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<p>(21) International Application Number: PCT/US00/11151</p> <p>(22) International Filing Date: 25 April 2000 (25.04.00)</p> <p>(30) Priority Data:</p> <table border="0"> <tr> <td>60/131,059</td> <td>26 April 1999 (26.04.99)</td> <td>US</td> </tr> <tr> <td>09/557,821</td> <td>25 April 2000 (25.04.00)</td> <td>US</td> </tr> </table> <p>(71) Applicant (for all designated States except US): SARAWAK MEDICHEM PHARMACEUTICALS, INC. [US/US]; 12305 South New Avenue, Lemont, IL 60439 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (for US only): XU, Ze-Qi [CN/US]; 1150 Greensfield Drive, Naperville, IL 60563 (US). YUAN, Hongwei [CN/US]; Suite 2808, 728 Bounty Drive, Foster City, CA 94404 (US). CRABB, Jennifer [US/US]; Unit 605, 3930 N. Pine Grove Avenue, Chicago, IL 60613 (US). SAMY, Raghu [IN/US]; Apartment #203, 1731 Locust Place, Schaumburg, IL 60173 (US). LI, Ailing [CN/US]; 124 Concord Lane, Carol Stream, IL 60188 (US). CAO, Hua [CN/US]; 5300 North Oriole Avenue, Chicago, IL 60656 (US).</p>	60/131,059	26 April 1999 (26.04.99)	US	09/557,821	25 April 2000 (25.04.00)	US	<p>(74) Agent: MCDONNELL, John, J.; McDonnell Boehnen Hulbert & Berghoff, 32nd Floor, 300 South Wacker Drive, Chicago, IL 60606 (US).</p> <p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>Without international search report and to be republished upon receipt of that report.</i></p>
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09/557,821	25 April 2000 (25.04.00)	US					
<p>(54) Title: METHODS FOR PREPARING ANTIVIRAL CALANOLIDE COMPOUNDS</p> <p>(57) Abstract</p> <p>The present invention relates to methods for preparing 2,2-dimethyl-5-acyloxy-10-propyl-2<i>H</i>,8<i>H</i>-benzo[1,2-<i>b</i>:3,4-<i>b'</i>]dipyrans-8-one (5) and 2,2-dimethyl-5-hydroxy-10-propyl-2<i>H</i>,8<i>H</i>-benzo[1,2-<i>b</i>:3,4-<i>b'</i>]dipyrans-8-one (6) and their use as intermediates for the synthesis of antiviral calanolide compounds. For example, Fries rearrangement on compound 5 or Friedel-Crafts reaction on 6, yields intermediate 2,2-dimethyl-5-hydroxy-6-propionyl-10-propyl-2<i>H</i>,8<i>H</i>-benzo[1,2-<i>b</i>:3,4-<i>b'</i>]dipyrans-8-one (4), which, in turn, can be converted to (+)-calanolide A and (-)-calanolide B. The coupling of compound 6 with the appropriate chiral molecule under Mitsunobu or nucleophilic displacement leads to the asymmetric synthesis of antiviral calanolide compounds.</p>							

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METHODS FOR PREPARING ANTIVIRAL CALANOLIDE COMPOUNDS

CROSS-REFERENCE

5 This application is a continuation-in-part of U.S. Provisional application No. 60/131,059, filed April 26, 1999.

FIELD OF THE INVENTION

This invention relates to methods for preparing calanolides and calanolide analogues.

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BACKGROUND OF THE INVENTION

Viruses, an important etiologic agent in infectious disease in humans and other mammals, are a diverse group of infectious agents that differ greatly in size, shape, chemical composition, host range, and effects on hosts. After several decades of study, only a limited number of antiviral agents are available for the treatment and/or prevention of diseases caused by viruses such as HIV, hepatitis B, herpes simplex type 1 and 2, cytomegalovirus, varicella zoster virus, Epstein Barr virus, influenza A and B, parainfluenza, adenovirus, measles, and respiratory syncytial virus. Because of their toxic effects on a host, many antiviral agents are limited to topical applications. Accordingly, there is a need for safe and effective antiviral agents with a wide-spectrum of anti-viral activity with reduced toxicity to the host.

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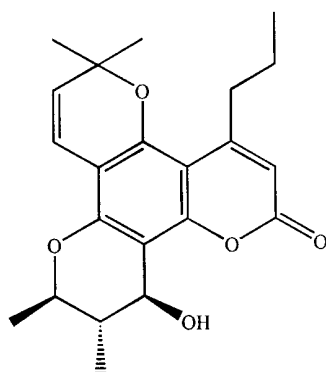
A. Human Immunodeficiency Virus (HIV)

Human immunodeficiency virus (HIV), which was also called human T-lymphotropic virus type III (HTLV-III), lymphadenopathy-associated virus (LAV) or AIDS-associated retrovirus (ARV), was first isolated in 1982 and has been identified as the etiologic agent of the acquired immunodeficiency syndrome (AIDS) and related diseases. Since then, chemotherapy of AIDS has been one of the most challenging scientific endeavors. So far, fourteen drugs have been approved by FDA and are being clinically used as drugs for the treatment of AIDS and AIDS-related complex. Although these FDA-approved drugs can extend the life of AIDS patients and improve their quality of life, none of these drugs are capable of curing the disease. Side effects as well as the emergence of drug-resistant viral strains limit the long-term use of these agents.¹ On the other hand, the number of AIDS patients worldwide has increased dramatically within the past decade and estimates

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of the reported cases in the very near future also continue to rise dramatically. It is therefore apparent that there is a great need for other promising drugs having improved selectivity and activity to combat AIDS.¹ Several approaches including chemical synthesis, natural products screening, and biotechnology have been utilized to identify compounds targeting different stages of HIV replication for therapeutic intervention.²

The natural product screening program at the National Cancer Institute has discovered a class of remarkably effective anti-HIV compounds, named calanolides, from the rain forest tree *Calophyllum lanigerum*, with (+)-calanolide A, **1**, being the most potent compound in the reported series.³ For example, (+)-calanolide A demonstrated 100% protection against the cytopathic effects of HIV-1, one of two distinct types of HIV, down to a concentration of 0.1 μM . This agent also halted HIV-1 replication in human T-lymphoblastic cells (CEM-SS)($\text{EC}_{50}=0.1 \mu\text{M}/\text{IC}_{50}=20 \mu\text{M}$).³ More interestingly and importantly, (+)-calanolide A was found to be active against both the AZT-resistant G-9106 strain of HIV as well as the pyridinone-resistant A17 virus.³ Thus, the calanolides, classified



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as HIV-1 specific reverse transcriptase inhibitors, represent novel anti-HIV chemotherapeutic agents for drug development.

B. Hepatitis B Virus (HBV)

The hepatitis B virus (HBV) infects people of all ages. It is one of the fastest-spreading sexually transmitted diseases, and also can be transmitted by sharing needles or by behavior in which a person's mucus membranes are exposed to an infected person's blood, semen, vaginal secretions, or saliva. While the initial sickness is rarely fatal, ten percent of the people who contract hepatitis are infected for life and run a high risk of developing serious, long-term liver diseases, such as cirrhosis of the liver and liver cancer, which can cause serious complications or death.⁴ The World Health Organization lists HBV as the ninth leading cause of death. It is estimated that about 300 million persons are chronically infected with HBV worldwide, with over 1 million of those in the United States. The Center for Disease Control and Prevention estimates that over 300,000 new cases of acute HBV infection occurs in the United States each year, resulting in 4,000 deaths due to cirrhosis and 1,000 due to hepatocellular carcinoma.⁵ The highest rates of HBV infections occur in Southeast Asia, South Pacific Islands, Sub-Saharan Africa, Alaska, Amazon, Bahai, Haiti, and the Dominican Republic, where approximately 20% of the population is chronically infected.⁶

Hepatitis B virus (HBV) infection is currently the most important chronic virus infection, but no safe and effective therapy is available at present. The major therapeutic option for carriers of HBV is alpha interferon, which can control active virus replication. However, even in the most successful studies, the response rate in carefully selected patient groups has rarely exceeded 40%.^{7,8} One of the reasons cited for interferon failure is the persistence of viral supercoiled DNA in the liver.⁹ Clinical exploration of many promising antiviral agents such as nucleoside analogues is hampered because their aspecific body distribution leads to significant toxic side effects. Recently, a new nucleoside analogue, 2',3'-dideoxy-3'-thiacytidine (3TC), was approved to treat HBV infection with only minimal side effects.¹⁰⁻¹²

C. Influenza Virus

Influenza is a viral infection marked by fever, chills, and a generalized feeling of weakness and pain in the muscle, together with varying signs of soreness in the respiratory tract, head, and abdomen. Influenza is caused by several types of myxoviruses, categorized as groups A, B, and C₄. These influenza viruses generally lead to similar symptoms but are completely unrelated antigenically, so that infection with one type confers no immunity against the other. Influenza tends to occur in wavelike epidemics throughout the world; influenza A tends to appear in cycles of two to three years and influenza B in cycles of four to five years. Influenza is one of the few common infectious diseases that are poorly controlled by modern medicine. Its annual epidemics are occasionally punctuated by devastating pandemics. For example, the influenza pandemic of 1918, which killed over 20 million people and affected perhaps 100 times that number, was the most lethal plague ever recorded. Since that time, there have been two other pandemics of lesser severity, the so-called Asian flu of 1957 and the Hong Kong flu of 1968. All of these pandemics were characterized by the appearance of a new strain of influenza virus to which the human population had little resistance and against which previously existing influenza virus vaccines were ineffective. Moreover, between pandemics, influenza virus undergoes a gradual antigenic variation that degrades the level of immunological resistance against renewed infection.¹³

