.6\text{ Hz}$, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 177.338, 153.886, 145.779, 110.214, 63.414, 58.628, 37.903, 37.866, 32.833, 28.632, 25.381, 22.538, 18.165, 18.132, 14.901.

[00249] **(2S)-2,6-Dimethyl-hept-6-en-1-ol (75)**

[00250] As reported by Schinzer *et al.*¹⁰⁴, a solution of lithium aluminum hydride (8.4 ml of 1.0M solution in THF, 8.4 mmol, 1.5 equiv) was added dropwise to a solution of compound

74 (1.5 g, 5.62 mmol, 1equiv) in ether (40 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before it was warmed to room temperature and stirred for an additional 10 h. The reaction mixture was cooled again to 0 °C and excess hydride was quenched by dropwise addition of water (0.32 ml), 15% aqueous sodium hydroxide (0.32 ml), and water (1 ml). Anhydrous sodium sulfate was added, and the resulting suspension was stirred at room temperature for 4 h. The white precipitate formed was filtered through a plug of celite and washed with ether. The filtrate and washings were concentrated *in vacuo* to give a crude oil that was purified by flash column chromatography (15% EtOAc/hexanes) to give alcohol **75** (0.772 g, 97%) as a colorless oil. The column was eluted with ethyl acetate to recover the chiral auxiliary: $[\alpha]_D^{22} = -10.3$ (c=0.8, CHCl₃); TLC R_f = 0.39 (silica gel, 25 % EtOAc / hexanes); ¹H NMR (600 MHz, CDCl₃) δ 4.670 (s, 1H), 4.64 (s, 1H), 3.50-3.46 (m, 1H), 3.41-3.37 (m, 1H), 2.02-1.92 (m, 2H), 1.685 (s, 3H), 1.65-1.34 (m, 4H), 1.12-1.04 (m, 1H), 0.909-0.89 (d, ³J = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 146.224, 110.011, 68.538, 38.237, 35.898, 32.948, 25.146, 22.576, 16.787.

[00251] **(2S)-2,6-Dimethyl-hept-6-enal (67)**

[00252] As reported by Schinzer *et al.*¹⁰⁴ Dess-Martin periodinane (3.23 g, 7.61 mmol, 1.2 equiv) was added to a solution of alcohol **75** (0.9 g, 6.34 mmol) in methylene chloride (12 ml). The mixture was stirred at room temperature for 15 min before it was subjected to flash column chromatography (10% EtOAc/hexanes) to furnish aldehyde **67** (0.745 g, 84%) as highly volatile colorless liquid: $[\alpha]_D^{22} = +11.8$ (c=0.5, CHCl₃); TLC R_f = 0.64 (silica gel, 25 % EtOAc / hexanes); ¹H NMR (600 MHz, CDCl₃) δ 9.57-9.56 (d, ³J = 1.8 Hz, 1H), 4.661 (s, 1H), 4.62 (s, 1H), 2.34-2.28 (m, 1H), 2.01-1.95 (t, ³J = 7.8 Hz, 2H), 1.69-1.62 (m, 4H), 1.48-1.27 (m, 3H), 1.06-1.04 (d, ³J = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 205.282, 145.420, 110.441, 46.390, 37.845, 30.20, 24.969, 22.444, 13.523.

[00253] **(3S)-3-(tert-Butyl-dimethyl-silyloxy)-4,4-dimethyl-5-oxo-heptanal (76)**

[00254] Ozonolysis of olefin **26** was performed by adapting an analogues procedure to Nicolaou's *et al.* procedure.⁸⁷ ¹H NMR (600 MHz, CDCl₃) δ 9.77-9.76 (dd, ³J = 1.8 Hz, ²J = 2.4 Hz, 1H), 4.55-4.53 (dd, ³J = 4.8 Hz, ²J = 6 Hz, 1H), 2.55-2.43 (m, 4H), 1.12 (s, 3H), 1.08 (s, 3H), 1.0-0.97 (t, ³J = 7.2 Hz, 3H), 0.84 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H).

[00255] **(5S)-5,7-Bis-(tert-butyl-dimethyl-silyloxy)-4,4-dimethyl-heptan-3-one (68)**

[00256] Sodium borohydride (570 mg, 15.4 mmol, 2 equiv) was dissolved in methylene

chloride (175 ml) and dry ethanol (75 ml). The mixture was cooled to $-78\text{ }^{\circ}\text{C}$ for 15 min after which a solution of aldehyde **76** (2.2 g, 7.7 mmol, 1 equiv) in methylene chloride (5 ml) was added. After stirring for 1 h water (6 ml) was added and the reaction mixture was allowed to warm to room temperature. Methylene chloride (400 ml) was added and the mixture was washed with saturated aqueous sodium bicarbonate before it was dried over anhydrous sodium sulfate and concentrated *in vacuo* to give crude alcohol mixture **77** and **78**. The crude alcohol mixture was dissolved in methylene chloride (40 ml) and cooled to $0\text{ }^{\circ}\text{C}$. Imidazole (3.14 g, 46.15 mmol, 6 equiv) and *tert*-butyldimethylsilyl chloride (3.47 g, 23.1 mmol, 3 equiv) were added and the reaction mixture was stirred at room temperature for 16 hr. Saturated aqueous ammonium chloride (30 ml) was added and the layers were separated. The aqueous layer was further extracted with ethyl acetate (3 x 30) and combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography (1% - 5% EtOAc/Hexanes) gave the bis(silylether) **68** (2.5 g, 81% over two steps) as a colorless oil: $[\alpha]_{\text{D}}^{22} = -7.4$ ($c = 1.8$, CHCl_3); TLC $R_f = 0.70$ (silica gel, 20% EtOAc / hexanes); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 4.058-4.022 (dd, 1H), 3.62-3.54 (m, 2H), 2.57-2.50 (dq, 1H), 2.48-2.40 (dq, 1H), 1.53-1.41 (m, 2H), 1.085 (s, 3H), 1.022 (s, 3H), 0.985-0.96 (t, 3H), 0.86-0.85 (d, 18 H), 0.067 (s, 3H), 0.018 (s, 3H), 0.013 (s, 3H), 0.002 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 215.783, 73.613, 60.286, 53.247, 37.458, 31.76, 26.276, 26.116, 22.386, 20.199, 18.533, 18.441, 7.941, -3.805, -3.834, -5.105; HRMS calcd for $\text{C}_{21}\text{H}_{46}\text{O}_3\text{Si}_2 + \text{Na}^+$ 425.2883; found 425.2885 $[\text{M} + \text{Na}^+]$.

[00257] **(3S,6R,7S,8S)-1,3-Bis-(tert-butyl-dimethyl-silanyloxy)-7-hydroxy-4,4,6,8,12-pentamethyl-tridec-12-en-5-one (79)**

[00258] A solution of ketone **68** (1.8 g, 4.48 mmol, 2.3 equiv) in THF (5 ml) was added dropwise to a solution of freshly prepared LDA in THF [prepared by adding *n*-butyllithium (2.92 ml of 1.6 M solution in hexanes, 4.67 mmol) to diisopropylamine (4.67 mmol, 0.655 ml) in THF (5 ml) at $-78\text{ }^{\circ}\text{C}$, then warming the solution to $0\text{ }^{\circ}\text{C}$ for 20 min, and finally cooling back to $-78\text{ }^{\circ}\text{C}$]. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h and at $-40\text{ }^{\circ}\text{C}$ for 30 min and was cooled back to $-78\text{ }^{\circ}\text{C}$. A pre-cooled ($-78\text{ }^{\circ}\text{C}$) solution of aldehyde **67** (0.272 g, 1.95 mmol, 1 equiv) in THF (10 ml) was then added via cannula to the mixture over 2 min. The reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 15 min before it was quenched rapidly by injection of a solution of acetic acid (0.55 ml) in THF (1.64 ml). The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for

5 min and brought to room temperature. Saturated aqueous ammonium chloride (20 ml) and ether (25 ml) were added and the layers were separated. The aqueous layer was extracted with ether (3 x 25 ml) and the organic extracts were combined, dried over anhydrous sodium sulfate, and concentrated *in vacuo*. Flash column chromatography (4-20% ether/hexanes) gave recovered ketone **68** (0.78 g) followed by *syn* aldol **79** (0.87 g, 83%) as the pure diastereomer along with other *syn* aldol diastereomer (74 mg, 7%) as colorless oils: $[\alpha]_D^{22} = -39.6$ ($c=0.7$, CHCl_3); TLC $R_f = 0.57$ (silica gel, 20% ether / hexanes); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 4.665 (s, 1H), 6.646 (s, 1H), 3.89-3.87 (dd, $^3J = 2.4$ Hz, $^2J = 7.8$ Hz, 1H), 3.67-3.63 (m, 1H), 3.60-3.55 (m, 1H), 3.30-3.267 (m, 2H), 2.05-1.95 (m, 2H), 1.69 (s, 3H), 1.76-1.26 (m, 7H), 1.187 (s, 3H), 1.074 (s, 3H), 1.02-1.00 (d, $^3J = 6.6$ Hz, 3H), 0.881 (s, 9H), 0.866 (s, 9H), 0.826-0.814 (d, $^3J = 7.2$ Hz, 3H), 0.087 (s, 3H), 0.062 (s, 3H), 0.017 (s, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 222.265, 146.460, 109.855, 75.094, 74.327, 60.707, 54.246, 41.468, 38.440, 35.692, 32.820, 26.388, 26.322, 26.169, 25.030, 23.108, 22.646, 20.702, 18.569, 18.512, 15.590, 9.843, -3.500, -3.847, -5.043; HRMS calcd for $\text{C}_{30}\text{H}_{62}\text{O}_4\text{Si}_2 + \text{Na}^+$ 565.4084; found 565.4067 $[\text{M} + \text{Na}^+]$.

[00259] **(3S,6R,7S,8S)-Carbonic acid-1-[4,6-bis-(tert-butyl-dimethyl-silanyloxy)-1,3,3-trimethyl-2-oxo-hexyl]-2,6-dimethyl-1-hept-6-enyl ester 2,2,2-trichloro-ethyl ester (80)**

[00260] To a solution of aldol **79** (0.80 g, 1.48 mmol) in methylene chloride (30 ml) at 0 °C was added pyridine (0.96 ml, 11.84 mmol, 8 equiv) followed by 2,2,2-trichloroethyl chloroformate (0.8 ml, 5.92 mmol, 4 equiv), and the reaction mixture was stirred at 0°C for 1 h. Saturated aqueous sodium bicarbonate (50 ml) was added and the organic layer was separated. The aqueous layer was extracted with methylene chloride (3 x 50 ml), and the combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (2% EtOAc/hexanes) afforded protected aldol **80** (0.98 g, 93%) as a colorless oil: $[\alpha]_D^{22} = -51.5$ ($c = 1.6$, CHCl_3); TLC $R_f = 0.72$ (silica gel, 17% EtOAc / hexanes); $^1\text{H NMR}$ (600 MHz, CDCl_3) δ 4.85 (d, $^2J = 12$ Hz, 1H), 4.80-4.77 (dd, $^3J = 4.2$ Hz, $^2J = 7.8$ Hz, 1H), 4.66 (d, $^2J = 12$ Hz, 1H), 4.66 (s, 1H), 4.62 (s, 1H), 3.73-3.71 (dd, $^3J = 2.4$ Hz, $^2J = 7.8$ Hz, 1H), 3.63-3.59 (m, 1H), 3.58-3.53 (m, 1H), 3.50-3.45 (m, 1H), 1.98-1.91 (m, 2H), 1.72-1.61 (m, 2H), 1.67 (s, 3H), 1.51-1.42 (m, 2H), 1.31-1.24 (m, 3H), 1.34 (s, 3H), 1.044-1.033 (d, $^3J = 6.6$ Hz, 3H), 0.99 (s, 3H), 0.947-0.936 (d, $^3J = 6.6$ Hz, 3H), 0.88 (s, 9H), 0.85 (s, 9H), 0.082 (s, 6H), 0.001 (s, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ

215.766, 154.468, 145.791, 110.288, 95.014, 83.144, 76.852, 75.824, 60.513, 53.846, 42.693, 38.225, 34.978, 31.541, 26.351, 26.140, 24.911, 23.718, 22.559, 21.231, 18.578, 16.341, 11.320, -3.281, -4.123, -5.047, -5.080; HRMS calcd for C₃₃H₆₃Cl₃O₆Si₂ + Na⁺ 739.3126; found 739.3163 [M + Na⁺].

[00261] **(3S,6R,7S,8S)-Carbonic acid-1-[4-(tert-butyl-dimethyl-silanyloxy)-6-hydroxy-1,3,3-trimethyl-2-oxo-hexyl]-2,6-dimethyl-1-hept-6-enyl ester 2,2,2-trichloro-ethyl ester (81)**

[00262] A solution of bis-silyl compound **80** (0.8 g, 1.11 mmol, 1 equiv) in methylene chloride (30 ml) and methanol (20 ml) was cooled to 0 °C. To this solution was added a solution of (1S)-(+)-10-camphorsulfonic acid (77 mg, 0.33 mmol, 0.3 equiv) in methanol (10 ml). The reaction mixture was stirred at 0 °C for 7 h before it was quenched with saturated aqueous sodium bicarbonate (10 ml). The solid precipitate was filtered and the filtrate was concentrated *in vacuo*. The residue was diluted with ether (100 ml) and washed with brine. The organic layer was separated and the aqueous layer was extracted with ether (3 x 20 ml). The combined organic phases were dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc/hexanes) afforded the unstable alcohol **81** (0.583 g, 87%). It was used directly in the next step; TLC R_f = 0.57 (silica gel, 33% EtOAc / hexanes); ¹H NMR (600 MHz, CDCl₃) δ 4.87-4.80 (m, 2H), 4.694.61 (m, 3H), 3.93-3.90 (dd, ³J = 3.0 Hz, ²J = 7.8 Hz, 1H), 3.67-3.59 (m, 2H), 3.45-3.40 (m, 1H), 1.98-1.90 (m, 2H), 1.66 (s, 3H), 1.1.70-1.42 (m, 8H), 1.256 (s, 3H), 1.07-1.06 (m, 6H), 0.957-0.946 (d, ³J = 6.6 Hz, 3H), 0.886 (s, 9H), 0.101 (s, 3H), 0.084 (s, 3H).

[00263] **(3S,6R,7S,8S)-3-(tert-butyl-dimethyl-silanyloxy)-4,4,6,8,12-pentamethyl-5-oxo-7-(2,2,2-trichloro-ethoxycarbonyloxy)-tridec-12-enoic acid (83)**

[00264] Dess-Martin periodinane (0.545 g, 1.28 mmol, 1.4 equiv) was added to a solution of alcohol **81** (0.550 g, 0.914 mmol) in methylene chloride (4 ml). The mixture was stirred at room temperature for 15 min. Additional amount of Dess-Martin reagent (0.23 g, 0.6 equiv) was added and the reaction mixture was stirred for 15 min and then was subjected to flash column chromatography (10% EtOAc/hexanes) to furnish crude aldehyde **82** that was used directly in the next step. A solution of sodium dihydrogenphosphate (270 mg, 2.25 mmol, 2.46 equiv) and sodium chlorite (270 mg, 3 mmol, 3.27 equiv) in distilled water (5 ml) was added to the crude aldehyde **82** (*ca* 0.914 mmol) in *t*-butanol (25 ml) and 2-methyl-2butene (6

ml). The mixture was stirred at room temperature for 1 h and quenched by addition of saturated aqueous ammonium chloride (50 ml) and water (50 ml). The mixture was extracted with ethyl acetate (3 x 60 ml), and the combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc/hexanes) afforded the pure carboxylic acid **83** (0.505 g, 90% over two steps) as a colorless oil; $[\alpha]_D^{22} = -53.7$ ($c = 0.8$, CHCl_3); TLC $R_f = 0.58$ (silica gel, 40% EtOAc / hexanes); $^1\text{H NMR}$ (600 MHz, CDCl_3) 4.858-4.838 (d, $^2J = 12$ Hz, 1H), 4.78-4.75 (dd, $^3J = 4.2$ Hz, $^2J = 7.2$ Hz, 1H), 4.66 (d, $^2J = 12$ Hz, 1H), 4.66 (s, 1H), 4.617 (s, 1H), 4.227-4.210 (dd, $^3J = 3.6$ Hz, $^2J = 6.6$ Hz, 1H), 3.47-3.41 (m, 1H), 2.62-2.57 (dd, $^3J = 3.6$ Hz, $^2J = 17.4$ Hz, 1H), 2.226-2.187 (dd, $^3J = 6.6$ Hz, $^2J = 16.8$ Hz, 1H), 1.96-1.913 (m, 2H), 1.74-1.68 (m, 1H), 1.66 (s, 3H), 1.52-1.42 (m, 2H), (s, 3H), 1.289-1.261 (d, $^3J = 16.8$ Hz, 3H), 1.055 (s, 6H), 0.949-0.937 (d, $^3J = 7.2$ Hz, 3H), 0.859 (s, 9H), 0.099 (s, 3H), 0.029 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 215.511, 177.734, 154.746, 145.771, 124.163, 110.296, 94.968, 82.665, 76.876, 75.045, 53.784, 42.446, 39.962, 38.204, 34.949, 31.537, 26.289, 26.173, 24.841, 23.029, 22.559, 20.306, 18.367, 16.275, 11.481, -4.300, -4.325; HRMS calcd for $\text{C}_{27}\text{H}_{47}\text{Cl}_3\text{O}_7\text{Si} + \text{Na}^+$ 639.2054; found 639.2079 $[\text{M} + \text{Na}^+]$.