Anti-influenza vaccines, containing killed strains of types A and B virus currently in circulation, are available, but have only a 60 to 70% success rate in preventing infection. The standard influenza vaccine has to be redesigned each year to counter new variants of the virus. In addition, any immunity provided is short-lived. The only drugs currently effective in the prevention and treatment of influenza are amantadine hydrochloride and rimantadine hydrochloride.¹⁴⁻¹⁶ While the clinical use of amantadine has been limited by the excess rate of CNS side effects, rimantadine is more active against influenza A both in animals and human beings, with fewer side effects.^{17,18} It is the drug of choice for the chemoprophylaxis of influenza A.^{13, 19, 20} However, the clinical usefulness of both drugs is limited by their effectiveness against only influenza A viruses, by the uncertain therapeutic efficacy in severe influenza, and by the recent findings of recovery of drug-resistant strains in some treated patients.²¹⁻²⁵ Ribavirin has been reported to be therapeutically active, but it remains in the investigational stage of development.^{26,27}

D. Cytomegalovirus (CMV)

Cytomegalovirus (CMV) is a member of the herpes virus family, other well-known members of which include herpes simplex virus, types I and II, Epstein Barr virus and Varicella Zoster virus. Although these viruses are related taxonomically, all comprising double-stranded DNA viruses, infections due to these viruses manifest in clinically distinct ways. In the case of CMV, medical conditions arising from congenital infection include jaundice, respiratory distress and convulsive seizures that may result in mental retardation, neurologic disability or death. Infection in adults is frequently asymptomatic, but may manifest as mononucleosis, hepatitis, pneumonitis or retinitis, particularly in immunocompromised patients such as AIDS sufferers, chemotherapy patients and organ transplant patients undergoing tissue rejection therapy.

Up to 45% of all HIV-infected persons will develop cytomegalovirus-induced disease before their lives end.²⁸ Although two antiviral agents--ganciclovir and foscarnet--are available to treat human cytomegalovirus (HCMV), they act as virustatic agents to slow but not halt progression of disease; hence, disease routinely progresses despite daily maintenance with either agent. Moreover, therapy using either agent is problematic because both agents are associated with serious toxicities.²⁹

Classical drug therapies have generally focused upon interactions with proteins in efforts to modulate their disease-causing or disease-potentiating functions. Such therapeutic approaches have failed for cytomegalovirus infections. Effective therapy for CMV has not yet been developed despite studies on a number of antiviral agents. Interferon, transfer factor, adenine arabinoside (Ara-A), acycloguanosine (Acyclovir) and certain combinations of these drugs have been ineffective in controlling CMV infections. Based on preclinical and clinical data, foscarnet and ganciclovir show limited potential as antiviral agents. Foscarnet treatment has resulted in the resolution of CMV retinitis in five AIDS patients to date. Ganciclovir studies have shown efficacy against CMV retinitis and colitis. However, though ganciclovir seems to be well tolerated by most treated individuals, the appearance of a reversible neutropenia, the emergence of resistant strains of CMV upon long-term administration, and the lack of efficacy against CMV pneumonitis limit the long term applications of this compound. Cidofovir was approved to treat CMV in certain AIDS patients due to its undesired toxicities. The development of more effective and less toxic therapeutic compounds and methods is needed for both acute and chronic use.

Several HCMV vaccines have been developed or are in the process of development. Vaccines based on live attenuated strains of HCMV have been described. A proposed HCMV vaccine using a recombinant vaccinia virus expressing HCMV glycoprotein B has also been described. However, vaccinia models for vaccine delivery are believed to cause local reactions. Additionally, vaccinia vaccines are considered possible causes of encephalitis.

E. Other Herpes Viruses

Varicella zoster virus (VZV) is the etiologic agent that produces both varicella (chickenpox) and zoster (shingles). As with other herpes viruses, VZV causes both an acute illness and lifelong latent infection. Acute primary infection (varicella) typically occurs during childhood, where the resulting infection is relatively mild. Conversely, primary infection in adults can be more severe. Herpes zoster cutaneous eruptions are caused by reactivation of VZV present in sensory ganglia.³⁰ Herpes zoster occurs more frequently with elderly and immunosuppressed individuals, and is eight times more likely to develop in HIV-infected individuals than in other individuals in comparable age groups.³¹

Along with other immunosuppressed patients, HIV-infected patients may develop severe and in certain cases life-threatening illnesses following either primary or recurrent VZV infection. Therapy for HIV-infected patients experiencing VZV infection generally involves administering acyclovir or vidarabine (Ara-A), with hospitalization required in many instances. To inhibit VZV replication, serum levels of acyclovir are about ten times greater than those needed to to inhibit Herpes Simplex Type 1 and 2.

Herpes simplex virus type 1 and type 2 (HSV-1 and HSV-2) can establish latency following primary infection and can thus subsequently reactivate to induce recurrent disease. Upon primary infection, herpes simplex type 1 induces diseases including primary gingivostomatitis, encephalitis, and kerato-conjunctivitis, while herpes simplex type 2 induces primary genital herpes and neonatal herpes. Upon recurrence, herpes simplex type 1 induces diseases including recurrent oral herpes and recurrent kerato-conjunctivitis, while herpes simplex type 2 induces recurrent genital herpes.³² HSV infection in HIV-infected patients can produce widespread and occasionally life-threatening lesions.

Acyclovir, delivered either intravenously, orally, or topically, shortens clinical illness in both immunocompetent and immunosuppressed patients. Vidarabine also has been used in treating HSV. Some vaccine strategies have been investigated with a view towards

preventing initial primary infection. However, protecting only against primary disease but not protecting against latency and subsequent recurrence is inadequate for those persons already initially infected. Moreover, acyclovir-resistant HSV infections recently have been observed, in many cases occurring among HIV-infected patients treated successfully with acyclovir in the past. The existence of such acyclovir-resistant infections in HIV-infected patients is troubling in view of the limited number of alternative therapeutic options available.

Respiratory Syncytial Virus (RSV) is the prime etiologic agent producing lower respiratory tract disease. RSV causes extensive yearly epidemics during which there is a marked increase in hospital admissions of patients, especially infants and young children, experiencing severe lower respiratory tract disease. Immunosuppressed patients infected with RSV are at high risk of mortality. Ribavirin is the only currently approved drug for treating RSV infections. However, this drug appears to have limited efficacy. Additionally, development of effective vaccines has proven difficult to date.

F. Opportunistic Infections

The viruses described above can act as sole causes of infection or can act to produce opportunistic infections in patients already battling immunosuppressing infections such as HIV. Acting by themselves, these viruses can present therapeutic challenges. But when acting to produce opportunistic infections in HIV-infected or other immunosuppressed patients, these viruses dramatically increase the difficulty and complexity of successful treatment.

In addition to the viruses discussed above, other viral, bacterial, fungal, and protozoal pathogens can induce opportunistic infections. Common opportunistic pathogens in addition to those described above include *Mycobacterium avium* complex (MAC), *Pneumocystis carinii* (PC), and *M. tuberculosis*.

Present therapies for HIV-infected patients also suffering from opportunistic infection generally involve administering a plurality of antiviral compounds. In such a treatment regimen, termed combination therapy, each antiviral compound employed demonstrates best antiviral activity against a distinct viral infection. For example, a combination therapy of AZT and ganciclovir can be used for an HIV-infected patient also experiencing CMV retinitis, where AZT targets the HIV infection and ganciclovir targets the CMV infection. Thus, combination therapies can be powerful therapeutic tools. Even more powerful and

desirable, however, would be a single antiviral compound that demonstrates antiviral activity against both HIV and other viruses.

While some limited success has been realized in the search for viable therapeutics for treatment of the viral infections discussed above, therapeutic agents for many viruses remain severely limited. Furthermore, there are no known safe and therapeutic treatments for HBV, influenza and HIV. In HBV, with the possible exception of the drug 3TC, the use of nucleoside-based antiviral agents leads to toxicity, probably due to cross-inhibition of cellular mitochondrial DNA. Clearly, there is a need for a new class of antiviral agents which could minimize the toxicity associated with cross-inhibition. In influenza, amantadine and rimantadine have been shown to be moderately effective against only influenza A viruses, with amantadine having excessive side effects. Recently, strains of influenza A resistant to amantadine and rimantadine have been isolated. Accordingly, there is a need for new types of therapeutic antiviral agents particularly against both influenza A and influenza B, as well as against HIV, HBV and HIV and other viruses. Furthermore, due to the loss of CD4 T lymphocytes in an HIV infected person, leading to immunodeficiency and thus increasing susceptibility to a broad range of opportunistic viral, bacterial, fungal, and protozoal pathogens, identifying anti-HIV agents having a spectrum of antiviral and antimicrobial activities is of particular interest. These agents would be not only effective against HIV infection, but also effective against or preventive of opportunistic infections in AIDS patients.

A class of coumarin compounds, either natural products isolated from several tropical plants of the genus *Calophyllum*^{3, 33-38} or synthetic analogues,³⁹⁻⁴¹ have been demonstrated to be active against HIV-1. (+)-Calanolide A (1), the most active one in this class, has been selected for further pharmacological and clinical development.^{42,43} However, a natural source of (+)-calanolide A is limited. This limited availability fueled the desire to develop practical synthesis routes to enable further study and development to be carried out on this active and promising series of compounds. Herein, we describe improved synthetic approaches for the synthesis of important intermediates for the synthesis of antiviral calanolide compounds.

SUMMARY OF THE INVENTION

The present invention relates to synthetic approaches for preparing antiviral calanolides and key intermediates thereof. A number of total syntheses of calanolide

compounds have been reported by us⁴⁴⁻⁴⁶ and by others.⁴⁷⁻⁵¹ In our previous syntheses (Figure 1),⁴⁴⁻⁴⁶ 2,2-dimethyl-5-hydroxy-6-propionyl-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one (4) was the key intermediate, which was derived from 5,7-dihydroxy-8-propionyl-4-propylcoumarin (3). In this application, we report a novel approach to the synthesis of 2,2-dimethyl-5-acyloxy-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one (5) and 2,2-dimethyl-5-hydroxy-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one (6) (Figures 3 and 4). These compounds serve as important intermediates for the synthesis of antiviral calanolide compounds. For example, Fries rearrangement⁵²⁻⁵⁴ on compound 5a, or Friedel-Crafts reaction on 6, yields intermediate 4, which, in turn, can be converted to (+)-calanolide A and (-)-calanolide B⁴⁴⁻⁴⁶ (Figures 1 and 5).

Thus, in one embodiment of the invention, a method for preparing (+)-calanolide A using 6 is provided. According to the method, 6 is coupled to compound 11 to provide compound 13. Compound 13 is subsequently hydrolyzed to produce 13 (Y=OH). Compound 13 (Y=OH) is then subjected to an intramolecular Friedel-Crafts reaction to provide ketone (+)-10. Ketone (+)-10 is then subjected to Luche reduction to produce (+)-calanolide A 1 (Figure 6).

Alternatively, compound 13 may be prepared from compound 6 by treating the latter compound with 12 to produce 14. Compound 14 is then subject to a Swern oxidation to produce aldehyde 13 (Y=H). Compound 13 (Y=H) is subsequently oxidized to provide 13 (Y=OH) (Figure 7).

In another embodiment of the invention, a general method for providing calanolide analogues is provided. According to this method, 1,3,5-triphenol is reacted with β -keto 25 ester under Peckman conditions.⁴⁴⁻⁴⁶ The resulting compound 15 is then selectively acylated to provide compound 16. Compound 16 is then chromenylated to produce compound 17.⁴⁴⁻⁴⁶ Hydrolysis of 17 produced compound 18 which is then coupled with ester 19 to produce 20. Compound 20 was then cyclized under Friedel-Crafts conditions to produce 21. Reduction of 21 with a suitable reagent, e.g. sodium borohydride, results in calanolide analogue 22 (Figure 8).⁴⁴⁻⁴⁶

Alternatively, compound 20 may be prepared from compound 18 by coupling the latter compound with 23 to produce 24. Compound 24 was then subject to swern oxidation to produce the aldehyde analogue 20 (Y=H). The aldehyde analogue was then oxidized to produce the carboxylic analogue 20 (Y=OH) (Figure 9).

These and other embodiments of the invention will become apparent in light of the detailed description below.

DETAILED DESCRIPTION OF THE FIGURES

5 Figure 1 is a schematic illustrating the conversion of compounds **5(a)** and **6** to **4**, a key intermediate for the preparation of calanolides such as (+)-calanolide A.

Figure 2 is a retrosynthetic schematic illustrating the conversion of intermediates **2** to **7** to **5a**.

10 Figure 3 illustrates selective acylation reactions of coumarin **2** to form compounds **7a-c** and **8a-c**.

Figure 4 illustrates the chromenylation of coumarin compounds **7a-c** to **5a-b** and the basic hydrolysis of acylated chromeno-coumarin **5a-b** to compound **6**.

Figure 5 illustrates the conversion of key intermediates **5a** and **6** to (\pm)-calanolide A.

15 Figures 6 and 7 further illustrate preparation of (+)-calanolide A from **6**.

Figures 8 and 9 illustrate preparation of calanolide analogues.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods for preparing (+)-calanolide A and calanolide analogues. In one embodiment of the invention, a novel approach to the
20 synthesis of 2,2-dimethyl-5-acyloxy-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one (**5**) and 2,2-dimethyl-5-hydroxy-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one (**6**) is provided. These compounds serve as important intermediates for the synthesis of antiviral calanolide compounds. For example, Fries rearrangement⁵²⁻⁵⁴ on compound **5a**, or Friedel-Crafts reaction on **6**, yields intermediate **4**, which, in turn, can be converted to (+)-calanolide A and (-)-calanolide B⁴⁴⁻⁴⁶ (**Figures 1 and 5**).

The strategy for synthesis of compound **5a** is based on the fact that under the modified Friedel-Crafts reaction conditions 5-hydroxy-7-propionyloxy-4-propylcoumarin (**7a**) was selectively formed from **2** in 10% yield.⁴⁵ Chromenylation^{44,45} on **7a** is expected
30 to deliver compound **5a** (**Figure 2**). Due to the low yields from the Friedel-Crafts acylation reaction, a more practical procedure needed to be developed for the synthesis of **7a** from **2**. A variety of reaction conditions were investigated, which is summarized in

Table I in Example 1. Accordingly, improved acylation conditions were discovered which provided surprisingly increased production yields of **7a**.

In conducting this reaction, a solution of suitable acylating agent, e.g., acyl chloride or anhydride, in a suitable solvent, e.g., THF, was added in a dropwise manner to a vigorously stirred solution of 5,7-dihydroxy-4-propylcoumarin **2**, a Lewis acid catalyst or a catalytic amount of a base, and an organic solvent cooled in an ice bath. Dropwise addition of the acylating agent is conducted such that the temperature of the reaction mixture is maintained at a temperature ranging between 0 °C and about 30 °C.

In making compounds of the invention, the amount of acylating agent used generally ranges between about 0.5 and about 6 moles, preferably ranging between about 1 and about 2 moles, per mole of **2**.

Non-limiting examples of Lewis acid catalysts useful in the acylation reaction include AlCl₃, BF₃, SnCl₄, ZnCl₂, POCl₃ and TiCl₄. A preferred Lewis acid catalyst is AlCl₃. The amount of Lewis acid catalyst relative to 5,7-dihydroxy-4-propylcoumarin, **2**, ranges between about 0.5 and about 12 moles, preferably ranging between about 2 and about 5 moles, per mole of 5,7-dihydroxy-4-propylcoumarin, **2**.

Non-limiting examples of a base useful in the acylation reaction include pyridine and 4-dimethylaminopyridine (DMAP). Catalytic amounts (0.1 eq) of the base may be used in combination with a suitable reaction solvent. Alternatively, the base may be used as the reaction solvent, however, complex product mixtures may result (Example 1).

Non-limiting examples of organic solvent for use in the acylation reaction include THF, dichloroethane, pyridine, and mixtures thereof.

Upon completion of the addition of acylating agent, the vigorously stirred reaction mixture is maintained at a temperature ranging between about 0 °C and about 30 °C, preferably about room temperature (25 °C) until the reaction reaches completion as monitored by conventional means such as TLC analysis. The reaction mixture is then poured onto ice and extracted several times with a suitable solvent such as ethyl acetate, chloroform, methylene chloride, tetrahydrofuran, or a mixture of chloroform/methanol. A preferred solvent for this extraction is ethyl acetate. The extracts are then dried over a suitable drying agent, e.g., sodium sulfate, and the product may be purified by conventional means such as silica gel column chromatography.

Chromenylation of **7a** was initially attempted employing 4,4-dimethoxy-2-methylbutan-2-ol according to the literature method,^{44,45} and only ca. 5% of **5a** was

detected by ^1H NMR. However, when 3-chloro-3-methyl-1-butyne was used,^{47,55} **5a** was obtained in 27% isolated yield (**Figures 4 and 5**). The same procedure on **7b** afforded **5b** in 73% yield. In contrast, no **5c** could be detected when **7c** was reacted with 3-chloro-3-methyl-1-butyne under the same conditions. Instead, a tripyranone derivative **9**⁵⁶ was formed. The structure assignment of **9** was based on ^1H NMR and MS (**Figure 4**). This indicated that the TBMDs-protecting group was lost during the course of chromenylation.

Hydrolysis of **5a** to produce **6** under basic conditions proceeded smoothly. For example, conversion of **5a** to **6** was uneventful with sodium bicarbonate in aq. MeOH in 44% yield (**Figures 4 and 5**). This represents a substantial yield improvement over previous methods for preparing **6**. For instance, prior reported direct chromenylation of **2** with 4,4-dimethoxy-2-methylbutan-2-ol furnished a mixture of product, with **6** being isolated in less than 10% yield.⁵⁵ Fries rearrangement on **5a** or Friedel-Crafts reaction on **6** led to intermediate **4** which can then be converted to (+)-calanolide A and (-)-calanolide B (**Figure 1**) using previously reported procedures.⁴⁴⁻⁴⁶

Figure 5 illustrates preparation of (\pm)-calanolide A from **5a** or **6**. Thus, treatment of **2** using the inventive acylation method resulted in **7a**. Chromenylation of **7a** with 3-chloro-3-methyl-1-butyne resulted in **5a** which can be converted directly to **4** via Fries rearrangement in the presence of AlCl_3 . Alternatively, **4** may be obtained by the hydrolysis of **5a** to yield **6**, followed by a Friedel-Crafts reaction as discussed above.