[00265] **(1S,2E,5S)-Triethyl-(2-methyl-3-phenyl-5-vinyl-cyclopent-2-enyloxy)-silane (84)**

[00266] To a pre-cooled (0 °C) solution of methyltriphenylphosphonium bromide (455 mg, 1.27 mmol, 2 equiv) in THF (5 ml) was added n-butyllithium (0.775 ml of 1.6 M solution in hexanes, 1.24 mmol, 1.95 equiv) dropwise. The reaction mixture was stirred at 0 °C for 30 min. A solution of aldehyde **56** (0.2 g, 0.633 mmol) in THF (2 ml) was added and the mixture was stirred at 0 °C for 30 min and quenched with a saturated aqueous ammonium chloride (5 ml). The solvent was removed under reduced pressure, and the aqueous residue was extracted with ethyl acetate (3 x 5 ml). The combined organic extract was dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (5% ether / hexanes) afforded pure olefin **84** (0.14 g, 71%) as a colorless oil: $[\alpha]_D^{22} = -14.3$ ($c = 0.4$, CHCl_3); TLC $R_f = 0.73$ (silica gel, 10% ether/hexanes); $^1\text{H NMR}$ (600 MHz, CDCl_3) 7.34-7.21 (m, 5H), 5.94-5.88 (m, 1H), 5.14-5.10 (d, $^2J = 16.8$ Hz, 1H), 5.05-5.03 (dd, $^3J = 1.8$ Hz, $^2J = 10.2$ Hz, 1H), 4.53-4.52 (d, $^2J = 4.8$ Hz, 1H), 2.88-2.82 (m, 1H), 2.74-2.68 (m, 1H), 2.52-2.47 (m, 1H), 1.82 (s, 3H), 0.99-0.96 (t, $^2J = 7.8$ Hz, 9H), 0.68-0.63 (q, $^2J = 7.8$ Hz, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 141.063, 138.117, 136.318, 135.736,

128.561, 128.277, 127.959, 127.584, 126.915, 115.198, 87.030, 52.072, 40.420, 13.11 7.190, 5.482; HRMS calcd for C₂₀H₃₀OSi + Na⁺ 337.1964 found 337.1970 [M + Na⁺].

[00267] **(1S,2E,5S)-2-Methyl-3-phenyl-5-vinyl-cyclopent-2-enol (69)**

[00268] To a solution of compound **84** (0.48 g, 1.53 mmol) in THF (7 ml) at 0 °C was added tetrabutylammonium fluoride (1.53 ml of 1 M solution in THF, 1.53 mmol) dropwise. The reaction mixture was stirred at 0 °C for 30 min and then water (6 ml) and ethyl acetate (10 ml) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 10 ml). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography (10% EtOAc/hexanes) afforded pure alcohol **69** (0.245 g, 80%) as a white solid: $[\alpha]_D^{22} = -14.17$ (c= 1.2, CHCl₃); TLC R_f = 0.45 (silica gel, 33% EtOAc / hexanes); ¹H NMR (600 MHz, CDCl₃) 7.36-7.23 (m, 5H), 6.00-5.94 (p, 1H), 5.21-5.16 (dd, ³J = 1.2 Hz, ²J = 16.8 Hz, 1H), 5.10-5.07 (dd, ³J = 0.6 Hz, ²J = 10.2 Hz, 1H), 4.48-4.47 (d, ³J = 6.6 Hz, 1 H), 2.85-2.81 (m, 1H), 2.71-2.65 (m, 1H), 2.59-2.54 (m, 1H), 1.89 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 140.407, 137.762, 136.322, 135.893, 128.388, 127.864, 127.146, 115.408, 86.349, 52.369, 39.756, 12.958; HRMS calcd for C₁₄H₁₆O + Na⁺ 223.1099; found 223.1100 [M + Na⁺].

[00269] **(3S,6R,7S,8S)-3-(tert-Butyl-dimethyl-silyloxy)-4,4,6,8,12-pentamethyl-5-oxo-7-(2,2,2-trichloro-ethoxycarbonyloxy)-tridec-12-enoic acid-(1S,2E,5S)-2-methyl-3-phenyl-5-vinyl-cyclopent-2-enyl ester (85)**

[00270] To a solution of acid **83** (13 mg, 0.021 mmol), alcohol **69** (4.6 mg, 0.023 mmol, 1.1 equiv), and DMAP (1 mg, 0.008 mmol, 0.4 equiv) in methylene chloride (0.5 ml) at 0 °C was added DCC (0.027 ml of 1 M solution in CH₂Cl₂, 0.027 mmol, 1.3 equiv) dropwise. The reaction mixture was stirred for 15 min at 0 °C and for 16 h at room temperature. The solid precipitate was filtered off and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography (5% ether / hexanes) afforded ester **85** (11 mg, 64%) as a colorless oil: $[\alpha]_D^{22} = -53.2$ (c= 0.85, CHCl₃); TLC R_f = 0.67 (silica gel, 25% EtOAc / hexanes); ¹H NMR (600 MHz, CDCl₃) 7.36-7.25 (m, 5H), 5.98-5.91 (m, 1H), 5.71-5.69 (d, ³J = 4.2 Hz, 1H), 5.12-5.09 (d, ³J = 17.4 Hz, 1H), 5.04-5.02 (d, ³J = 10.2 Hz, 1H), 4.88-4.85 (m, 1H), 4.72-4.69 (dd, ³J = 3 Hz, ²J = 8.4 Hz, 1H), 4.66-4.60 (m, 3H), 4.30-4.28 (t, ³J = 4.2 Hz, 1H), 3.50-3.46 (m, 1H), 2.96-2.92 (m, 1H), 2.86-2.81 (m, 1H), 2.70-2.66 (dd, ³J = 3.6 Hz, ²J = 17.4 Hz, 1H), 2.59-2.55 (m, 1H), 2.25-2.21 (dd, ³J = 5.4 Hz, ²J = 17.4 Hz, 1H), 1.95-1.87 (m, 2H),

1.75 (s, 3H), 1.66 (s, 3H), 1.54-1.53 (m, 6H), 1.33-1.27 (m, 6H), 1.06-1.04 (m, 3H), 0.966-0.955 (d, $^3J = 6.6$ Hz, 3H), 0.87 (s, 9H), 0.129 (s, 3H), 0.054 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 172.341, 154.439, 145.783, 139.611, 139.334, 137.267, 132.349, 128.417, 127.959, 127.435, 115.284, 110.284, 95.010, 88.252, 82.347, 76.860, 75.020, 55.987, 54.007, 47.570, 42.223, 40.465, 40.267, 38.217, 35.151, 34.883, 31.826, 31.170, 26.219, 25.678, 24.927, 24.795, 22.666, 22.547, 20.653, 18.363, 16.069, 13.103, 11.081, -4.069, -4.532; HRMS calcd for $\text{C}_{41}\text{H}_{61}\text{Cl}_3\text{O}_7\text{Si} + \text{Na}^+$ 821.3150; found 821.3178 $[\text{M} + \text{Na}^+]$.

[00271] **(3S,6R,7S,8S)-3,7-Dihydroxy-4,4,6,8,12-pentamethyl-5-oxo-tridec-12-enoic acid-(1S,2E,5S)-2-methyl-3-phenyl-5-vinyl-cyclopent-2-enyl ester (66)**

[00272] To a solution of ester **85** (12 mg, 0.015 mmol) in dry ethanol (1.5 ml) was added anhydrous ammonium chloride (75 mg) followed by zinc dust (75 mg). The reaction mixture was stirred at room temperature for 45 min before it was diluted with ethyl acetate (5 ml) and filtered through a plug of celite. The solution was concentrated and passed through a small plug of silica gel to give compound **86** that was used in the next step without further purification. To the crude solution of compound **86** was added a solution of tris(dimethylamino)sulfur(trimethylsilyl)difluoride (TAS-F) (5 mg, 0.187 mmol, 1 equiv) in 0.2 ml *N,N*-dimethylformamide. After 24 h, another 5 mg of TAS-F was added and the mixture was diluted with ethyl acetate (5 ml) and washed with pH 7 buffer (5 ml). The aqueous layer was extracted with ethyl acetate (3 x 5 ml) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (10% EtOAc / hexanes) to give pure compound **66** (4.7 mg, 62% over two steps) as a colorless material: $[\alpha]_D^{22} = -77.5$ ($c = 0.2$, CHCl_3); TLC $R_f = 0.74$ (silica gel, 50% EtOAc / hexanes); ^1H NMR (600 MHz, CDCl_3) 7.37-7.25 (m, 5H), 6.0-5.92 (m, 1H), 5.76-5.75 (d, $^3J = 3.6$ Hz, 1H), 5.15-5.11 (d, $^3J = 16.8$ Hz, 1H), 5.07-5.04 (d, $^3J = 10.2$ Hz, 1H), 4.67-4.64 (d, $^3J = 10.2$ Hz, 1H), 4.29-4.26 (m, 1H), 3.39-3.35 (m, 2H), 3.27-3.23 (m, 2H), 2.99-2.93 (m, 1H), 2.88-2.83 (m, 1H), 2.61-2.57 (m, 1H), 2.54-2.50 (dd, $^3J = 1.8$ Hz, $^2J = 16.2$ Hz, 1H), 2.46-2.41 (dd, $^3J = 10.2$ Hz, $^2J = 16.2$ Hz, 1H), 2.04-1.96 (m, 2H), 1.79 (s, 3H), 1.72-1.75 (m, 1H), 1.69 (s, 3H), 1.54-1.52 (m, 1H), 1.36-1.30 (m, 1H), 1.20-1.18 (s overlapping with m, 4H), 1.15 (s, 3H), 1.07-1.05 (d, $^3J = 7.2$ Hz, 3H), 0.85-0.83 (d, $^3J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 222.479, 173.245, 146.443, 139.776, 139.392, 137.114, 131.784, 128.467, 127.922, 127.559, 115.487, 109.888, 88.553, 75.049, 72.680,

52.278, 47.843, 41.105, 40.391, 38.431, 36.913, 35.688, 32.713, 25.047, 22.642, 21.478, 19.172, 15.722, 13.094, 10.210; HRMS calcd for C₃₂H₄₆O₅ + Na⁺ 533.3243; found 533.3213 [M + Na⁺].

[00273] **2E,4S,7S,10R,11S,12S,16Z,18S)-7,11-Dihydroxy-3,8,8,10,12,16-hexamethyl-2-phenyl-3a,7,8,10,11,12,13,14,15,17a-decahydro-1H,6H-4-oxa-cyclopentacyclohexadecene-5,9-dione (6b)**

[00274] A solution of the second generation Grubb's catalyst (2 mg, 0.0024 mmol) (weighed under argon) in methylene chloride (1.5 ml) was added to a solution of compound **66** in methylene chloride (0.5 ml). The reaction mixture was heated at 50 °C for 16 h and applied directly to a preparative TLC (3:1 hexanes / EtOAc) to give slightly impure *E* and *Z* **6b** separately (~55% overall yield). The *Z* isomer was purified by a second preparative TLC using (3% methanol in methylene chloride) to remove the last traces of the catalyst and to furnish the desired target molecule *Z* **6b** (0.5 mg). ¹H NMR (600 MHz, CDCl₃) 7.36-7.33 (m, 2H), 7.27-7.24 (m, 3H), 5.83-5.81 (d, ³*J* = 7.2 Hz, 1H), 5.26-5.23 (d, ³*J* = 10.2 Hz, 1H), 4.2-4.17 (m, 1H), 3.69-3.66 (m, 1H), 3.22-3.15 (m, 2H), 2.83-2.79 (dd, ³*J* = 8.4 Hz, ²*J* = 15.6 Hz, 1H), 2.67-2.66 (d, ³*J* = 4.2 Hz, 1H), 2.6-2.55 (dd, ³*J* = 10.8 Hz, ²*J* = 16.8 Hz, 2H), 2.52-2.47 (m, 1H), 2.39-2.31 (m, 2H), 1.80-1.75 (s overlapping with m, 4H), 1.68 (s, 3H), 1.66-1.62 (m, 3H), 1.36 (s, 3H), 1.18-1.17 (d, ³*J* = 6.6 Hz, 3H), 1.07 (s, 3H), 0.99-0.98 (d, ³*J* = 7.2 Hz, 3H); HRMS calcd for C₃₀H₄₂O₅ + Na⁺ 505.2930 found 505.2893 [M + Na⁺].

[00275] **Ethyl-2-hydroxy-3-methyl-4-(5-methylpyridin-2-yl)-cyclopent-3-enecarboxylate (88, 89)**

[00276] Trifluoroacetic acid (0.297 ml, 3.86 mmol) was added to a stirred solution of compound **87** (0.5 g, 1.93 mmol) in methylene chloride (6ml). The solvent was removed on the rotavapor. The resulting residue was dissolved in methanol (7 ml) and cooled to 0 °C. To this solution at 0 °C was added sodium borohydride (0.73 g, 19.3 mmol) rapidly at once. After stirring at 0 °C for 45 min, chloroform was added and the mixture was washed with saturated sodium bicarbonate solution and brine. The organic layer was dried over anhydrous Na₂SO₄, concentrated to get a cis/trans mixture of **88-91** (0.459 g, 91%, cis/trans-1:2) which were separated by silica gel chromatography (16-25% EtOAc / hexanes).

[00277] **Cis mixture (90, 91)**

[00278] TLC R_f = 0.29 (silica gel, 25% EtOAc/hexane); ¹H NMR (C₆D₆, 600 MHz): δ 8.38

(s,1H), 6.88-6.87 (m, 2H), 4.61 (s, 1H), 3.99-3.89 (m, 2H), 3.54-3.49 (m, 1H), 3.05-3.01 (m,1H), 2.88-2.84 (m, 1H), 2.34-2.32 (d, 1H, $^3J = 7.8$ Hz), 2.13 (s, 3H), 1.77 (s, 3H), 0.92-0.89 (q, 3H, $^3J = 14.4$); ^{13}C NMR (C_6D_6 , 100 MHz): δ 172.878, 153.487, 149.938, 138.605, 136.162, 135.910, 130.716, 121.957, 81.993, 60.365, 46.457, 36.159, 17.766, 14.131, 13.801. HRMS calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_3 + \text{Na}^+$ 284.1263; found 284.1248 ($\text{M} + \text{Na}^+$).

[00279] **(1R,2S)-Ethyl-2-acetoxy-3-methyl-4-(5-methylpyridin-2-yl)cyclopent-3-enecarboxylate (92)**

[00280] Vinyl acetate (0.95 ml, 10.3 mmol) was added to a solution of (+/-) **88/89** (0.27 g, 1.03 mmol) in anhydrous pentane (3 ml). Amano PS-D lipase (0.27 g) and 4 Å MS (0.27 g) were added and the suspension was stirred at room temperature. The reaction was monitored by TLC and ^1H NMR and after 3 days 49-50% conversion of (+/-) **88/89** to acetate **92** was achieved. The sieves and lipase were filtered and washed with ether. The solvent was removed and crude product was purified by column chromatography on silica (16% EtOAc/hexane) to give **93** (0.154 g, 49%) as a pale yellow oil. $[\alpha]_{\text{D}}^{20} = -40.6$ ($c = 1.0$, CHCl_3); TLC $R_f = 0.26$ (silica gel, 75% EtOAc/hexanes); ^1H NMR (CDCl_3 , 600 MHz) δ 8.44 (s, 1H), 7.48-7.46 (d, 1H, $^3J = 7.8$ Hz), 7.20-7.19 (d, 1H, $^3J = 7.8$ Hz), 6.07 (s, 1H), 4.20-4.18 (q, 2H, $^3J = 14.4$ Hz), 3.22-3.16 (m, 1H), 3.05-3.01 (m, 2H), 2.32 (s, 3H), 2.09 (s, 3H), 1.28-1.25 (q, 3H, $^3J = 7.2$ Hz). ^{13}C NMR (CDCl_3 , 100 MHz) δ 174.107, 170.926, 152.537, 150.004, 137.238, 136.727, 135.023, 137.767, 122.476, 85.867, 61.144, 48.470, 37.478, 21.268, 18.516, 14.398, 13.197. HRMS calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_4 + \text{Na}^+$ 326.1368; found 326.1354 ($\text{M} + \text{Na}^+$).