The conversion of **5a** to **4** under Fries rearrangement conditions is straightforward. A mixture of compound **5a** with anhydrous aluminium chloride in an amount ranging from about 0.1 to about 20 moles, preferably about 10 moles, per mole of compound **5a** is heated for a time period ranging between about 0.5 to about 6 hours, preferably about 2 hours at a temperature ranging between about 40 °C to about 250 °C, preferably about 160 °C. The mixture is then cooled to r.t. and treated with ice and hydrochloric acid to precipitate out the product. The precipitated product is taken into a suitable solvent, preferably ethyl acetate, and the aqueous solution is extracted with the same solvent. The extracts are combined and dried over any suitable drying agent, e.g., Na_2SO_4 and concentrated *in vacuo*. The crude product thus obtained may then be purified by any suitable means such as silica gel column chromatography using any suitable solvent or solvent mixtures, e.g., 25% ethyl acetate in hexane.

Compound **4** can be converted to 12-oxocalanolide **11** using a variety of reagents including chlorotitanium-mediated aldol reaction with acetaldehyde followed by the Mitsunobu reaction, and treatment with paraaldehyde or $\text{CH}_3\text{CH}(\text{OEt})_2$ as described in U.S. Patents No. 5,489,697; 5,869,324; 5,874,591; 5,840,921; 5,847,164; 5,892,060; 5,872,264; 5,981,770; 5,977,385; 6,043,271; and co-pending application 09/173,143, filed October 15, 1998 which are incorporated by reference in their entirety. Luche reduction of **11** with NaBH_4 and $\text{CeCl}_3(\text{H}_2\text{O})_7$ yields (\pm)-calanolide A as described in U.S. Patent Nos. 5,489,697; 5,869,324; 5,874,591; 5,840,921; 5,847,164; 5,892,060; 5,872,264; 5,981,770; 5,977,385; 6,043,271; and co-pending application 09/173,143, filed October 15, 1998.

Figure 6 and **Figure 7** further illustrate preparation of (+)-calanolide A from compound **6**. According to **Figure 6**, a method for preparing (+)-calanolide A using **6** is provided. The introduction of the chiral side chains at the desired 7-position of **6** can be achieved using a variety of readily available chiral compounds **11**⁵⁷⁻⁶⁰ and **12**. The latter compound, **12** ($Z = \text{H}$), is resulted from reduction of **11** ($X = \text{OH}$, $Y = \text{OMe}$) with LiAlH_4 . The primary OH group in **12** ($Z = \text{H}$) is then selectively protected such that Z is, for example, t-butyldimethylsilyl (TBDMS), tetrahydropyran (THP), p-toluenesulfonyl (Ts) or COR_{10} wherein R_{10} represents C_{1-6} alkyl, aryl- C_{1-6} alkyl, mono- or poly- fluorinated C_{1-6} alkyl, aryl or heterocycle. According to the method, **6** is coupled to compound **11** ($X = \text{OH}$) under Mitsunobu conditions (PPh_3 , diethyl azodicarboxylate) to provide compound **13**. Compound **13** is subsequently hydrolyzed to produce **13** ($Y = \text{OH}$). Compound **13** ($Y = \text{OH}$) is then subjected to an intramolecular Friedel-Crafts reaction to provide ketone (+)-**10**. Ketone (+)-**10** is then subjected to Luche reduction to produce (+)-calanolide A **1**.

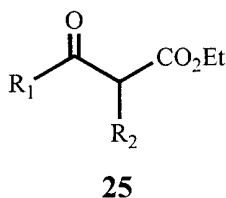
The reaction of **6** with **11** ($X = \text{TsO}$) under nucleophilic substitution conditions also generates compound **13**. Hydrolysis (NaOH , LiCl) of **13** ($Y = \text{OMe}$), or removal of the chiral auxiliary (LiOH or LiOOH) from **13** ($Y = \text{oxazolidinone}$), followed by intramolecular Friedel-Crafts cyclization, yields the chromanone (+)-**10**. Luche reduction of (+)-**10** affords (+)-calanolide A. It should be noting that a substantial elimination from **11** ($X = \text{OH}$ or TsO) occurred under both Mitsunobu and the nucleophilic substitution conditions, resulting in a requirement for excessive amount of the chiral moiety and a reduction in yield of **13**.

In order to avoid the β -elimination from **11**, a selectively protected chiral diol compound **12** is devised. Thus, Mitsunobu reaction (PPh_3 , diethyl azodicarboxylate) of **6**

with **12** ($Z = \text{TBDMS}$) leads to the formation of **14** ($Z = \text{H}$), followed by removal of TBDMS protecting group (**Figure 7**). No β -elimination from **12** was observed in this process. Swern oxidation of **14** ($Z = \text{H}$) furnishes aldehyde derivative **13** ($Y = \text{H}$), which is further oxidized using NaClO_2 to form the carboxylic acid, **13** ($Y = \text{OH}$). As described in **Figure 6**, intramolecular Friedel-Crafts cyclization on **13** ($Y = \text{OH}$) followed by Luche reduction yields (+)-calanolide A.

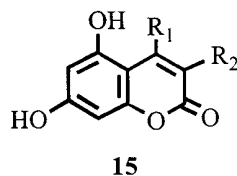
The synthetic sequence for (+)-calanolide A is extended to the synthesis of calanolide analogues (**Figures 8 and 9**). Thus, Pechmann reaction of phloroglucinol with various β -ketoesters yields substituted 5,7-dihydroxycoumarin **15**. Selectively protecting the 7-hydroxy group leads to the formation of **16**. Chromenylation of **16** can be achieved by reacting with β -hydroxyaldehyde dimethylacetal, providing chromenocoumarin **17**, which is deprotected to furnish the free hydroxy group in **18**. Mitsunobu reaction of **18** with **19** ($X = \text{OH}$), or nucleophilic substitution with **19** ($X = \text{TsO}$), followed by the hydrolysis, results in **20** ($Y = \text{OH}$). Intramolecular Friedel-Crafts cyclization on **20** ($Y = \text{OH}$) gives chromanone **21**, which is reduced by NaBH_4 to form the final calanolide analogues **22**.

According to **Figure 8**, 1,3,5-trihydroxybenzene was reacted with β -keto ester **25** under Pechmann conditions (See U.S. Patent No. 5,489,697; 5,869,324; 5,874,591; 5,840,921; 5,847,164; 5,892,060; 5,872,264; 5,981,770; 5,977,385; 6,043,271; and co-pending application 09/173,143, filed October 15, 1998, incorporated by reference in its entirety) to produce compound **15**. The amount of β -keto ester **25** to 1,3,5-trihydroxybenzene generally ranges between about 1 to about 3, preferably about 1 per mole of 1,3,5-trihydroxybenzene. β -ketoester **25** is represented by the structure:



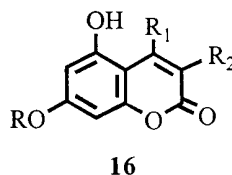
wherein R_1 is H, halogen, hydroxyl, amino, C_{1-6} alkyl, aryl- C_{1-6} alkyl, mono- or poly-fluorinated C_{1-6} alkyl, hydroxy- C_{1-6} alkyl, C_{1-6} alkoxy, amino- C_{1-8} alkyl, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-8} alkylamino- C_{1-8} alkyl, di(C_{1-6} alkyl) amino- C_{1-8} alkyl, cyclohexyl,

aryl, or heterocycle, wherein the aryl or the heterocycle may each be unsubstituted or substituted with one or more of the following: C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy-C₁₋₄ alkyl, hydroxyl, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, amino-C₁₋₈ alkyl, C₁₋₈ alkylamino-C₁₋₈ alkyl, di(C₁₋₆ alkyl-amino-C₁₋₈ alkyl, nitro, azido or halogen; and R₂ is H, halogen, hydroxyl, C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, aryl or heterocycle. Compound **15** is represented by the structure:



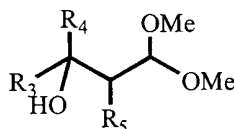
10 wherein R₁ and R₂ are as described above.

Thereafter, compound **15** is acylated with an acylating agent (RCO)₂O under conventional acylation conditions to produce **16** wherein R represents C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly- fluorinated C₁₋₆ alkyl, aryl or heterocycle. The amount of acylating agent to compound **15** generally ranges between about 0.5 to about 6, preferably about 1 per mole of **15**. Compound **16** is represented by the structure:



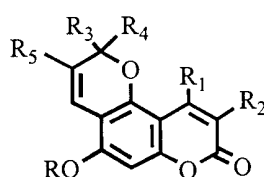
wherein R, R₁, and R₂ are as described above.

20 Compound **17** is produced by chromenylation of **16** with substituted β-hydroxyaldehyde dimethylacetal **26** under the reaction conditions described in U.S. Patents No. 5,489,697; 5,869,324; 5,874,591; 5,840,921; 5,847,164; 5,892,060; 5,872,264; 5,981,770; 5,977,385; 6,043,271; and co-pending application 09/173,143, filed October 15, 1998, incorporated by reference in their entirety. Representative examples of substituted β-hydroxyaldehyde dimethylacetal **26** comprise:



26

wherein R_3 and R_4 are independently selected from the group consisting of H, C_{1-6} alkyl, aryl-
 5 C_{1-6} alkyl, mono- or poly-fluorinated C_{1-6} alkyl, aryl or heterocycle; R_3 and R_4 can be taken
 together to form a 5-7 membered saturated cycle ring or heterocycle ring; and R_5 is H,
 halogen, methyl, ethyl. Compound **17** is represented by the structure:

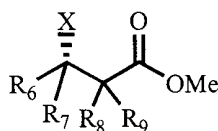


17

10

wherein R, R_1 , R_2 , R_3 , R_4 , and R_5 are as described above.

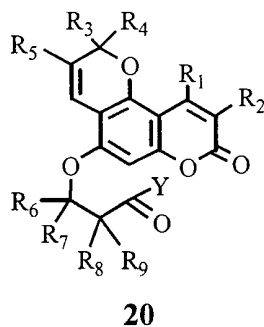
Thereafter, compound **17** is hydrolyzed to produce compound **18** under the basic
 hydrolysis conditions described above. Compound **18** is then coupled to **19** under Mitsunobu
 15 conditions to produce compound **20**. Compound **19** is represented by the structure:



19

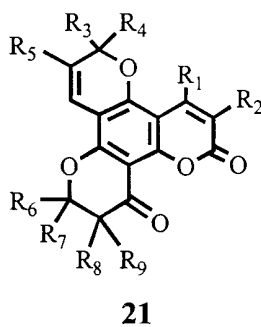
20 wherein R_6 , R_7 , R_8 and R_9 are independently selected from the group consisting of H,
 halogen, hydroxy, amino, mono- or dialkylamino- C_{1-6} alkyl, aryl- C_{1-6} alkyl, mono- or poly-
 fluorinated C_{1-6} alkyl, hydroxy- C_{1-6} alkyl, amino- C_{1-6} alkyl, aryl or heterocycle; or R_6 and R_7
 together form a 5 to 7 membered cycle ring or heterocycle ring; or R_8 and R_9 together form a
 5 to 7 membered cycle ring or heterocycle ring.

25 Compound **20** is represented by the structure:



wherein R₁₋₉ are as described above and Y represents hydrogen, OH, or OMe.

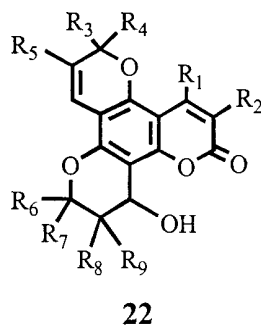
- 5 Friedel-Crafts cyclization of **20** under conditions described above provides compound **21** which structure is represented below.



10

wherein R₁₋₉ are as described above.

Reduction of compound **21** using any suitable reagent, e.g., sodium borohydride, results in calanolide analogue **22** whose structure is represented below.



15

wherein R₁₋₉ are as described above.

- 20 Except as expressly defined otherwise, the following definition of terms is employed throughout this specification.

The terms "alkyl", "lower alkyl" or "C₁₋₆ alkyl" mean a straight or branched hydrocarbon having from 1 to 6 carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, and the like. The alkyl group can also be substituted with one or more of the substituents listed below
5 for aryl.

By "alkoxy", "lower alkoxy" or "C₁₋₆ alkoxy" in the present invention is meant straight or branched chain alkoxy groups having 1-6 carbon atoms, such as, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, pentoxy, 2-pentyl, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy.

10 The term "halogen" includes chlorine, fluorine, bromine, and iodine, and their monovalent radicals.

The term "aryl" means an aromatic carbocyclic group having a single ring (e.g., phenyl), multiple rings (e.g., biphenyl), or multiple condensed rings in which at least one is aromatic (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl, anthryl, or phenanthryl),
15 unsubstituted or substituted by 1 to 3 substituents selected from alkyl, O-alkyl and S-alkyl, OH, SH, -CN, halogen, 1,3-dioxolanyl, CF₃, NO₂, NH₂, NHCH₃, N(CH₃)₂, NHCO-alkyl, -(CH₂)_mCO₂H, -(CH₂)_mCO₂-alkyl, -(CH₂)_mSO₃H, -NH alkyl, -N(alkyl)₂, -(CH₂)_mPO₃H₂, -(CH₂)_mPO₃(alkyl)₂, -(CH₂)_mSO₂NH₂, and -(CH₂)_mSO₂NH-alkyl wherein alkyl is defined as above and m is 0, 1, 2, or 3.

20 The term "cyclic ring" as referred to herein means a monocyclic or polycyclic moiety. By "polycyclic" is meant two or more rings that share two or more carbon atoms. A "carbocyclic group" which contains hetero atoms as one or more of its members can be referred to as a "heterocycle" or a "heterocyclic ring". Such a "heterocycle" can likewise be "monocyclic" or "polycyclic". A cyclic ring and a heterocyclic ring can be saturated,
25 can contain one or more double bonds or can be aromatic. Each ring can be unsubstituted or substituted by 1 to 3 substituents selected from the group as described above for aryl.

The following examples are illustrative and do not serve to limit the scope of the invention as claimed. All references, patents and patent applications cited herein are hereby incorporated by reference in their entirety.

5 EXPERIMENTAL SECTION

General: Melting points were uncorrected. All commercial reagents and solvents were used without further purification. The ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) were run in indicated deuterated solvent and chemical shifts are reported in ppm with tetramethylsilane as the internal standard.

10

EXAMPLE 1

Determination of acylation conditions for the conversion of 2 to 7a

Due to the low yields from the Friedel-Crafts acylation reaction, a more practical procedure needed to be developed for the synthesis of 7a from 2. A variety of reaction conditions were investigated, which is summarized in Table I. Without Lewis acid such as AlCl_3 or base such as pyridine and 4-dimethylaminopyridine (DMAP), no reaction took place between coumarin 2 and propionyl anhydride (entries 1 and 2 in Table I). The reported conditions using AlCl_3 ⁴⁵ were repeated and led to 20% conversion of 2 to 7a, as indicated by HPLC analysis (entry 3). The best results were obtained when a catalytic amount of pyridine was used (entry 4), with 47% conversion to 7a along with a small amount of undesired diester 8a and some unreacted starting material 2. If pyridine was used as the solvent, a complex mixture of products was formed. The formation of the undesired diester 8a could be minimized by shortening the reaction time or lowering the reaction temperature, which, however, could also decrease the yield of the desired product 7a with increasing of the unreacted starting 2 (entry 5). On the other hand, prolonged reaction time or increasing the reaction temperature would increase the conversion of the starting material 2 to 7a, however, this was accompanied by an increase in the formation of undesired 8a and led to a more difficulty in purification of 7a. It appeared that DMAP might be too strong a base (entries 6 and 7) and propionyl chloride too reactive an acylating agent (entry 8) for the selective acylation. Therefore, the pyridine promoted acylation was scaled up in a 50-gram scale reaction, affording 36% isolated yield of 7a. For introduction of a more bulky group at the 7-position of 2, a more reactive acylating agent such as acyl chloride can be used. For example, reaction between 2 and pivaloyl

chloride at r.t. in the presence of pyridine yielded 7-monosubstituted **7b** and 5,7-disubstituted **8b** in isolated yields of 36% and 18%, respectively. It is worthwhile noting that reaction of **2** with 1.0 equivalent TBDMS-Cl in the presence of imidazole in DMF afforded 31% of 7-TBDMS substituted **7c**, along with 24% of 5,7-bis(TBDMS) substituted **8c** (Figure 3).

Table I. Acylation of Coumarin 2 with Propionyl Anhydride to Form 7-monoester 7a

Entry	Scale of 2	Reaction Conditions	HPLC Yield of 7a
1	2.5 g	in THF at 0 °C for 2 hr	no reaction
2	2.5 g	in THF at 30 °C for 2 hr	no reaction
3	5 g	AlCl ₃ (2 eq.) in 1,2-dichloroethane at r.t for 24 hr	20%
4	2.5 g	pyridine (3 drops) in THF at r.t for 1.5 hr	47%
5	2.5 g	pyridine (3 drops) in THF at r.t for 1 hr	26%
6	5 g	4-dimethylaminopyridine (0.1 eq.) in 1,2-dichloroethane at r.t for 4 hr	complicated results
7	5 g	4-dimethylaminopyridine (0.1 eq.) in 1,2-dichloroethane at 0 °C for 45 min	47% isolated yield of 8a
8	5 g	propionyl chloride in pyridine at 0 °C for 4 hrs	complicated results

10 EXAMPLE 2

5-Hydroxy-7-propionyloxy-4-propylcoumarin (7a):

To a 2 L three-neck round-bottom flask equipped with a stir bar, additional funnel, N₂ inlet and outlet were added 50 g (2.27 mol) of 5,7-dihydroxy-4-propylcoumarin (**2**) and 500 mL of anhydrous THF. To this reaction mixture was added dropwise 33 g (2.27 mol) of propionic anhydride at r.t with stirring. After 90 min, the reaction was stopped and reaction mixture washed with 5 % aq. NaHCO₃ solution. The organic layer was separated and washed with 1 N HCl and brine. The aqueous layers were extracted with dichloromethane. The organic layers were combined and washed with brine. After being dried over Na₂SO₄, the crude product was obtained from rotary evaporation and dried *in vacuo* to give 62 g crude product. TLC (1:1 Hexane/EtOAc) analysis indicated that the

crude material contained the desired product (**7a**), starting compound **2** and a small amount of 5,7-diester **8a**. The obtained crude product was then purified by silica gel column chromatography on a Biotage column eluting with 2:1 Hexane/EtOAc to give 12 g of **7a** (36% yield) as white solid. mp: 166-168 °C; ¹H NMR (DMSO-d₆), 0.97 (3H, t, *J* = 7.2 Hz), 1.14 (3H, t, *J* = 7.4 Hz), 1.62 (2H, sextet, *J* = 7.5 Hz), 2.62 (2H, q, *J* = 7.5 Hz), 2.92 (2H, t, *J* = 7.5 Hz), 6.09 (1H, s), 6.57 (1H, d, *J* = 2.4 Hz), 6.67 (1H, d, *J* = 2.4 Hz), 11.10 (1H, s); ¹³C NMR (CDCl₃), 8.6, 13.7, 22.4, 26.9, 37.2, 101.4, 105.3, 106.2, 111.9, 153.0, 155.9, 157.2, 158.0, 159.7, 172.2; IR (film): 3300-3075, 2968, 1758, 1676, 1610, 1433, 1126 cm⁻¹; MS m/e 277 (M+1); Anal. Calcd. for C₁₅H₁₆O₅: C, 65.21; H, 5.84. Found: C, 64.61; H, 5.86.