[00281] **(1R,2S)-Ethyl-2-hydroxy-3-methyl-4-(5-methylpyridin-2-yl)cyclopent-3-enecarboxylate (88)**

[00282] Anhydrous potassium carbonate (45.6 mg, 0.33 mmol) was added to a solution of **92** (100 mg, 0.33 mmol) in dry ethanol (2.8 ml) at 0 °C and the solution was stirred at room temperature for 12 hr. Ethanol was removed under reduced pressure and the residue was dissolved in methylene chloride and washed with saturated aqueous solution of ammonium chloride. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica (25% EtOAc/hexane) to give compound **88** (81mg, 94%, 99% ee) as a pale yellow oil.: $[\alpha]_{\text{D}}^{20} = -8.1$ ($c = 0.26$, CHCl_3); TLC $R_f = 0.27$ (silica gel, 75% EtOAc/hexanes); ^1H NMR (C_6D_6 , 600

MHz) δ 8.69 (s, 1H), 6.89-6.83 (m, 2H), 4.57 (s, 1H), 3.38-3.34 (m, 2H), 2.40-2.38 (m, 2H), 2.16-2.11 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 174.602, 153.069, 149.938, 138.385, 136.681, 134.969, 131.441, 122.385, 84.064, 61.037, 51.692, 35.927, 18.483, 14.518, 13.070. HRMS calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_3 + \text{Na}^+$ 284.1263; found 284.1279 ($\text{M} + \text{Na}^+$).

[00283] **(1R,2S)-3-Methyl-4-(5-methyl-pyridin-2-yl)-2-triethylsilyloxy-cyclopent-3-enecarboxylic acid ethyl ester (93)**

[00284] Triethylsilyl chloride (145 μL , 0.863 mmol, 1.5 equiv) was added dropwise to a solution of alcohol **88** (150 mg, 0.575 mmol) and imidazole (17 mg, 1.72 mmol, 3 equiv) in methylene chloride (4 ml) at 0 $^\circ\text{C}$. After stirring at 0 $^\circ\text{C}$ for 2 hr, the reaction was quenched with water (2.5 ml), and extracted with ethyl acetate (3 x 5 ml). The organic extracts were washed with brine (3.5 ml), and dried over anhydrous sodium sulfate. Filtration and evaporation of the solvents *in vacuo* furnished an oily crude product which was purified by flash column chromatography on silica (2-7% EtOAc / hexanes-) to give **93** (198 mg, 92%) as a yellow oil: $[\alpha]_{\text{D}}^{22} = -51.04$ ($c = 0.7$, CHCl_3); TLC $R_f = 0.29$ (silica gel, 25% EtOAc/hexanes); ^1H NMR (600 MHz, CDCl_3) δ 8.41 (s, 1H), 7.45-7.42 (dd, 1H, $^3J = 1.8$ Hz, $^2J = 8.4$ Hz), 7.2-7.18 (d, 1H, $^3J = 7.8$ Hz), 5.12 (d, 1H, $^3J = 4.8$ Hz), 4.2-4.16 (dd, 2H, $^3J = 7.2$ Hz, $^2J = 14.4$ Hz), 3.17-3.12 (m, 1H), 3.0-2.89 (m, 2H), 2.3 (s, 3H), 1.97 (s, 3H), 1.29-1.26 (t, 3H, $^3J = 14.4$ Hz), 0.98-0.95 (t, 9H, $^3J = 7.8$ Hz), 0.67-0.63 (q, 6H, $^3J = 7.8$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 175.31, 153.31, 149.87, 139.09, 136.51, 134.07, 131.15, 122.39, 84.53, 60.83, 51.58, 37.40, 18.42, 14.46, 13.31, 7.03, 5.15; HRMS calcd for $\text{C}_{21}\text{H}_{33}\text{NO}_3\text{Si} + \text{H}^+$ 376.2308; found 376.2302 [$\text{M} + \text{H}^+$].

[00285] **(1R,2S)-3-Methyl-4-pyridin-2-yl-2-triethylsilyloxy-cyclopent-3-enecarbaldehyde (94)**

[00286] A solution of DIBAL-H (0.44 ml, 1.0 M in hexane, 0.44 mmol, 1.1 equiv) was added dropwise to a solution of silyl ether **93** (150 mg, 0.4 mmol) in toluene (2 ml) at -78 $^\circ\text{C}$. The reaction mixture was stirred at that temperature for 1 hr and quenched by dropwise addition of saturated NH_4Cl solution (0.2 ml). The reaction mixture was allowed to reach room temperature and a saturated solution of Rochelle salt (1 ml) and brine (0.4 ml) were added. The mixture was extracted with ethyl acetate (3 x 2 ml) and the combined organic extracts were dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo* to give crude aldehyde **94** as a yellow liquid which was used in the next step without further purification.

[00287] **(3S,4S)-5-Methyl-2-(2-methyl-3-triethylsilyloxy-4-vinyl-cyclopent-1-enyl)-pyridine (95)**

[00288] To a pre-cooled (0 °C) solution of methyltriphenylphosphonium bromide (286 mg, 0.8 mmol, 2 equiv) in THF (3 ml) was added n-butyllithium (0.49 ml of 1.6 M solution in hexanes, 0.78 mmol, 1.95 equiv) dropwise. The reaction mixture was stirred at 0 °C for 30 min. A solution of crude aldehyde **94** (*ca* 0.4 mmol) in THF (1.5 ml) was added and the mixture was stirred at 0 °C for 30 min and quenched with a saturated aqueous ammonium chloride solution (3 ml). The solvent was removed under reduced pressure, and the aqueous residue was extracted with ethyl acetate (3 x 3 ml). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography on silica (7% EtOAc / hexanes) afforded pure olefin **95** (96 mg, 73%) as a yellowish oil: $[\alpha]_D^{22} = -21.29$ (*c* = 0.7, CHCl₃); TLC R_f = 0.66 (silica gel, 33% EtOAc/hexanes); ¹H NMR (600 MHz, CDCl₃) δ 8.42 (s, 1H), 7.45-7.42 (dd, , 1H, ³J = 1.8 Hz, ²J = 7.8 Hz), 7.19-7.17 (d, 1H, ³J = 7.8 Hz), 5.95-5.88 (m, 1H), 5.14-5.11 (d, , 1H, ³J = 16.8 Hz), 5.05-5.02 (d, 1H, ³J = 10.8 Hz), 4.54 (d, , 1H, ³J = 5.4 Hz), 2.97-2.93 (m, 1H), 2.74-2.68 (m, 1H), 2.6-2.56 (m, 1H), 2.3 (s, 3H), 1.96 (s, 3H), 0.99-0.96 (t, 9H, ³J = 7.8 Hz), 0.67-0.62 (q, , 6H, ³J = 7.8Hz); ¹³C NMR (100 MHz, CDCl₃) δ 153.95, 149.82, 140.95, 139.83, 136.52, 134.99, 130.91, 122.40, 115.19, 87.15, 51.85, 39.15, 18.45, 13.44, 7.16, 5.49; HRMS calcd for C₂₀H₃₁NOSi + H⁺ 330.2253 found 330.2258 [M + H⁺].

[00289] **(1S,5S)-2-Methyl-3-(5-methylpyridin-2-yl)-5-vinylcyclopent-2-enol (96)**

[00290] To a solution of compound **95** (50 mg, 0.152 mmol) in THF (1 ml) at 0 °C was added tetrabutylammonium fluoride (0.152 ml of 1 M solution in THF, 0.152 mmol) dropwise. The reaction mixture was stirred at 0 °C for 30 min and water (1 ml) and ethyl acetate (2 ml) were added. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 2 ml). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. Purification by flash column chromatography on silica (16-50% EtOAc/hexanes) afforded pure alcohol **96** (28 mg, 83%) as a white solid: $[\alpha]_D^{22} = -26.0$ (*c* = 0.3, CHCl₃); TLC R_f = 0.25 (silica gel, 50% EtOAc/hexanes); ¹H NMR (600 MHz, CDCl₃) δ 8.43 (s, 1H), 7.47-7.44 (dd, 1H, ³J = 1.8 Hz, ²J = 7.8 Hz), 7.19-7.17 (d, 1H, ³J = 7.8 Hz), 6.0-5.95 (m, 1H), 5.12-5.17 (d, 1H, ³J = 16.8 Hz), 5.09-5.06 (d, 1H, ³J = 10.2 Hz), 4.48 (s, 1H), 2.96-2.91 (m, 1H), 2.69-2.60 (m, 2H), 2.32 (s, 3H), 2.03 (s, 3H); ¹³C NMR (100 MHz,

CDCl₃) δ 153.62, 149.90, 140.25, 139.41, 136.65, 135.55, 131.19, 122.32, 115.43, 86.42, 52.26, 38.52, 18.49, 13.17; HRMS calcd for C₁₄H₁₇NO + Na⁺ 238.1208; found 238.1191 [M + Na⁺].

[00291] **(3S,6R,7S,8S,1'S,5'S)-3-(tert-Butyl-dimethyl-silanyloxy)-4,4,6,8,12-pentamethyl-5-oxo-7-(2,2,2-trichloro-ethoxycarbonyloxy)-tridec-12-enoic acid 2-methyl-3-(5-methylpyridin-2-yl)-5-vinyl-cyclopent-2-enyl ester (97)**

[00292] To a solution of acid **83** (8.0 mg, 0.013 mmol), alcohol **96** (3.0 mg, 0.014 mmol, 1.1 equiv), and DMAP (1 mg, 0.008 mmol, 0.6 equiv) in methylene chloride (0.5 ml) at 0 °C was added DCC (0.017 ml of 1 M solution in CH₂Cl₂, 0.017 mmol, 1.3 equiv) dropwise. The reaction mixture was stirred for 15 min at 0 °C and for 16 h at room temperature. The solid precipitate was filtered off and the filtrate was concentrated *in vacuo*. Purification by flash column chromatography on silica (5% EtOAc/ hexanes) afforded ester **97** (10 mg, 95%) as a colorless oil: [α]_D²² = -29.8 (c = 1, CHCl₃); TLC R_f = 0.48 (silica gel, 25% EtOAc / hexanes); ¹H NMR (600 MHz, CDCl₃) δ 8.43 (s, 1H), 7.47-7.45 (dd, 1H, ³J = 1.8 Hz, ²J = 7.8 Hz), 7.19-7.17 (d, 1H, ³J = 7.8 Hz), 5.98-5.91 (m, 1H), 5.74-5.72 (d, 1H, ³J = 4.8 Hz), 5.13-5.09 (d, 1H, ³J = 16.8 Hz), 5.03-5.01 (d, 1H, ³J = 10.2 Hz), 4.88-4.85 (d, 1H, ³J = 12 Hz), 4.73-4.70 (m, 1H), 4.67-4.61 (m, 3H), 4.3-4.28 (m, 1H), 3.5-3.45 (m, 1H), 3.06-3.02 (m, 1H), 2.88-2.83 (m, 1H), 2.7-2.65 (m, 1H), 2.89 (s, 3H), 2.25-2.21 (dd, 1H, ³J = 5.4 Hz, ²J = 17.4 Hz), 1.98-1.91 (m, 2H), 1.9 (s, 1H), 1.76-1.74 (m, 1H), 1.66 (s, 3H), 1.5-1.22 (m, 5H), 1.1-1.04 (m, 6H), 0.97-0.95 (d, 3H, ³J = 7.2 Hz), 0.87 (m, 12H), 0.127 (s, 3H), 0.05 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 215.42, 194.80, 172.30, 154.43, 153.12, 149.97, 145.78, 139.48, 138.30, 136.66, 135.68, 131.50, 125.53, 122.48, 115.36, 110.28, 95.01, 88.24, 82.37, 75.05, 53.98, 47.48, 42.24, 40.25, 39.19, 38.21, 34.89, 31.82, 29.93, 26.28, 24.79, 22.65, 22.54, 20.69, 18.49, 18.35, 16.08, 13.37, 11.08, -4.07, -4.54; HRMS calcd for C₄₁H₆₂Cl₃NO₇Si + H⁺ 814.3434; found 814.3481 [M + H⁺].

[00293] **(3S,6R,7S,8S,1'S,5'S)-3,7-Dihydroxy-4,4,6,8,12-pentamethyl-5-oxo-tridec-12-enoic acid 2-methyl-3-(5-methylpyridin-2-yl)-5-vinyl-cyclopent-2-enyl ester (99)**

[00294] To a solution of ester **97** (5 mg, 0.006 mmol) in DMF (0.2 ml) was added a solution of tris(dimethylamino)sulfur (trimethylsilyl)difluoride (TAS-F) (1.7 mg, 0.008 mmol, 1 equiv) in 0.2 ml *N,N*-dimethylformamide. After 24 h, another 1.7 mg of TAS-F was added and the mixture was diluted with ethyl acetate (3 ml) and washed with pH 7 buffer (5 ml). The

aqueous layer was extracted with ethyl acetate (3 x 5 ml) and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (10% EtOAc / hexanes) to give compound **98** which was dissolved in dry ethanol (1.2 ml) and treated with anhydrous ammonium chloride (62 mg) followed by zinc dust (62 mg). The reaction mixture was stirred at room temperature for 45 min before it was diluted with ethyl acetate (3 ml) and filtered through a plug of celite. The solution was concentrated and purified by silica gel chromatography (20% EtOAc / hexanes) to give pure compound **99** (2 mg, 62% over two steps) as a colorless material: ^1H NMR (500 MHz, CDCl_3) 8.48 (s, 1H), 7.50 (m, 1H), 7.22-7.20 (d, $^3J = 8.5$ Hz, 1H), 5.98 (m, 1H), 5.81 (m, 1H), 5.18-5.14 (d, $^3J = 17.5$ Hz, 1H), 5.08-5.06 (d, $^3J = 10.5$ Hz, 1H), 4.69-4.67 (d, $^3J = 9$ Hz, 2H), 4.31-4.28 (d, $^3J = 10.5$ Hz, 1H), 3.40 (m, 2H), 3.27 (dd, $^3J = 7$ Hz, $^2J = 14.5$ Hz, 2H), 3.07 (m, 1H), 2.91 (m, 1H), 2.70 (m, 1H), 2.54 (dd, $^3J = 2.5$ Hz, $^2J = 16.5$ Hz, 1H), 2.46 (dd, $^3J = 10.5$ Hz, $^2J = 16.5$ Hz, 1H), 2.36 (s, 3H), 1.98 (s, 3H), 1.72 (s, 3H), 1.26 (s, 3H), 1.22 (s, 3H), 1.17 (s, 3H), 1.08 (d, $^3J = 6.5$ Hz, 3H), 0.87 (d, $^3J = 7$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 222.14, 172.91, 152.80, 149.79, 146.19, 139.09, 139.13, 136.47, 135.04, 131.39, 122.29, 109.66, 88.31, 74.86, 72.54, 52.08, 47.50, 40.99, 38.96, 38.24, 36.79, 35.52, 32.53, 29.71, 24.88, 22.40, 21.29, 19.01, 18.28, 15.55, 13.16, 10.01; HRMS calcd for $\text{C}_{32}\text{H}_{47}\text{NO}_5 + \text{Na}^+$ 548.3352 found 548.3331 $[\text{M} + \text{Na}^+]$.

[00295] **(3S,6R,7S,8S,1'S,5'S)-7,11-Dihydroxy-3,8,8,10,12,16-hexamethyl-2-(5-methylpyridin-2-yl)-3a,7,8,10,11,12,13,14,15,17a-decahydro-1H,6H-4-oxa-cyclopentacyclohexadecene-5,9-dione (100)**

[00296] A solution of the second generation Grubb's catalyst (2 mg, 0.0024 mmol) (weighed under argon) in methylene chloride (1.5 ml) was added to a solution of compound **99** (2 mg, 0.0042 mmol) in methylene chloride (0.5 ml). The reaction mixture was heated at 50 °C for 16 h and applied directly to a preparative TLC (3:1 hexanes / EtOAc) to give the target **Z 100** (0.5 mg) and a long with phenyl analogue **101** and the dimer **102** (~ 0.5 mg each). Data for compound **100**: ^1H NMR (500 MHz, CDCl_3) 8.60 (s, 1H), 8.17 (d, $^3J = 8$ Hz, 1H), 7.54 (d, $^3J = 8$ Hz, 1H), 5.84 (d, $^3J = 7$ Hz, 1H), 5.25 (d, $^3J = 10$ Hz, 1H), 4.43 (d, $^3J = 10$ Hz, 1H), 3.63 (m, 1H), 3.43 (m, 1H), 3.23 (m, 2H), 2.81 (dd, $^3J = 2.5$ Hz, $^2J = 16.5$ Hz, 1H), 2.65 (dd, $^3J = 10.5$ Hz, $^2J = 16.5$ Hz, 1H), 2.59 (s, 3H), 2.0 (s, 3H), 1.72 (s, 3H), 1.42 (s, 3H), 1.16 (d, $^3J = 6.5$ Hz, 3H), 1.06 (s, 3H), 1.02 (d, $^3J = 7$ Hz, 3H); HRMS calcd for $\text{C}_{30}\text{H}_{43}\text{NO}_5 + \text{H}^+$

498.3219 found 498.3232 [M + H⁺].

[00297] In accordance with the provisions of the patent statutes, the principle and mode of operation of this invention have been explained and illustrated in its preferred embodiment. However, it must be understood that this invention may be practiced otherwise than as specifically explained and illustrated without departing from its spirit or scope.

[00298] All scientific and patent publications referenced herein are hereby incorporated by reference. The invention having now been described by way of written description and example, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments, that the foregoing description and example is for purposes of illustration and not limitation of the following claims.

[00299] References

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CLAIMS

What is claimed is:

1. A method for synthesizing epothilone analogues comprising: incorporating a molecular scaffold to hold at least one segment of the epothilone analogue in a predetermined orientation.
2. A method for synthesizing an epothilone analogue having a macrolactone ring and an aromatic side-chain, the method comprising:
incorporating a molecular scaffold to hold at least one segment of the epothilone analogue in a predetermined orientation, and
rigidifying a region between the macrolactone ring and the aromatic side-chain.
3. A method for synthesizing an epothilone analogue having a macrolactone ring and an aromatic side-chain, the method comprising:
incorporating a molecular scaffold that holds at least one sector of epothilone in a predetermined orientation for interaction with at least one tubulin receptor; and,
structurally rigidifying a region between the macrolactone ring and the aromatic side-chain in epothilone by incorporating a single-carbon bridge between C14 and C17 carbon atoms in epothilone in the form of a substituted cyclopentene ring.
4. The method of claim 3, in which the epothilone analogue has a predetermined orientation of structural residues, which allows for enhanced interaction with a tubulin receptor.
5. The method of claim 1, wherein the epothilone analogue comprises an open chain epothilone.

6. The method of claim 5, wherein the open chain epothilone analogue comprises **5a/5b**.

7. The method of claim 6, wherein **5a/5b** are formed by coupling between carboxylic acids **7a/7b** and alcohol **9**, wherein the coupling comprises at least the steps of: treating fragments **7a/7b** with trifluoroacetic acid in methylene chloride to form fully deprotected intermediates **8a/8b**; and, esterifying **8a/8b** and alcohol **9** to form **5a/5b**.

8. A method for synthesizing epothilone analogue comprising coupling a suitable aldehyde fragment, a suitable ketone fragment and a suitable alcohol fragment using a convergent strategy.

9. The method of claim 8, wherein the three fragments comprise **25**, **26** and **27**.

10. The method of claim 9, wherein the aldehyde **25** and the ketone **26** are coupled by a stereoselective aldol reaction; and using Yamaguchi macrolactonization to generate the epothilone analogue.

11. The method of claim 9, wherein the aldehyde **25** and the ketone **26** are coupled by stereoselective aldol reaction; inserting a northern segment (C10–C14); and, using Yamaguchi macrolactonization to generate the epothilone analogue.

12. The method of claim 9, wherein the aldehyde **25** and ketone **26** are coupled by a diastereoselective aldol reaction in order to construct a C6-C7 bond and establish absolute stereochemistry at the C6-C7 positions.

13. The method of claim 8, wherein the fragments comprise **67**, **68**, and **69**.

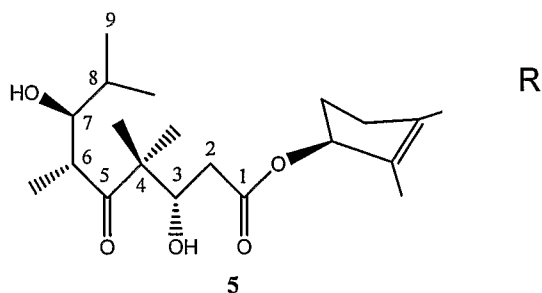
14. The method of claim 13, further including esterifying **67**, **68**, and **69** to form a macrolactone ring, then closing the macrolactone ring using an olefin metathesis approach.

15. A composition comprising a non-naturally occurring molecular scaffold, the molecular scaffold extending between a macrolactone ring and an aromatic side-chain in a macrocyclic analogue of an epothilone.

16. The composition of claim 15, wherein the epothilone analogue is adapted to interact with at least one tubulin receptor in a cell.

17. The composition of claim 15, wherein the molecular scaffold comprises a single-carbon bridge between C14 and C17 carbon atoms in an epothilone analogue in the form of a substituted cyclopentene ring.

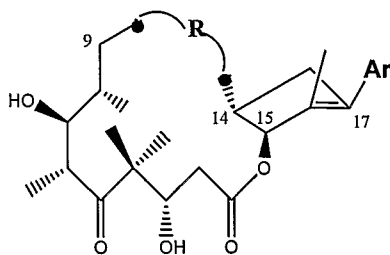
18. An epothilone analogue, or a salt thereof, comprising:



wherein R comprises phenyl, 2-pyridyl or other heteroaromatic.

19. The analogue of claim 18, wherein the epothilone analogue is adapted to interact with at least one tubulin receptor in a cell.

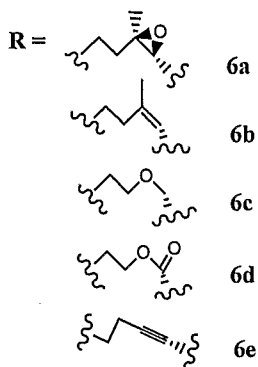
20. An epothilone analogue, or a salt thereof, comprising:



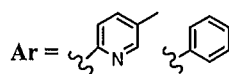
wherein Ar comprises phenyl, 2-pyridyl or other heteroaromatic, and wherein R a connecting link of variable hydrophobicity, length containing double bonds, or other heteroatom (such as

N, O, S) functionality, and other combinations thereof.

21. The epothilone analogue of claim 20, wherein R comprises at least one of:

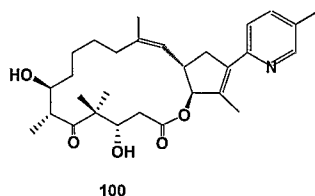


and, Ar comprises at least one of:

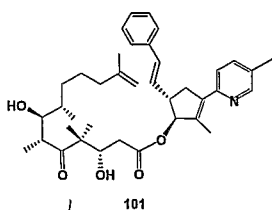


22. The epothilone analogue of claim 20, comprising 2E, 4S, 7S, 10R, 11S, 12S, 16Z, 18S) -7,11-Dihydroxy-3,8,8,10,12,16-hexamethyl-2-phenyl-3a, 7, 8, 10, 11, 12, 13, 14, 15, 17 a-decahydro-1H,6H-4-oxa-cyclopentacyclohexadecene-5,9-dione (**6b**).

23. The epothilone analogue of claim 20, comprising



24. The epothilone analogue of claim 20, comprising



25. The analogue of claim 20, wherein the epothilone analogue is adapted to interact with at least one tubulin receptor in a cell.
26. Pharmaceutical preparations that contain at least one epothilone analogue of claim 18 and 20 as well as a pharmaceutically compatible vehicle.
27. A purified compound of at least one of claim 18 and 20.
28. A pharmaceutical composition for the treatment of a disease or condition characterized by cellular hyperproliferation in a subject suffering therefrom, comprising a therapeutically effective amount of a compound of at least one of claim 18 and 20 and a pharmaceutically acceptable carrier.
29. A method for treating a disease or condition characterized by cellular hyperproliferation in a subject suffering therefrom, comprising administering to said subject a therapeutically effective amount of a compound of at least one of claim 18 and 20.
30. The method of claim 29, wherein the disease is cancer.
31. A pharmaceutical composition for the treatment of a disease or condition characterized by cellular hyperproliferation in a subject suffering therefrom, comprising a therapeutically effective amount of a compound of at least one of claim 18 and 20 and a pharmaceutically acceptable carrier.
32. A method for treating a disease or condition characterized by cellular hyperproliferation in a subject suffering therefrom, comprising administering to said subject a therapeutically effective amount of a compound of at least one of claim 18 and 20.