EXAMPLE 3

5-Hydroxy-7-pivaloyloxy-4-propylcoumarin (**7b**):

To a solution of coumarin **2** (1.10 g, 5 mmol) in THF (10 mL) was added pyridine (2.02 mL, 25 mmol), followed by pivaloyl chloride (0.612 mL, 5 mmol), and the reaction mixture was allowed to stir at room temperature for 6 days. The pyridinium hydrochloride was removed by filtration and washed a few times with ethyl acetate. The organic solutions were combined and washed, successively, with 1M HCl (2 x 25 mL), water (25 mL), aqueous saturated sodium bicarbonate (25 mL). After being dried over sodium sulfate and concentrated under vacuum, the crude product was purified by silica gel chromatography (8:1 hexane/ethyl acetate to 2:1 hexane/ethyl acetate) to obtain **8b** (350 mg, 18% yield) and 7-pivaloylated coumarin **7b** (550 mg, 36% yield) as a white solid. For compound **7b**, mp: 158-160 °C; R_f = 0.32 (4:1 hexane/ethyl acetate); ¹H NMR (CDCl₃), 0.97 (3H, t, *J* = 7.8 Hz), 1.37 (9H, s), 1.56 (2H, sextet, *J* = 7.4 Hz), 2.84 (2H, t, *J* = 7.8 Hz), 6.07 (1H, s), 6.43 (1H, d, *J* = 2.4 Hz), 6.61 (1H, d, *J* = 2.1 Hz), 8.09 (1H, s); ¹³C NMR (CDCl₃), 13.8, 22.4, 26.9, 37.8, 39.3, 102.4, 105.8, 107.2, 112.1, 153.3, 156.2, 156.3, 159.3, 161.9, 178.0; IR (film): 3358, 2971, 2365, 1730, 1615, 1431, 1275, 1146 cm⁻¹; MS m/e 305 (M+1); Anal. Calcd. for C₁₇H₂₀O₅: C, 67.09; H, 6.62. Found: C, 66.80; H, 6.70.

EXAMPLE 4

5,7-bis(pivaloyloxy)-4-propylcoumarin (**8b**):

To a solution of 5,7-dihydroxy-4-propylcoumarin (**2**) (1.10 g, 5 mmol) in pyridine (12 mL) and THF (6 mL) was added pivaloyl chloride (0.673 mL, 5.5 mmol) and the reaction mixture was allowed to stir at room temperature for 24 h. TLC revealed formation of a new less polar spot and unreacted starting material. In an effort to drive the reaction to completion, pivaloyl chloride (0.50 mL) was added and the reaction continued to stir at room temperature for another 72 h. The pyridinium hydrochloride was removed by filtration and washed a few times with ethyl acetate. The organic solutions were combined and washed, successively, with 1 M HCl (2 x 25 mL), water (25 mL), aqueous saturated sodium bicarbonate (25 mL). After being dried over sodium sulfate and concentrated under vacuum, the crude product was purified by silica gel chromatography (2:1 hexane/ethyl acetate) to obtain **8b** as a white solid (1.90g, 98% yield). mp 110-112 °C; R_f = 0.49 (4:1 hexane/ethyl acetate); $^1\text{H-NMR}$ (CDCl_3), δ : 1.03 (3H, t, J = 7.8 Hz), 1.36 (9H, s), 1.41 (9H, s), 1.69 (2H, sextet, J = 7.4 Hz), 2.81 (2H, t, J = 7.8 Hz), 6.22 (1H, s), 6.60 (1H, d, J = 2.4 Hz), 7.03 (1H, d, J = 2.1 Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ : 13.5, 20.7, 26.4, 26.8, 26.9, 36.4, 39.2, 39.4, 108.6, 111.5, 113.4, 114.2, 149.4, 152.7, 154.9, 155.4, 159.9, 177.1; IR (film): 3090, 2971, 2941, 2876, 1757, 1615, 1481, 1422, 1273 cm^{-1} ; MS m/e 389 (M+1); Anal. Calcd. for $\text{C}_{22}\text{H}_{28}\text{O}_6$: C, 68.02; H, 7.26. Found: C, 67.77; H, 7.18.

EXAMPLE 5

7-TBDMS and 5,7-bis(TBDMS) Substituted Coumarin (**7c** and **8c**):

A mixture of coumarin **2** (5.0 g, 23 mmol), TBDMS-Cl (5.8 g, 27 mmol), and imidazole (4.7 g, 69 mmol) in 50 ml of dry DMF was stirred at room temperature under nitrogen for 20 h, whereupon EtOAc (300 ml) was added to the reaction mixture. The precipitates formed were removed by filtration. The filtrate was washed, successively, with 1N HCl (100 mL x 2), water (100 mL x 3), and brine (200 mL). The organic layer was then dried with Na_2SO_4 . After removal of the drying agent by filtration, the organic solution was kept at room temperature and crystals were formed. The solid was collected. The mother liquor was concentrated and the residue was recrystallized in EtOAc. This process was repeated two more times to give overall 2.2 g (28% yield) of **7c** as white crystals. The residue from the mother liquor was further purified by column chromatography to give 2.5 g (24% yield) of solid that was assigned the structure of bis-TBDMS ether **8c**, additional 0.2 g of **22** (combined yield of 31%), and 0.2 g of unreacted starting material **2**. The analytical data of **7c** were: mp 220-223 °C; $^1\text{H NMR}$ (acetone- d_6)

0.28 (6H, s), 1.00 (12H, m), 1.69 (2H, m), 2.95 (2H, t, $J = 7.5$ Hz), 5.91 (1H, s), 6.33 (1H, d, $J = 2.7$ Hz), 6.42 (1H, d, $J = 2.4$ Hz), 9.55 (1H, s); ^{13}C NMR (DMSO- d_6) -4.7, -3.9, 13.7, 22.4, 25.4, 37.1, 99.2, 103.3, 103.5, 109.8, 156.7, 157.5, 158.4, 158.5, 160.1; IR 3497-3021 (s, broad), 1684 (s, sharp), 1616 (s, sharp) cm^{-1} ; LRMS m/e : 335 (M+1); Anal. Calcd. for $\text{C}_{18}\text{H}_{26}\text{O}_4\text{Si}$: C, 64.64; H, 7.83. Found: C, 64.31; H, 7.78. For **8c**, mp 78-79 °C; ^1H NMR 0.24 (6H, s), 0.36 (6H, s), 0.95-9.97 (21H, m), 1.59 (2H, q, $J = 7.5$ Hz), 2.91 (2H, t, $J = 7.5$ Hz), 6.02 (1H, s), 6.21 (1H, d, $J = 2.7$ Hz), 6.48 (1H, d, $J = 2.4$ Hz).

EXAMPLE 6

10 **2,2-Dimethyl-5-propionyloxy-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one (5a):**

To a solution of 7-propionate **7a** (0.83 g, 3.0 mmol) in 2-butanone (40 mL) and DMF (4 mL) were added tetrabutylammonium iodide (1.11 g, 3 mmol), K_2CO_3 (1.04 g, 7.5 mmol), and 3-chloro-3-methyl-1-butyne (1.11 g, 3 mmol). The reaction mixture was heated at 60 °C for 1 h before ZnCl_2 (3.9 mL of 1.0 M solution in ether, 3.9 mmol) was added. The temperature was then raised to 70 °C and maintained at that temperature for 21 h. The reaction mixture was cooled to room temperature and quenched with saturated aqueous NH_4Cl (100 mL). The mixture was extracted with EtOAc (100 mL x 2) and the combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4 . Evaporation of the solvent gave the crude product (1.9 g). After column chromatographic purification, 280 mg (27.1% yield) of the desired product **5a** was obtained as a waxy solid. ^1H NMR (DMSO- d_6) 1.00 (3H, t, $J = 7.2$ Hz), 1.16 (3H, t, $J = 7.5$ Hz); 1.47 (6H, s), 1.61 (2H, m), 2.71 (2H, q, $J = 7.5$ Hz), 2.89 (2H, t, $J = 7.8$), 5.84 (1H, d, $J = 9.9$ Hz), 6.17 (1H, s), 6.41 (1H, d, $J = 10.2$ Hz); ^{13}C NMR (DMSO- d_6) 8.6, 13.7, 22.8, 26.6, 27.2, 37.4, 78.3, 103.6, 107.2, 110.8, 113.4, 115.5, 130.1, 148.5, 151.4, 154.4, 156.9, 159.3, 172.2; IR 1767 (s and sharp), 1723 (s and sharp), 1616 (s and sharp) cm^{-1} ; MS m/e 343 (M+1); Anal. Calcd. for $\text{C}_{20}\text{H}_{22}\text{O}_5$: C, 70.16; H, 6.47. Found: C, 70.37; H, 6.51.