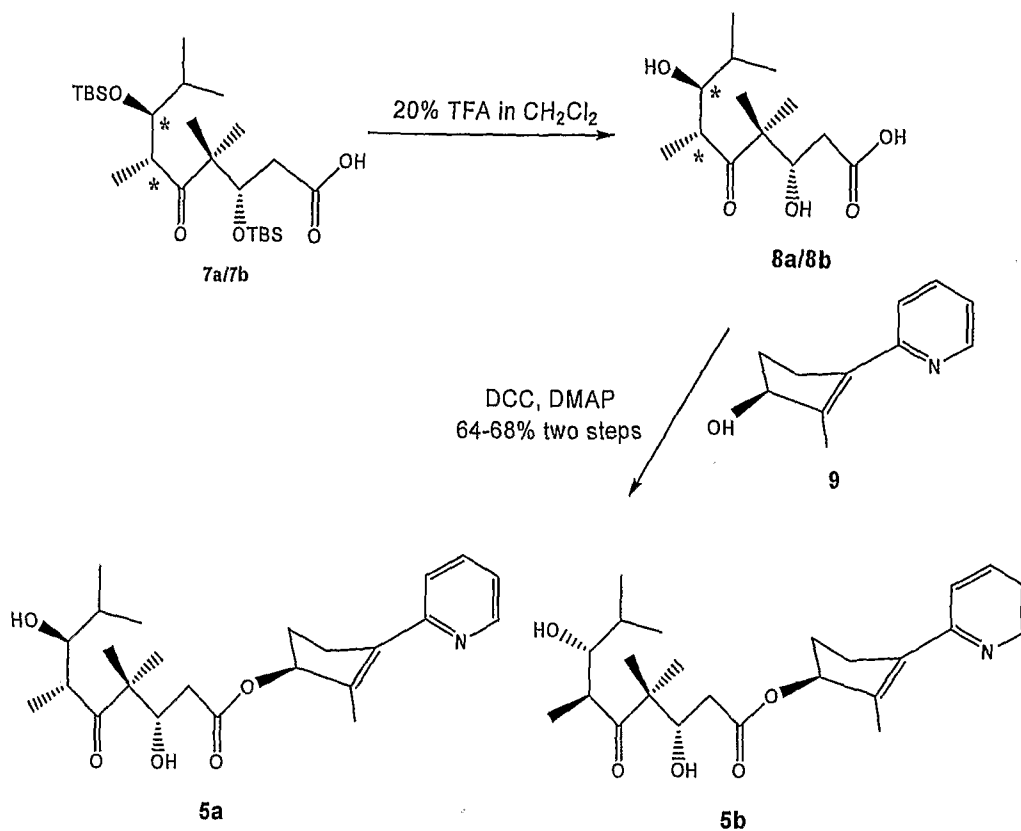


Fig. 1

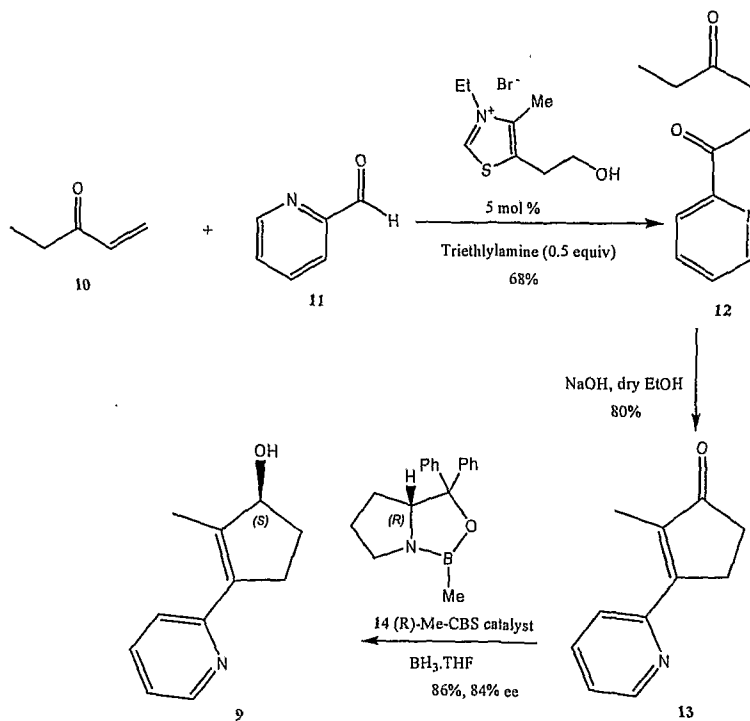


Fig. 2

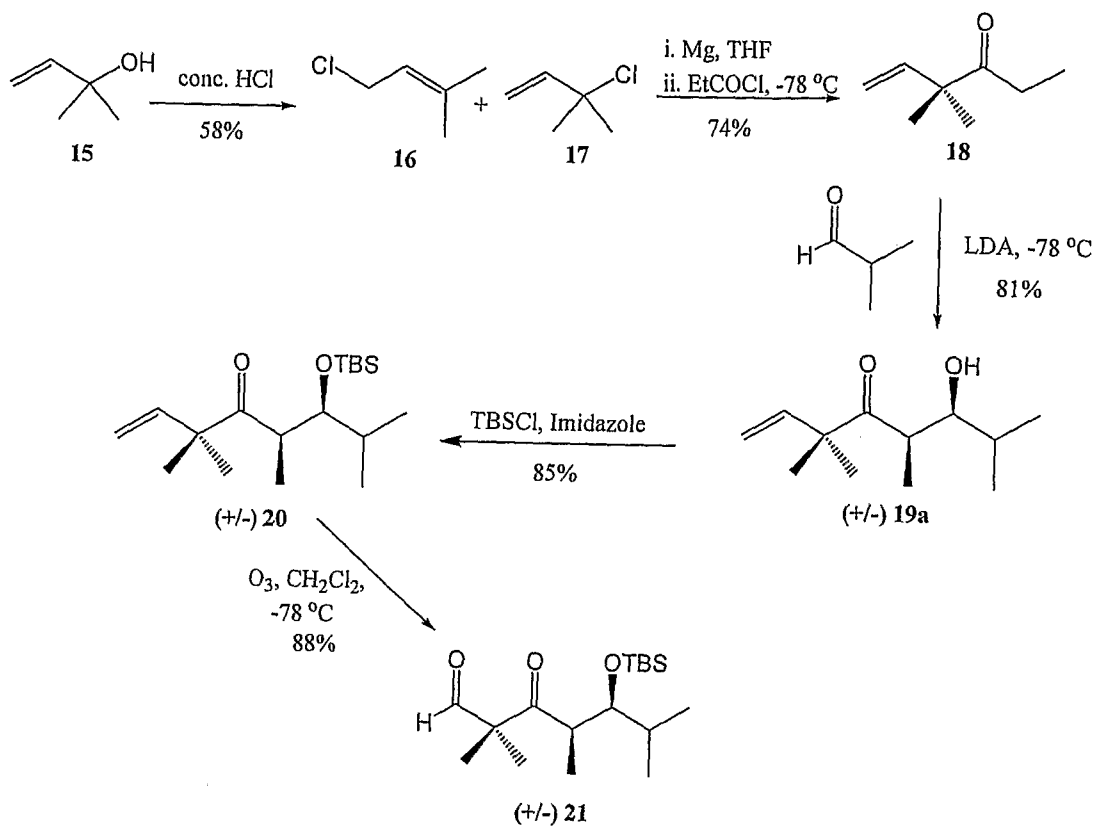


Fig. 3a

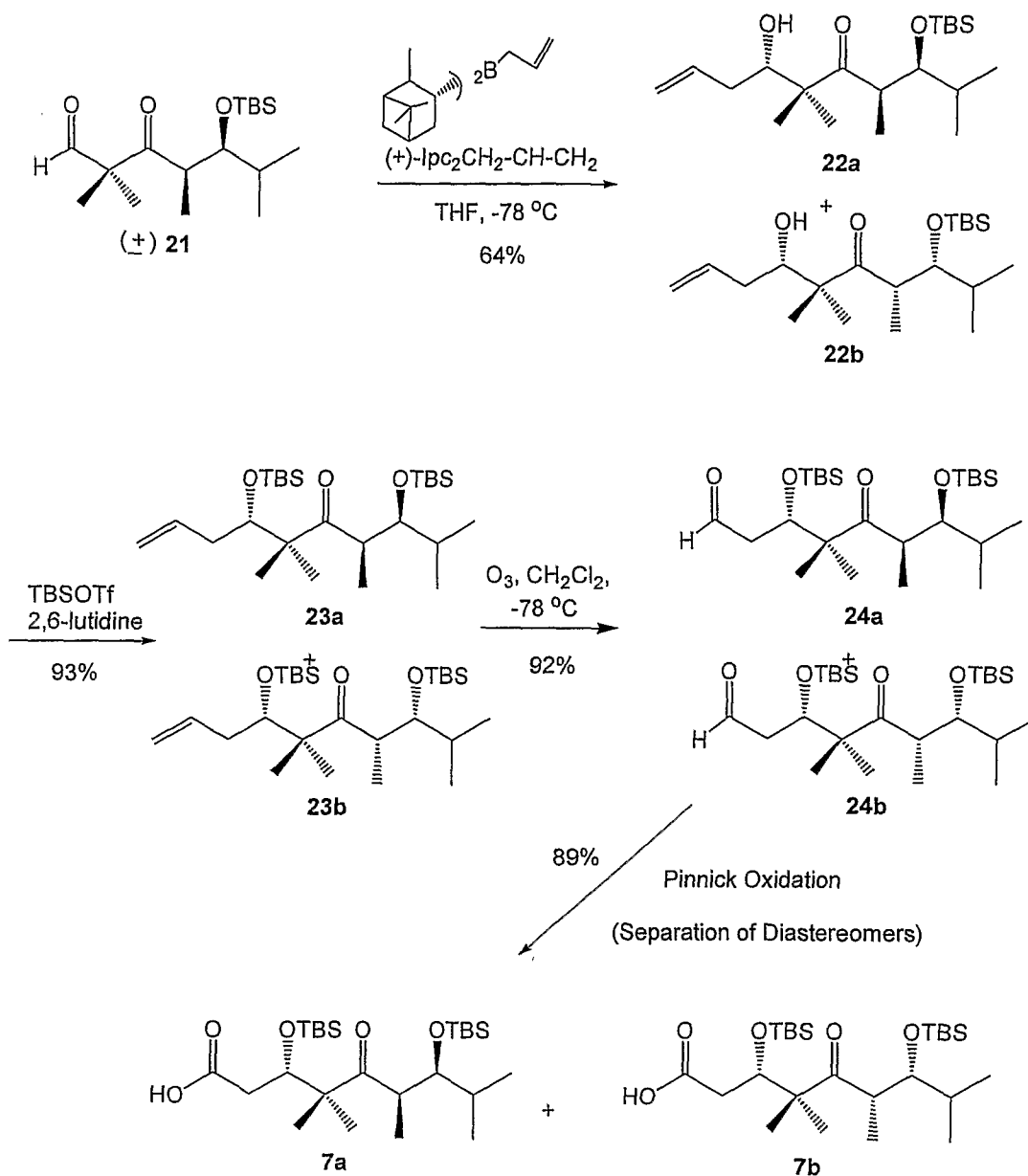


Fig. 3b

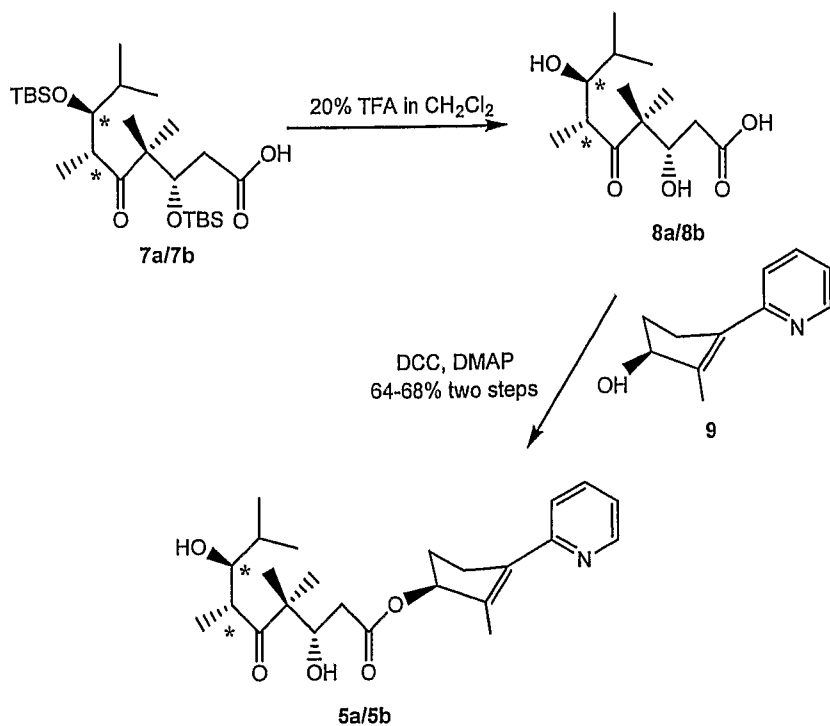


Fig. 4

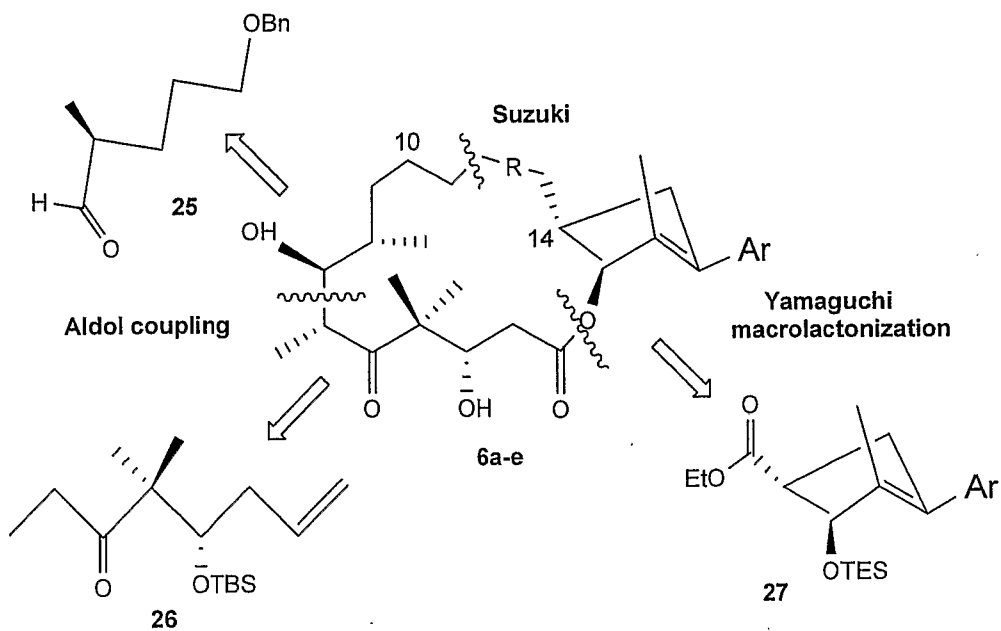


Fig. 5

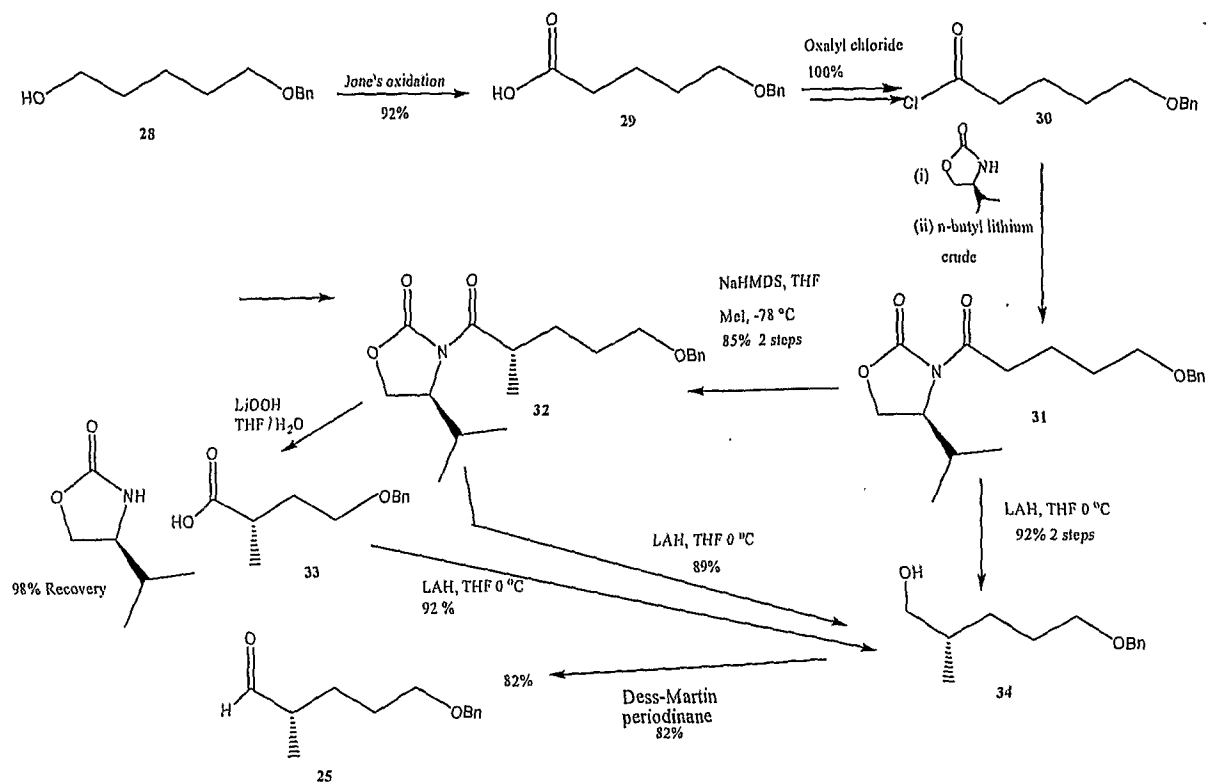


Fig. 6

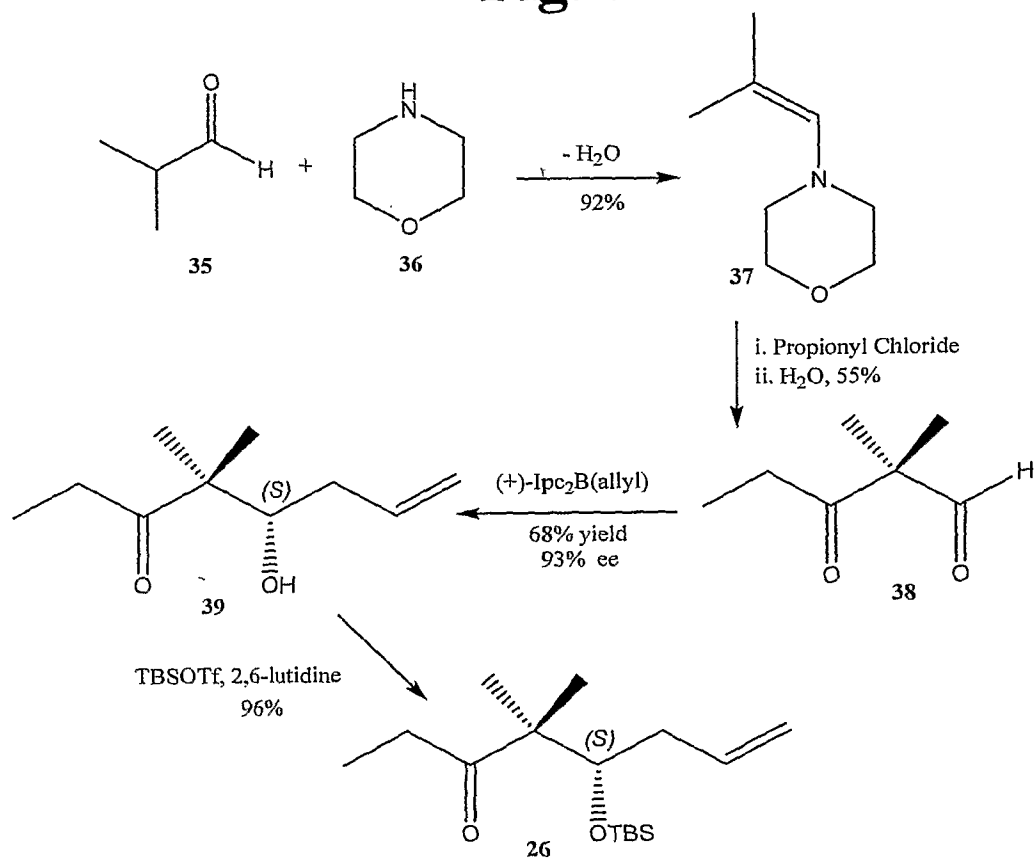


Fig. 7

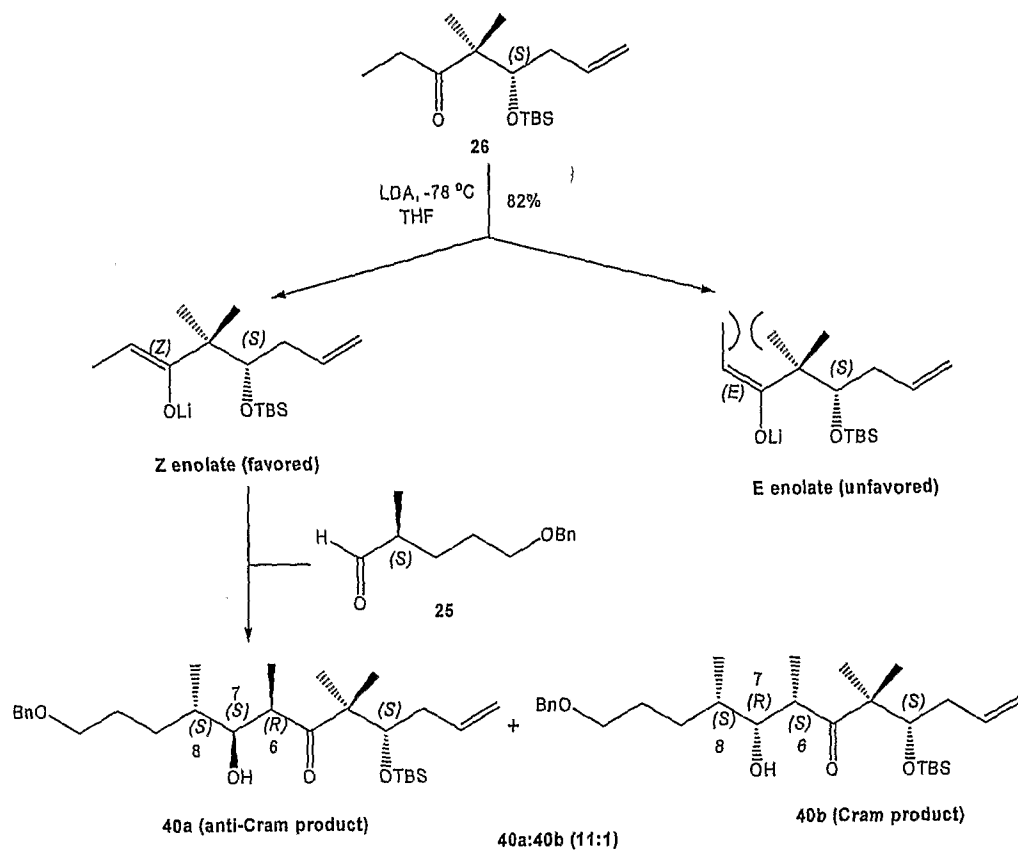


Fig. 8

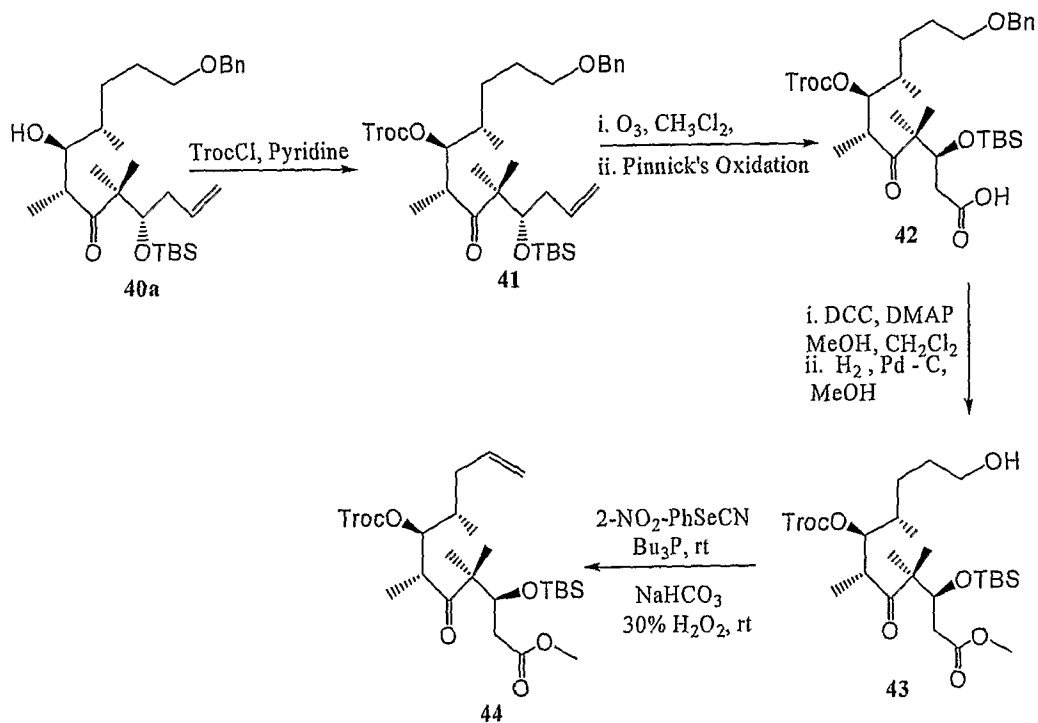


Fig. 9

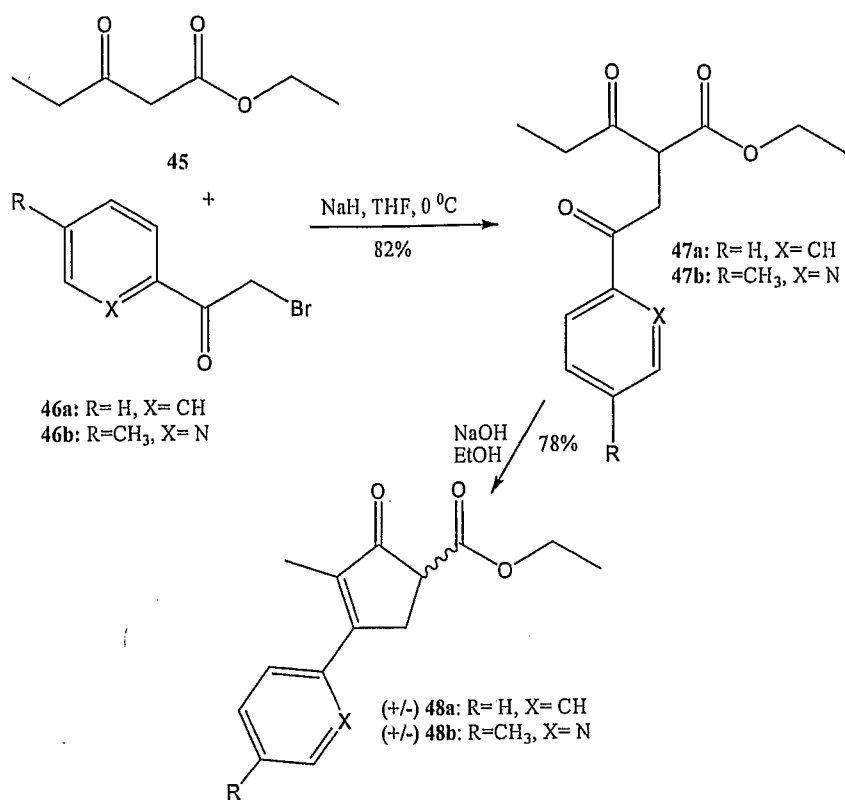


Fig. 10

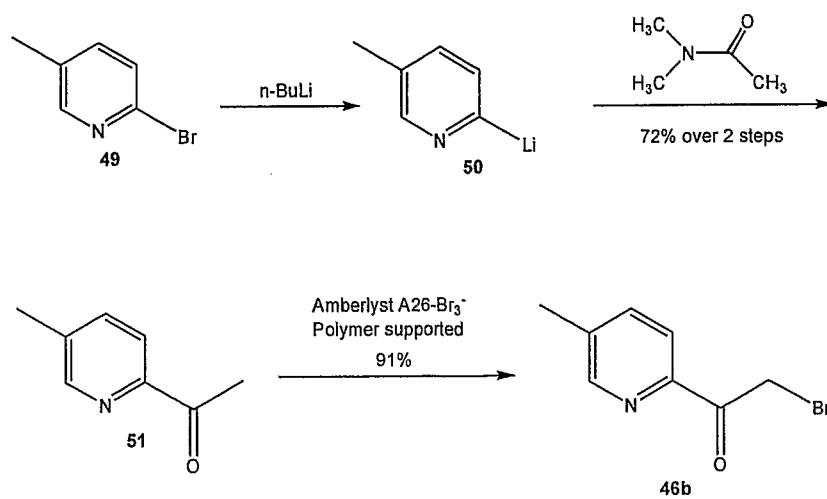


Fig. 11

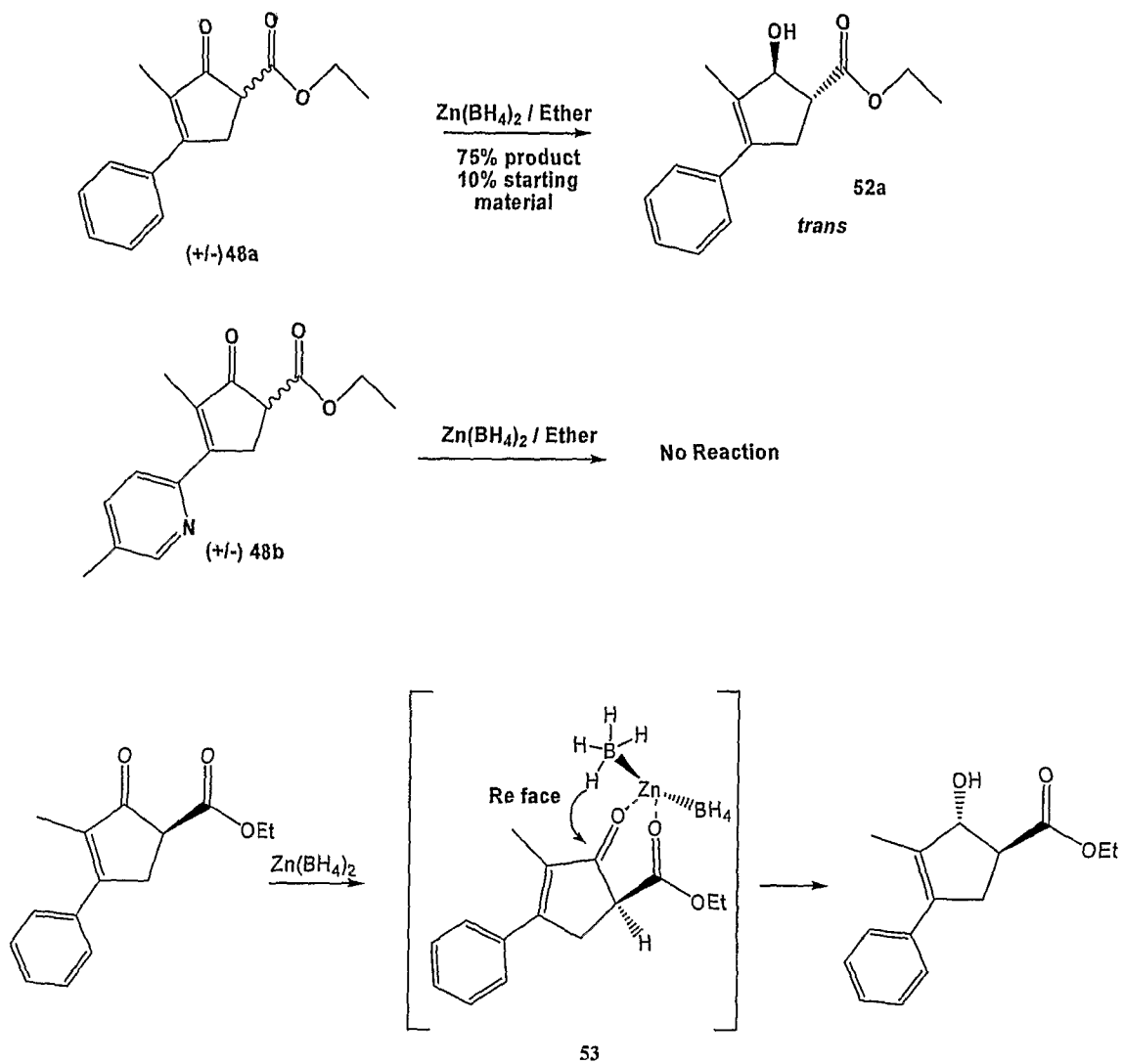


Fig. 12

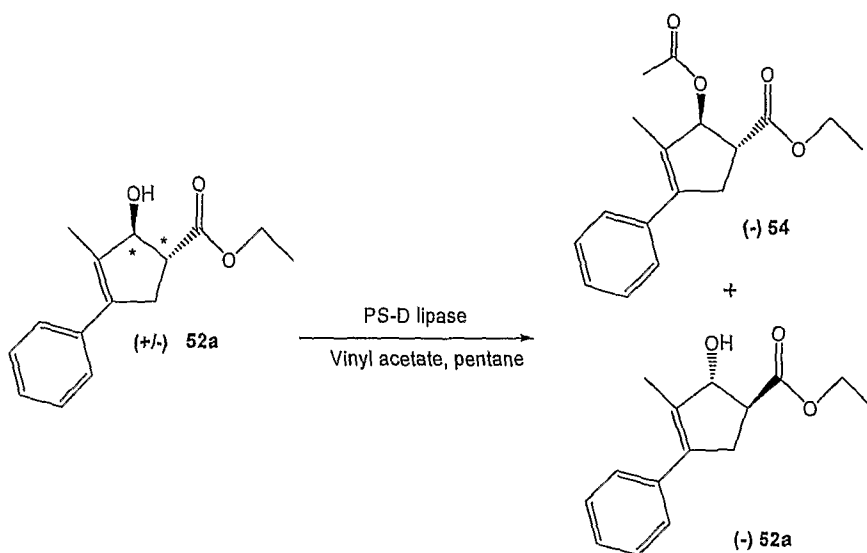


Fig. 13

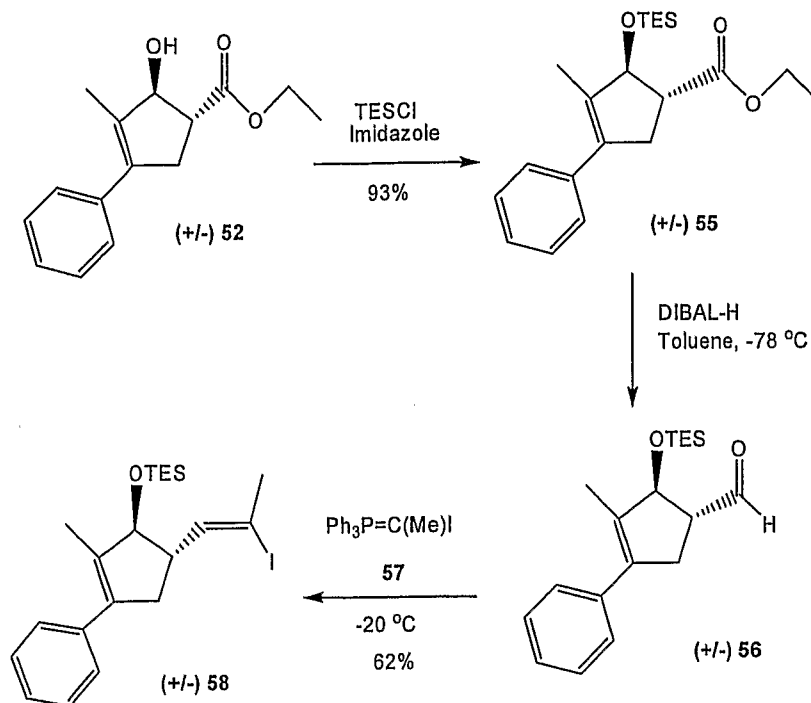


Fig. 16

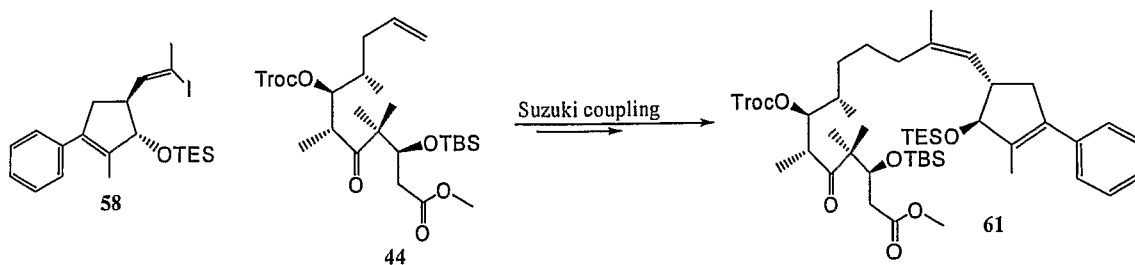


Fig. 17

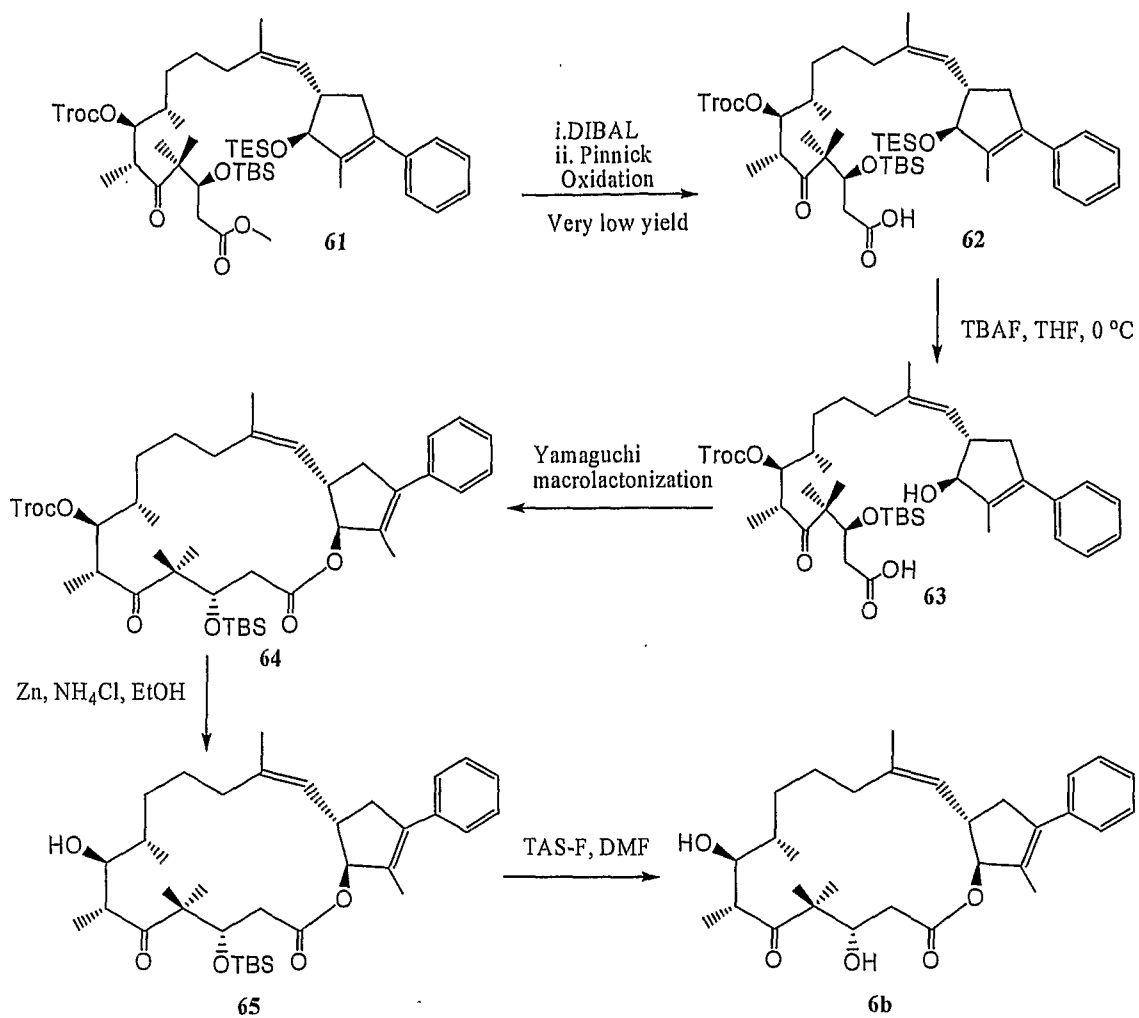


Fig. 18

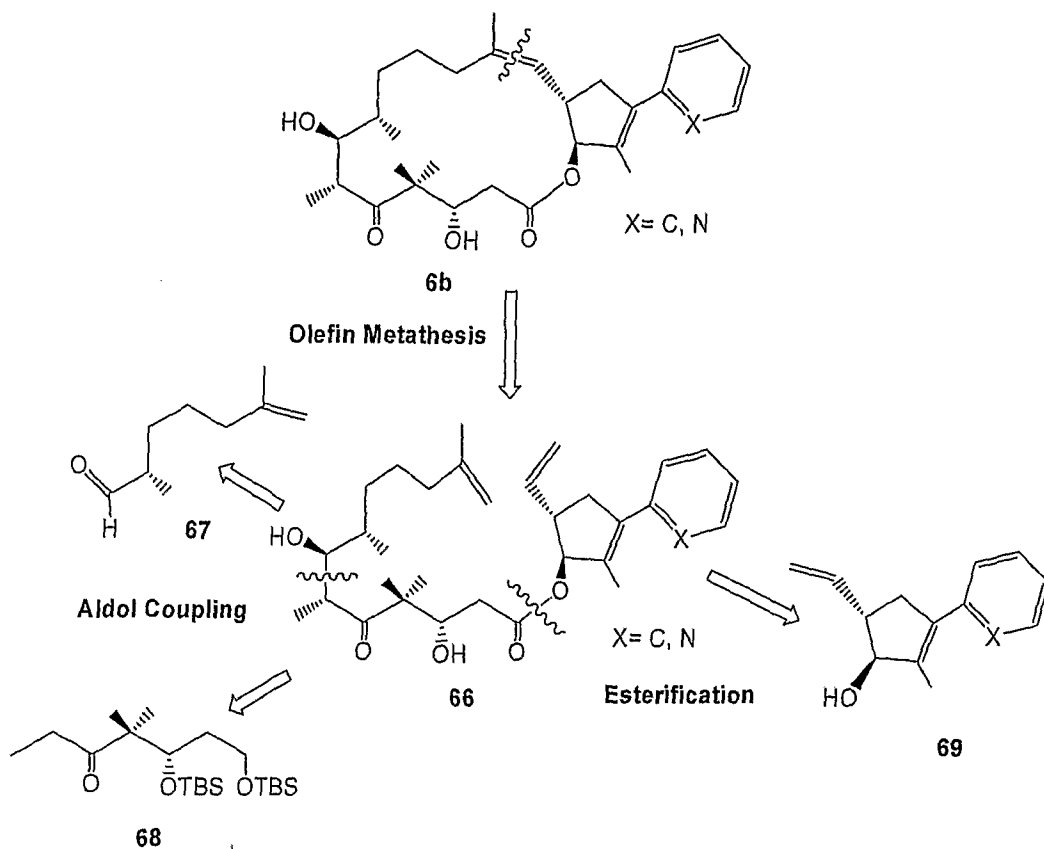