EXAMPLE 7

30 **2,2-Dimethyl-5-pivaloyloxy-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one (5b):**

To a suspension of compound **7b** (304 mg, 1 mmol) in 2-butanone (13 mL) and DMF (1.3 mL) was added potassium carbonate (346 mg, 2.5 mmol), 3-chloro-3-methyl-1-butyne (0.56 mL, 5 mmol) and tetrabutylammonium iodide (360 mg, 1 mmol). The

reaction mixture was heated to 60 °C for 1 h, then anhydrous ZnCl₂ (1.0 M solution in ether, 1.3 mL) was added. The reaction mixture was heated to 70 °C for 26 h, then cooled to r.t., quenched with saturated aqueous NH₄Cl (25 mL), and extracted with ethyl acetate (2 x 75 mL). The organic solutions were combined, washed with brine, dried (Na₂SO₄), and concentrated. The crude product obtained was purified by silica gel chromatography (8:1 hexane/ethyl acetate) to obtain **5b** as a yellow solid (270 mg, 73%). mp: 65-68 °C; R_f: 0.54 (4:1 hexane/ethyl acetate); ¹H NMR (CDCl₃) 1.04 (3H, d, *J* = 7.2 Hz), 1.39 (9H, s), 1.52 (6H, s), 1.66-1.71 (2H, m), 2.90 (2H, t, *J* = 7.8 Hz), 5.62 (1H, d, *J* = 10.2 Hz), 6.07 (1H, s), 6.30 (1H, d, *J* = 10.2 Hz), 6.62 (1H, s); ¹³C NMR (CDCl₃) 13.8, 22.9, 26.9, 27.8, 38.3, 39.3, 78.1, 103.5, 107.9, 110.9, 113.4, 115.9, 129.1, 148.9, 152.0, 155.1, 157.4, 160.6, 176.2; IR (film): 2967, 1750, 1616, 1364, 1142 cm⁻¹; MS m/e 371 (M+1); Anal. Calcd. for C₂₂H₂₆O₅: C, 71.33; H, 7.07. Found: C, 71.08; H, 7.35.

EXAMPLE 8

2,2-Dimethyl-5-hydroxy-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one (6):

To a solution of ester **5a** (223 mg, 0.65 mmol) in 15 mL of MeOH were added saturated aqueous solution of NaHCO₃ (7 mL) and water (7 mL). The reaction mixture was stirred at room temperature under nitrogen for 7 h until TLC indicated complete consumption of the starting material. The reaction mixture was then acidified with 10% aqueous HCl (100 mL), and extracted with EtOAc (50 mL). The organic solution was washed with brine (100 mL) and dried with Na₂SO₄. Evaporation of the solvent yielded the crude product that was purified by preparative TLC to afford 97 mg (52% yield) of **6** as a solid. mp 190-192 °C; ¹H NMR (DMSO-*d*₆) δ 0.99 (3H, t, *J* = 7.3 Hz), 1.45 (6H, s), 1.59 (2H, m), 2.83 (2H, t, *J* = 7.6 Hz), 5.66 (1H, d, *J* = 9.9 Hz), 5.92 (1H, s), 6.34 (1H, s), 6.57 (1H, d, *J* = 9.9 Hz), 10.77 (1H, s); ¹³C NMR (DMSO-*d*₆) δ 13.7, 22.9, 27.2, 37.5, 77.5, 95.7, 102.2, 106.1, 109.9, 116.3, 127.1, 151.7, 155.7, 156.4, 157.8, 160.0, 188.9; IR (film): 3185, 1686, 1582, 1381, 1157 cm⁻¹; MS m/e: 287 (M+1); Anal. Calcd. for C₁₇H₁₈O₄: C, 71.31; H, 6.34. Found: C, 71.39; H, 6.40.

EXAMPLE 9

Conversion of **5a** to **4** under Fries Rearrangement Conditions:

A mixture of compound **5a** (1 g, 2.9 mmol) with anhydrous aluminium chloride (5 g, 37.5 mmol) is heated for 2h at 160 °C. The mixture is then cooled to r.t. and treated

with ice and hydrochloric acid (1 N, 5 mL). The precipitated product is taken into ethyl acetate and the aqueous solution is extracted with the same solvent (80 mL x 3). The combined ethyl acetate solution is dried over Na₂SO₄ and concentrated *in vacuo*. The crude product thus obtained is chromatographed on a silica gel column eluting with 25% ethyl acetate in hexane to afford compound **4** (0.5 g, 50% yield).

EXAMPLE 10

Conversion of **6** to **4** under Friedel-Crafts Conditions:

A mixture of compound **6** (1 g, 3.5 mmol) and anhydrous aluminium chloride (0.9 g,, 7 mmol) in 1,2-dichloroethane (10 mL) is heated to 75 °C for 30 min, into which was added dropwise a mixture of propionyl anhydride (0.5 g, 3.5 mmol) and anhydrous aluminium chloride (0.9 g,, 7 mmol) in 1,2-dichloroethane (5 mL). The resulting mixture is heated at 75°C for an additional hour. After the mixture is allowed to be cooled to r.t., it is quenched with ice and 1 N HCl (5 mL). The precipitated product is taken into ethyl acetate and the aqueous solution is extracted with the same solvent (80 mL x 3). The combined ethyl acetate solution is dried over Na₂SO₄ and concentrated *in vacuo*. The crude product thus obtained is recrystallized from acetone to afford compound **4** (0.5 g, 50% yield).

EXAMPLE 11

Conversion of **4** to **11** (12-oxocalanolide)

A solution containing chromene **4** (344 mg, 1.0 mmol), acetaldehyde diethylacetal (473 mg, 4.0 mmol), trifluoroacetic acid (1.5 mL, 19.4 mmol) and anhydrous pyridine (0.7 mL) was heated at 140 °C under N₂. The reaction was monitored by TLC analysis. After 4 hours, the reaction mixture was cooled to room temperature, diluted with ethyl acetate and washed several times with 10% aqueous NaHCO₃ and brine. The organic layer was separated and dried over Na₂SO₄. The solvent was removed *in vacuo* and the crude product was purified by silica gel column chromatography eluting with ethyl acetate/hexane (2:3). Chromanone (±)-**11** (10,11-*trans*-dihydro-4-propyl-6,6,10,11-tetramethyl-2*H*,6*H*,12*H*-benzo[1,2-*b*:3,4-*b'*:5,6-*b''*]-tripyrans-2,12-dione) (110 mg, 30% yield) was obtained m.p. 176-177 °C. (Lit.⁴⁵ 130-132 °C). ¹HNMR⁴⁵ (CDCl₃) δ 1.02 (3H, t, J=7.5 Hz, CH₃); 1.21 (3H, d, J=6.8 Hz, CH₃); 1.51 (3H, d, J=7.0 Hz, CH₃); 1.55 (6H, 2s, 2 CH₃); 1.63 (2H, sextet, J=7.0 Hz, CH₂); 2.55 (1H, dq, J=6.9 Hz, J=11.0 Hz, H₁₁); 2.88 (2H, t, J=7.6 Hz, CH₂); 4.28 (1H,

dq, J=6.3 Hz, J=11.0 Hz, H₁₀); 5.60 (1H, d, J=9.9 Hz, H₇); 6.04 (1H, s, H₃); 6.65 (1H, d, J=11.8 Hz, H₈); MS (CI): 369 (100, M+1).

EXAMPLE 12

5 Preparation of (±)-Calanolide A:

To a solution of chromanone (±)-**11** (11 mg, 0.03 mmol) in ethanol (0.4 mL) was added sodium borohydride (2.26 g, 0.06 mmol) and CeCl₃(H₂O)₇ (11.2 mg, 0.03 mmol) in ethanol (5 mL) at room temperature. After stirring for 45 minutes, the mixture was diluted with H₂O and extracted with ethyl acetate. The organic layer was dried over Na₂SO₄ and concentrated. The crude product was purified by preparative TLC eluting with ethyl acetate/hexane (1:1) to afford (±)-calanolide A (**1**) (10.5 mg, 94%). m.p. 52-54 °C, which increased to 102 °C after it was dried thoroughly (Lit⁴⁵. 56-58 °C). ¹H NMR (CDCl₃): δ 1.03 (3H, t, J=7.3Hz, CH₃), 1.15 (3H, d, J=6.8Hz, CH₃), 1.46 (3H, d, J=6.8Hz, CH₃), 1.47 (3H, s, CH₃), 1.51 (3H, s, CH₃), 1.66 (2H, m, CH₂), 1.93 (1H, m, H₁₁), 2.89 (2H, m, CH₂), 3.52 (1H, broad-s, OH), 3.93 (1H, m, H₁₀), 4.72 (1H, d, J=7.8Hz, H₁₂), 5.54 (1H, d, J=10.0Hz, H₇), 5.94 (1H, s, H₃), 6.62 (1H, d, J=9.9Hz, H₈); MS (CI): 371 (75.4, M+1), 370 (16.1, M⁺), 353 (100, M-OH); Anal. calcd. for C₂₂H₂₅O₅: C, 71.33; H, 7.07; Found: C, 71.63; H, 7.21.