Fig. 19

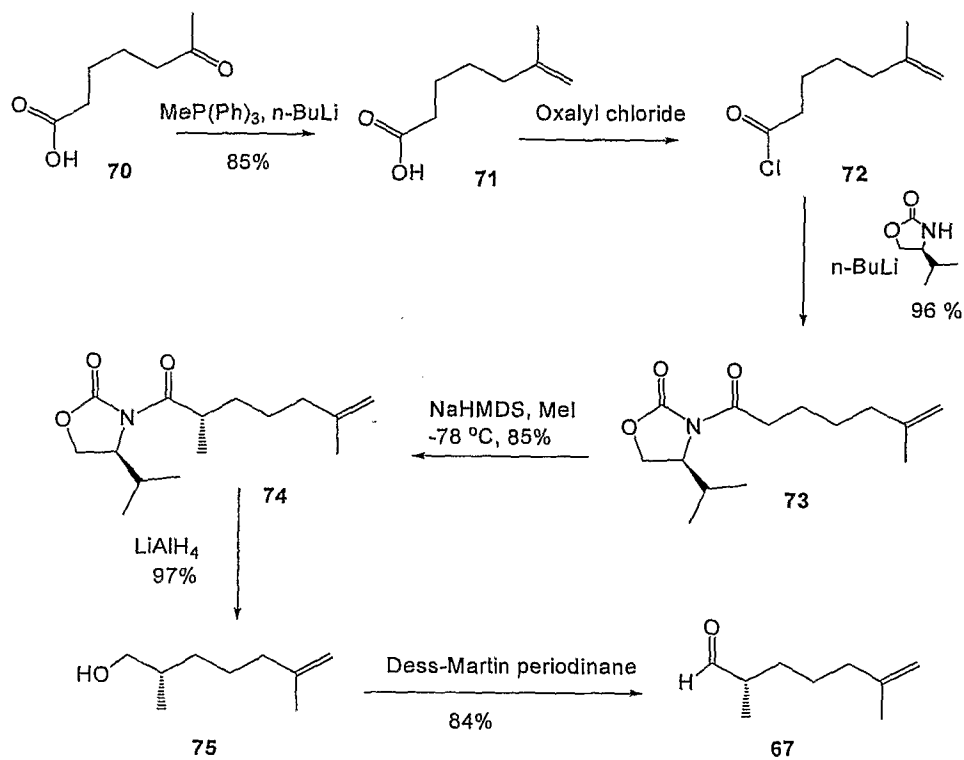


Fig. 20

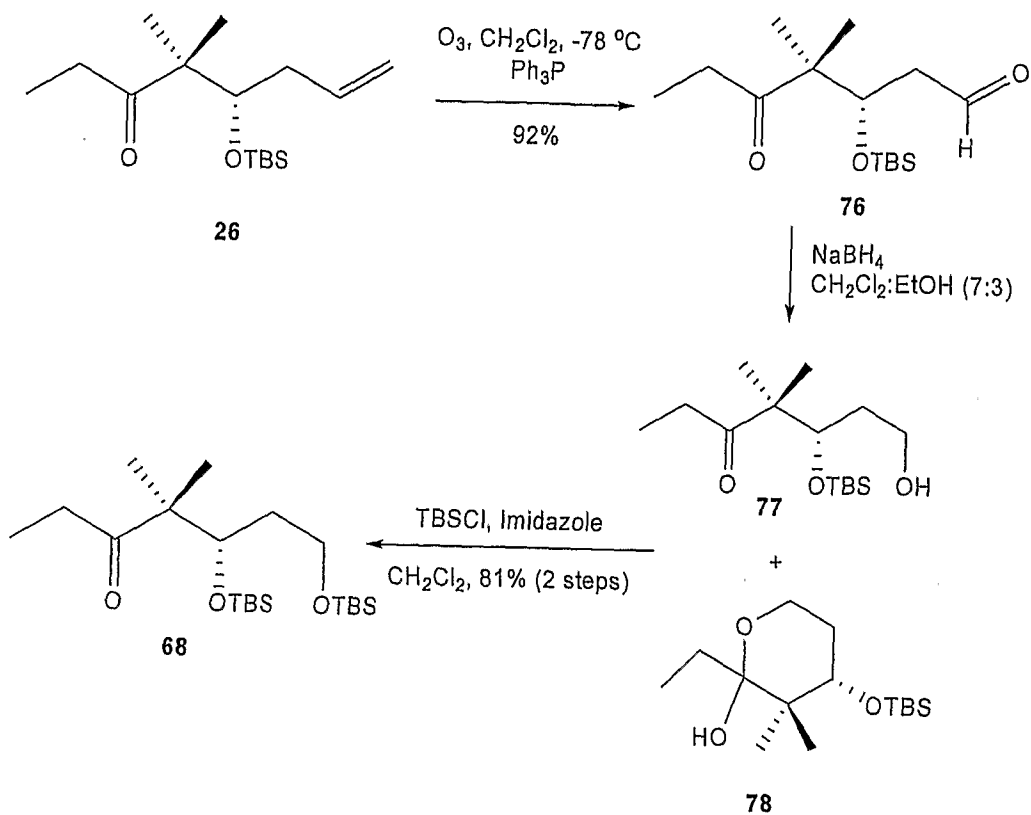


Fig. 21

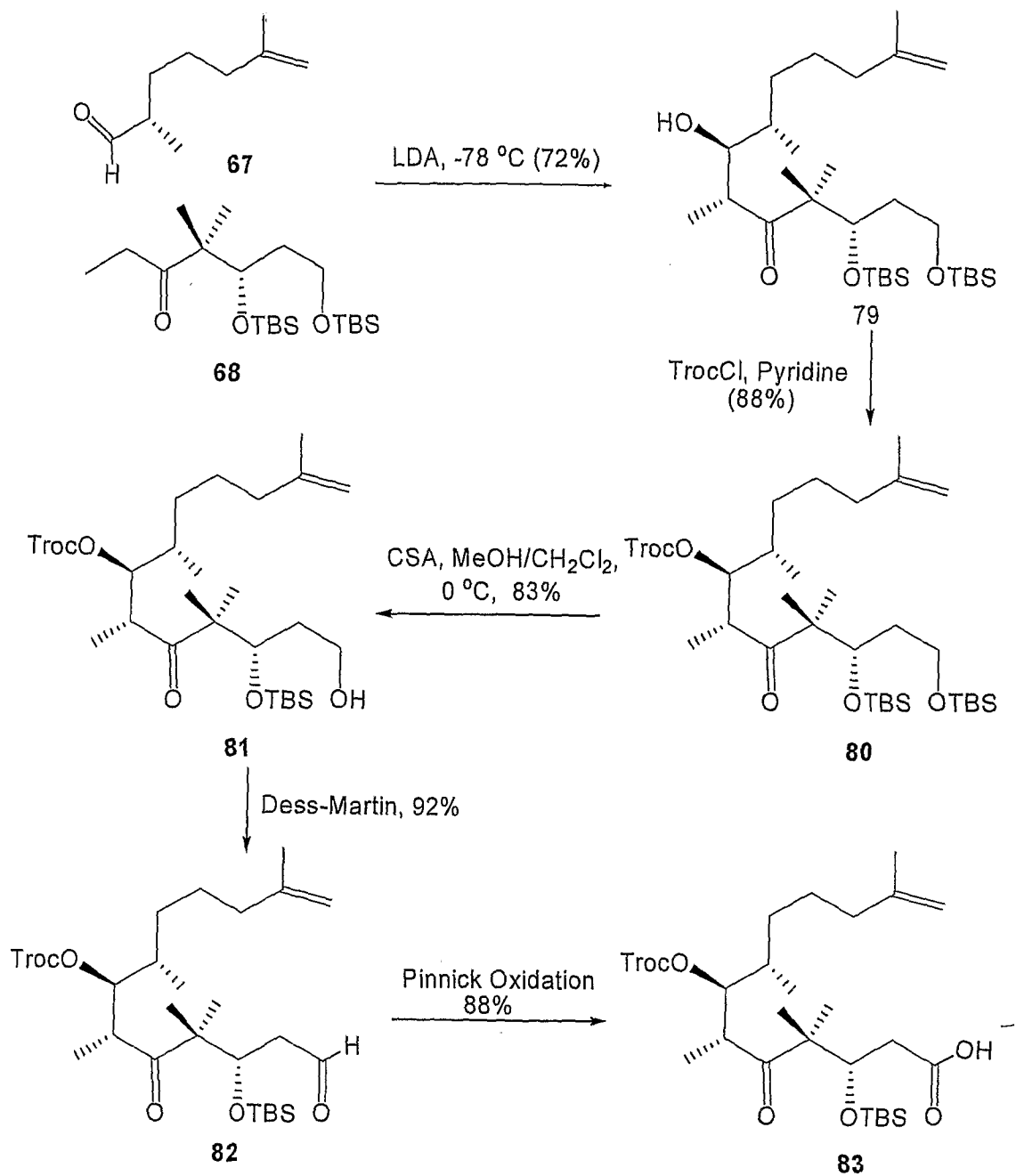


Fig. 22

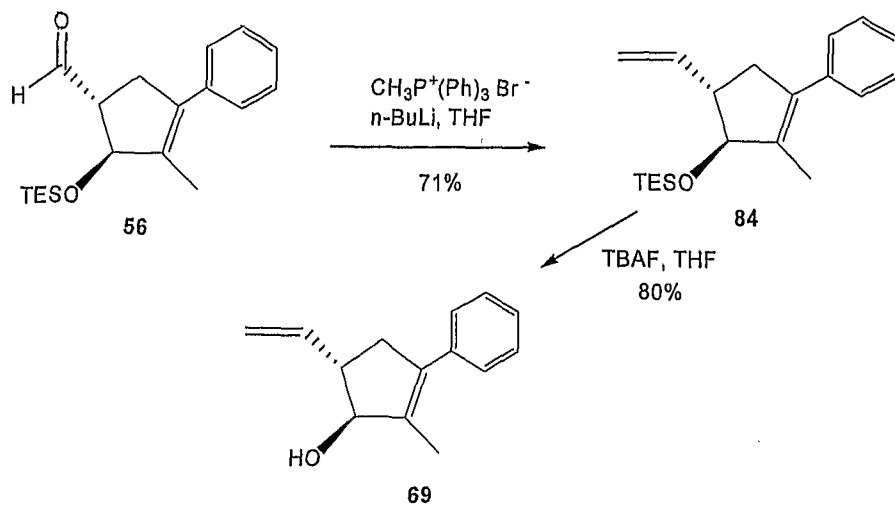


Fig. 23a

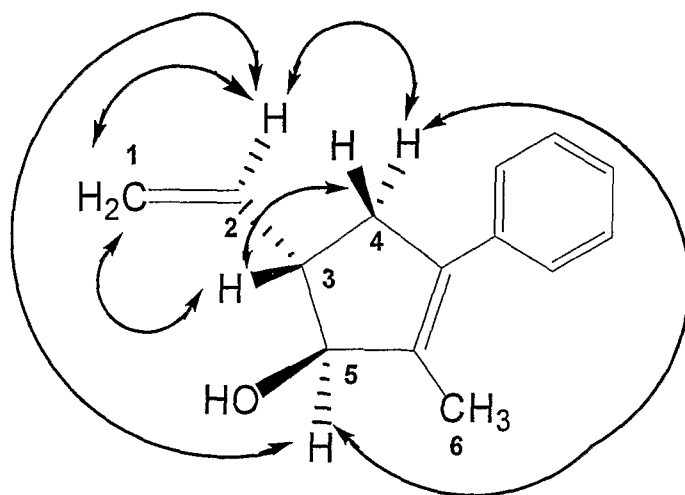


Fig. 23b

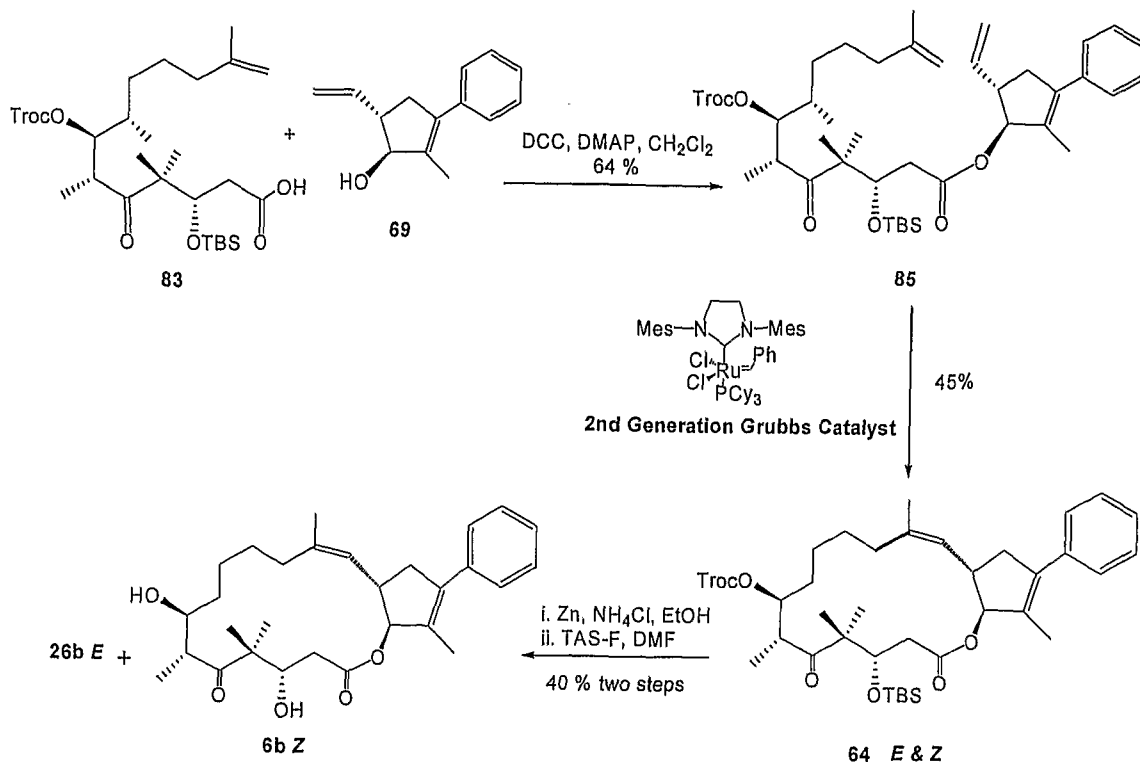


Fig. 24

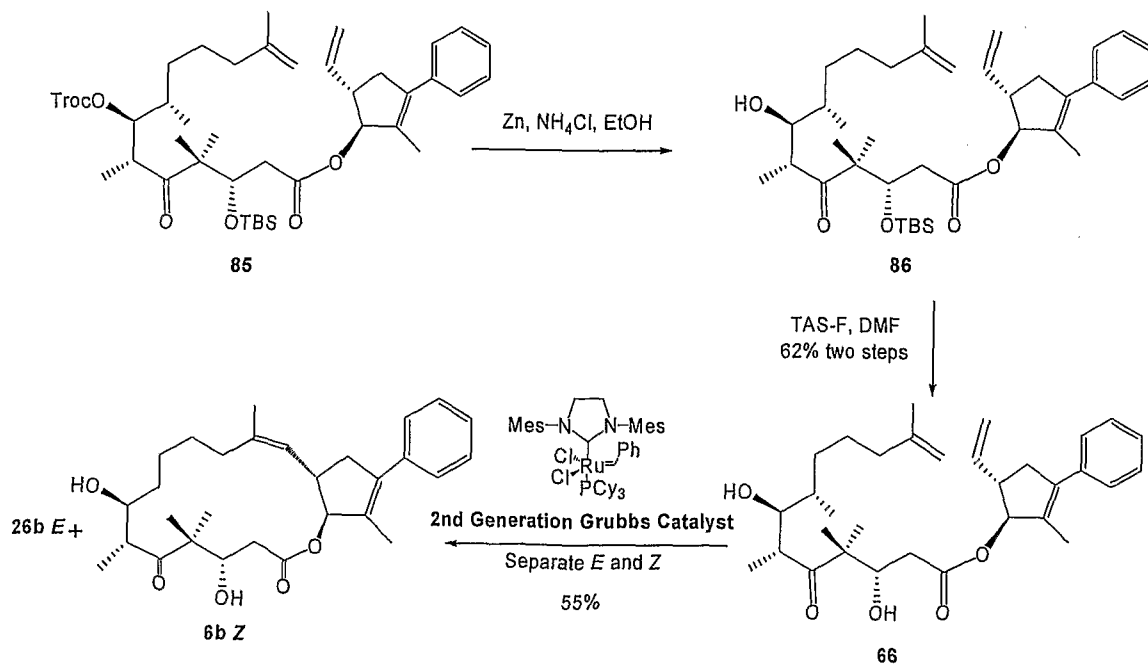
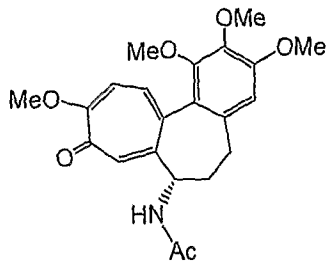
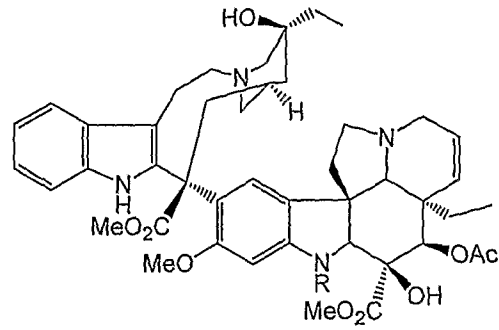


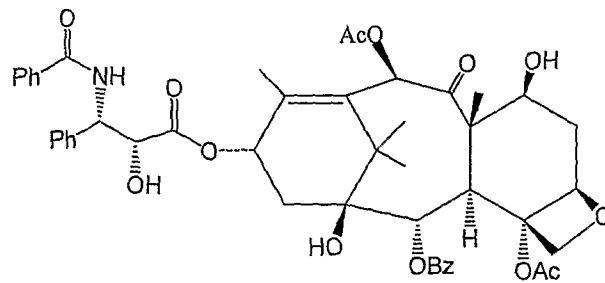
Fig. 25



1. Colchicine

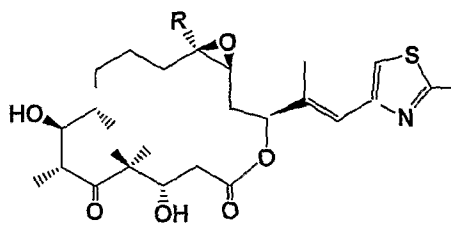


2. R = Me Vinblastine
R = CHO Vincristine

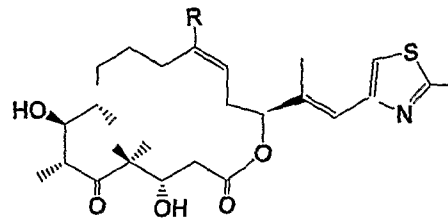


3. Paclitaxel (Taxol®)

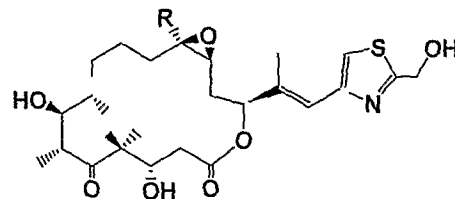
Fig. 26



4a. R = H : Epothilone A 20 nM
4b. R = Me : Epothilone B 2 nM

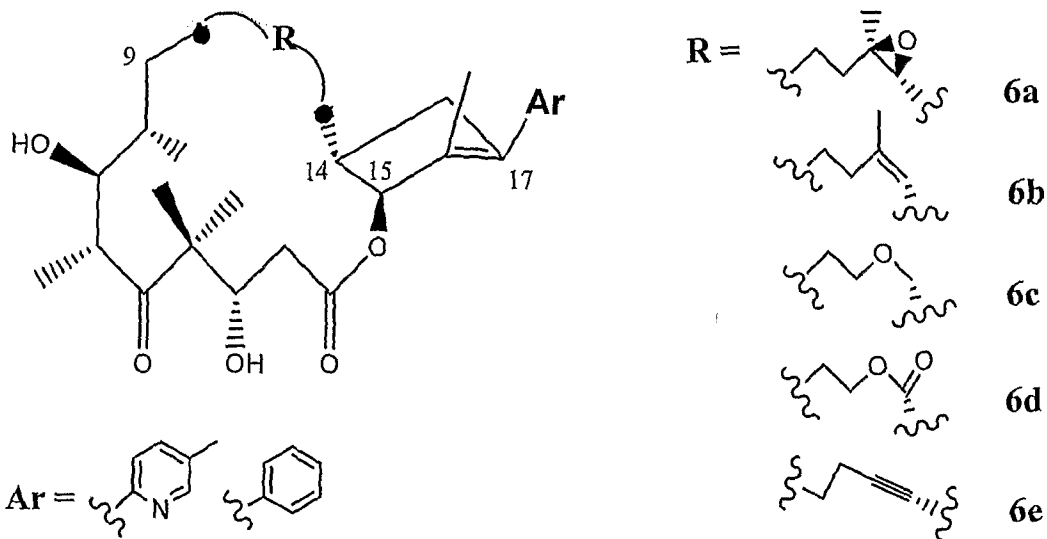


4c. R = H : Epothilone C 12 nM
4d. R = Me : Epothilone D 17 nM



4e. R = H : Epothilone E
4f. R = Me : Epothilone F

Fig. 27



calcd. Log P of R
Pyridine analogues

Compound	Epothilone B 4b	Epothilone D 4d	6a	6b	6c	6d	6e
calcd. Log P of R Pyridine analogues	4.68	4.46	4.17	5.3	3.81	3.77	4.88

Fig. 30

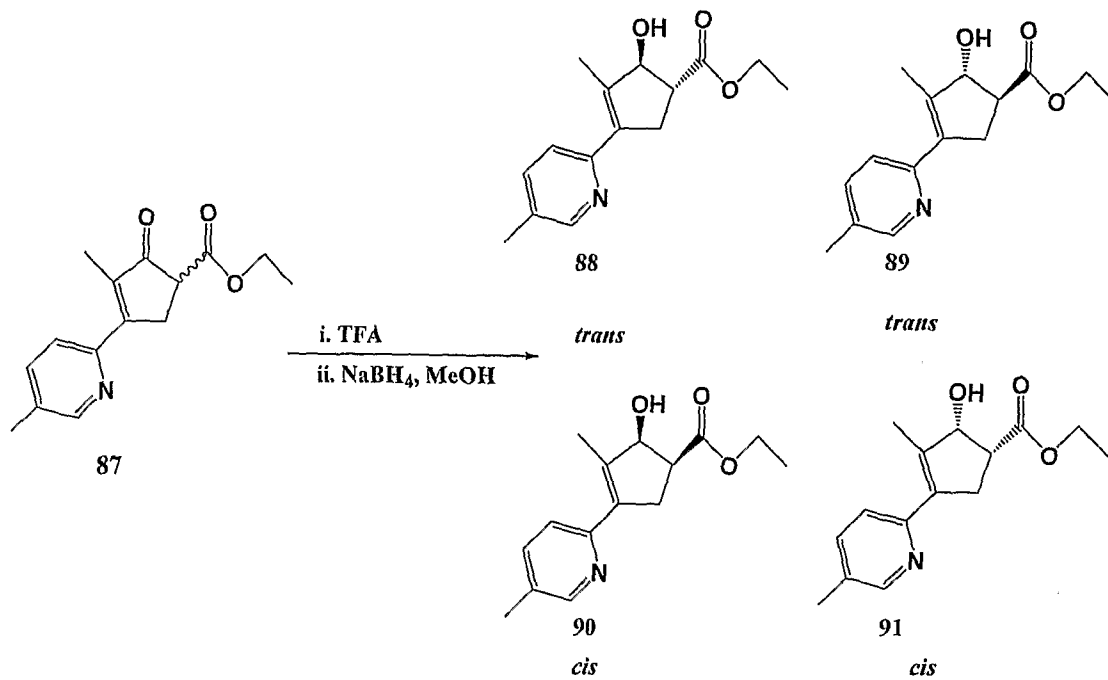


Fig. 31

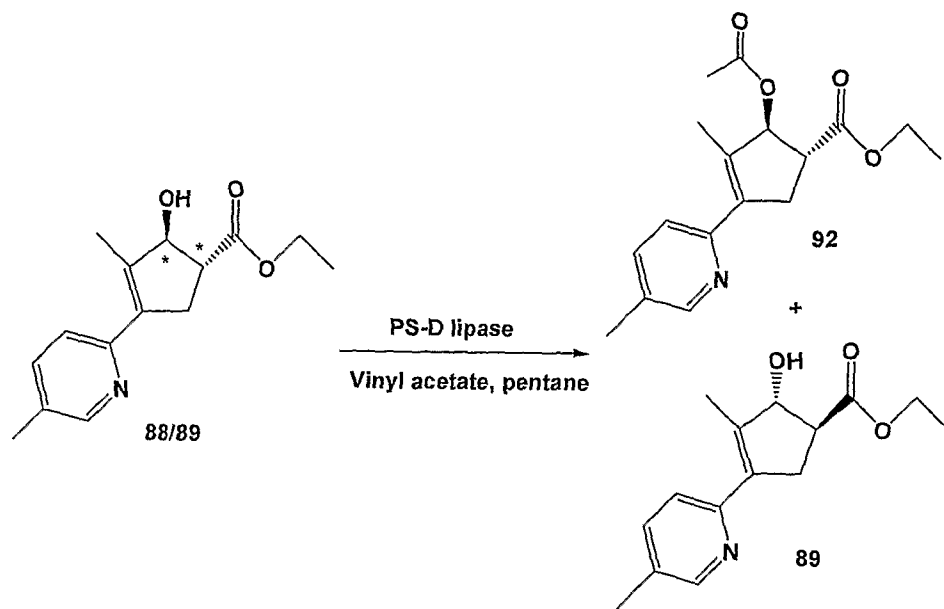


Fig. 32

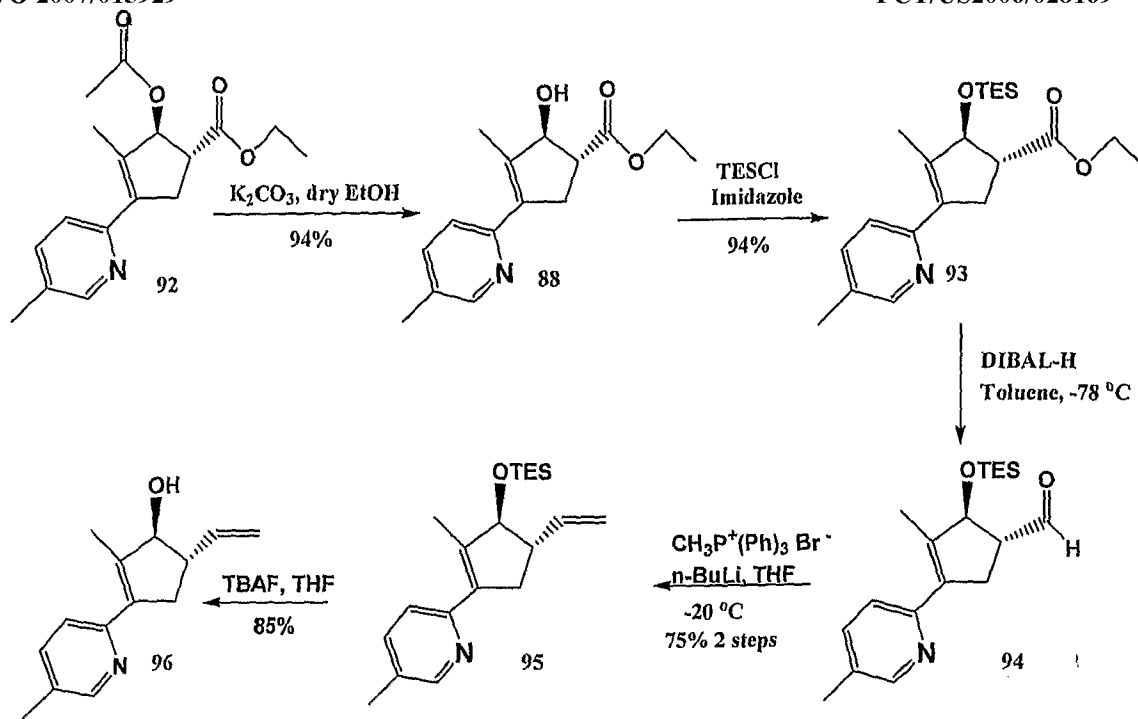


Fig. 33

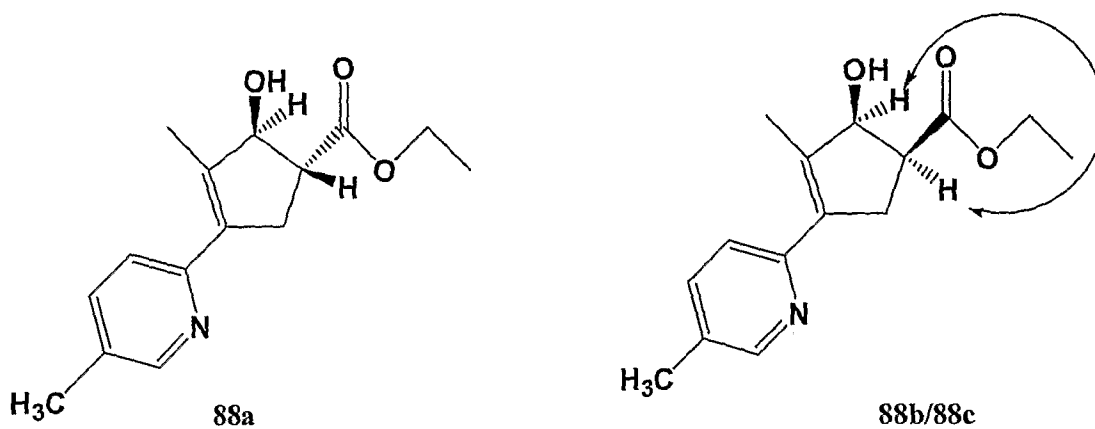


Fig. 34

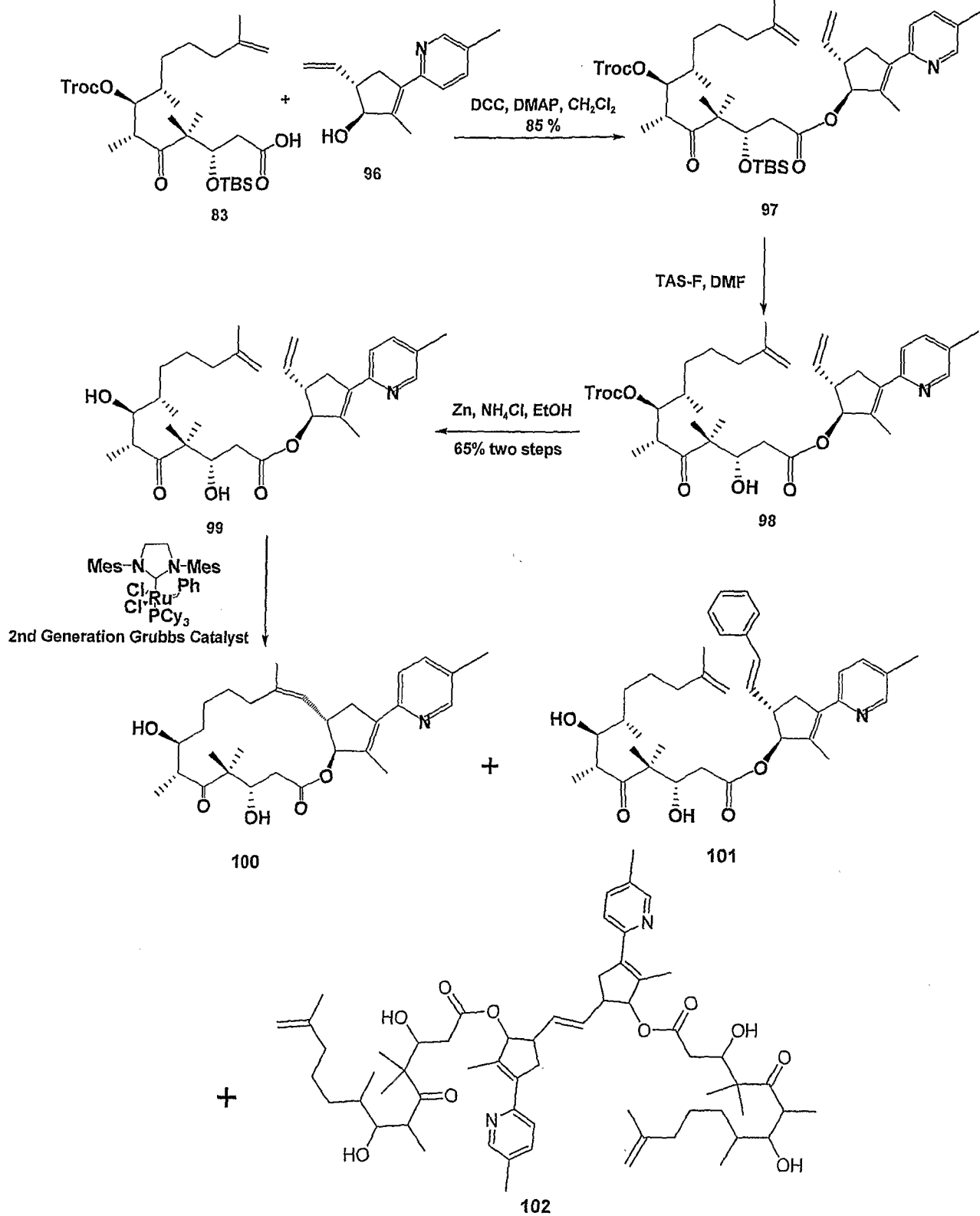


Fig. 35