EXAMPLE 13

20 Synthesis of Methyl 3-Hydroxy-2-methylbutyrate **11** (X=OH, Y=OMe) from D-Threonine according to the Literature Method.⁵⁷

An aqueous solution of D-threonine (5.95 g in 50 ml water) was treated with 48% aqueous HBr (10 ml) and KBr (21.0 g). The mixture was cooled to -15 °C and NaNO₂ (3.8 g) was slowly added to in small portions over 2.5 h. After overnight stirring while the temperature was warmed up to room temperature (3x150 mL), the mixture was extracted with ether. The ether solution was dried (Na₂SO₄) and concentrated *in vacuo* to give the crude bromoacid as an oil. The bromoacid was dissolved in absolute EtOH (75 mL) and cooled to -30 °C. A solution of KOH (5.05 g) in ethanol (40 mL) was added slowly, and the reaction mixture was stirred overnight while the temperature was allowed to warm up to room temperature. The solid KBr was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was transferred to a solution of 18-crown-6 (10.55 g) in methylene chloride (100 mL). Dimethyl sulfate (3.56 g) was added to the reaction mixture and stirring was continued for 2 h. Ether was added and the

precipitate formed was filtered off. The volatile solvent was removed by simple distillation to give crude epoxide that still contained the crown ether (1.3 g): ^1H NMR (CDCl_3) 1.39 (3H, d, $J = 5.1$ Hz), 3.30 (1H, m), 3.52 (1H, d, $J = 4.5$ Hz), 3.81 (3H, s).

A solution of MeLi in ether (21.7 mL of 1.4 M solution) was added to a stirred suspension of CuI (3.07 g) in ether (30 mL) at -30 °C. After 15 min of stirring, a solution of the crude epoxide (1.3 g) in ether (24 mL) was added to the reaction mixture. The mixture was stirred for 2 h before a solution of concentrated ammonium hydroxide in saturated ammonium chloride was added. The resulting biphasic solution was extracted with EtOAc and the combined organic solution was dried and the solvent was removed by simple distillation to give a complex mixture (0.26 g) that might contain **11** (X=OH, Y=OMe) as a yellow oil.

EXAMPLE 14

Synthesis of 3-Hydroxy-2-methylbutyric Acid 11 (X=OH, Y=OH) from Ethyl 2-methylacetoacetate according to the Literature Method.^{58,59}

To a 6 L erlenmeyer flask containing Baker's yeast (100g) and sucrose (150g) was added tap water (1000 mL) and the reaction mixture was mechanically stirred at room temperature for 0.5h. Ethyl 2-methylacetoacetate (10g, 0.0694 mol) was added to the reaction mixture and stirring continued for 24h. Sucrose (50g) was added and stirring continued for another 24h. Hyflo super cel (50g) was added to the reaction mixture and filtered through a sintered glass funnel. The aqueous solution was then extracted with ether (1.5 L), dried over sodium sulfate, and filtered. The solvent ether was removed via simple distillation to obtain ethyl 3-hydroxy-2-methylbutyrate (10g, 100%) as a mixture of two isomers: ^1H NMR (CDCl_3) δ 1.18-1.30 (18H, m), 2.47-2.52 (2H, m), 3.85-3.91 (1H, m), 4.05-4.10 (1H, m), 4.13-4.21 (4H, m).

To ethyl 2-methyl-3-hydroxybutyrate obtained above (10g, 0.0694 mol) was added 30% aqueous sodium hydroxide (40 mL), and the mixture was stirred at room temperature for 4h. The reaction mixture was concentrated under vacuum to obtain a yellow solid. The solid was dissolved in 1M HCl (100 mL) and extracted with ether (3x100 mL), dried over sodium sulfate and concentrated under vacuum to obtain 3-hydroxy-2-methyl butyric acid (2.0g, 24%) as a mixture of diastereomers. For the major isomer: ^1H NMR (CDCl_3) δ 1.21-1.24 (6H, m), 2.57-2.62 (1H, m), 4.11-4.15 (1H, m).

EXAMPLE 15**Synthesis of Oxazolidinone 11 (X=OH, Y=Oxazolidinone) according to the Literature Method.⁶⁰**

A 7 ml freshly prepared LDA (0.5 M in hexane-ether) was cooled at $-78\text{ }^{\circ}\text{C}$, and to this solution was added dropwise Evan's oxazolidinone in 20 ml ether. The reaction was stirred for 30 min, followed by the dropwise addition of chlorotitanium triisopropoxide (9 ml 1.0M in hexane, 3 mmol) at $-78\text{ }^{\circ}\text{C}$. The solution was allowed to warm up to $-40\text{ }^{\circ}\text{C}$ over 1 h then cooled down to $-78\text{ }^{\circ}\text{C}$. Acetaldehyde was added in one portion via a cold syringe. The temperature was maintained between $-78\text{ }^{\circ}\text{C} \sim -40\text{ }^{\circ}\text{C}$ under nitrogen for 3 h. Saturated aqueous solution of NH_4Cl (5 mL) was added. After filtration and extraction, the crude product (690 mg) was purified by column chromatography to afford 429 mg (62.4%) product **11** (X=OH, Y=Oxazolidinone) as an oil: $[\alpha]_{\text{D}} = +154.0^{\circ}$ (c 0.5, MeOH); ^1H NMR (CDCl_3) 0.91 (3H, d, $J = 6.6$ Hz), 0.93 (3H, d, $J = 7.2$ Hz), 1.17 (3H, d, $J = 6.9$ Hz), 1.22 (3H, d, $J = 6.6$ Hz), 2.38 (1H, m), 3.90 (1H, dq $J = 3, 6, 6.5$ Hz), 4.16 (1H, ddd, $J = 3.3, 6.4, 12.9$ Hz), 4.23 (1H, dd, $J = 3.2, 9.0$ Hz), 4.29 (1H, apparent t, $J = 8.6$ Hz), 4.47 (1H, m); ^{13}C NMR (CDCl_3) 10.5, 14.6, 17.8, 19.2, 28.5, 42.8, 58.6, 63.3, 68.5, 154.3, 176.6; IR 3302-3650 (m, broad), 1780 (s, sharp), 1699 (s, sharp) cm^{-1} ; LRMS cacl'd for $\text{C}_{11}\text{H}_{19}\text{NO}_4$ 229.3, found 229.9. Anal. Calcd for $\text{C}_{11}\text{H}_{19}\text{NO}_4$: C, 57.6; H, 8.4; N, 6.1. Found: C, 57.78; H 8.38; N, 6.07.

20

EXAMPLE 16**Synthesis of Oxazolidinone 11 (X=OTs, Y=Oxazolidinone):**

Alcohol **11** (X=OH, Y=Oxazolidinone) (242 mg, 1.06 mmol) was dissolved in 2 mL pyridine, and the solution was stirred at $-20\text{ }^{\circ}\text{C}$ while TsCl (262 mg, 1.38 mmol) was added quickly under nitrogen. The temperature was allowed to rise to room temperature. Stirring was continued for 42 h. Water (5 ml) was added slowly at $-20\text{ }^{\circ}\text{C}$ then the reaction was stirred for 40 min and diluted with 10 ml EtOAc. The two layers were separated and the organic layer was washed with 1N HCl (10 mL x 3), brine (10 mL), and dried with sodium sulfate. Evaporation of the solvent *in vacuo* afforded crude tosylate **11** (X=OTs, Y=Oxazolidinone) (192 mg). After preparative TLC purification, 92 mg (23%) of product was obtained as an oil: ^1H NMR (CDCl_3) δ ppm, 0.90 (6H, t, $J = 6.6$ Hz), 1.13 (3H, d, $J = 7.2$ Hz), 1.30 (3H, d, $J = 6.6$ Hz), 2.33 (1H, m), 2.44 (1H, m), 3.98 (1H, m), 4.21-4.29 (2H, m), 4.44 (1H, m), 5.00 (1H, m); ^{13}C NMR δ 12.9, 14.4, 17.9, 19.1, 21.5,

28.2, 42.9, 58.6, 63.2, 79.6, 127.9, 129.8, 134.4, 144.7, 153.9, 173.2. Anal. Calcd. for $C_{18}H_{25}O_6SN$: C, 56.38; H, 6.57; N, 3.65; Found: C, 56.12; H, 6.64; N, 3.51.

EXAMPLE 17

5 Synthesis of 1,3-Dihydroxy-2-methylbutane **12** (Z=H):

To ethyl 3-hydroxy-2-methylbutyrate (7.3 g, 50 mmol) in ether (250 mL) at 0 °C, added $LiAlH_4$ (5.9 g, 155.5 mmol). The gray solution was stirred at 0 °C for 10 minutes, cooling bath removed and stirring continued at room temperature for 6 h. The reaction mixture was cooled to 0 °C and quenched slowly by dropwise addition of water (6 mL),
10 1M NaOH (6 mL), water (6 mL). Excess $MgSO_4$ (100 g) was added to the reaction mixture and allowed to stir at room temperature overnight. Filtered the reaction mixture and washed the solid with ether (400 mL). The ether extracts was concentrated under vacuum to obtain 1,3-dihydroxy-2-methylbutane **12** (Z=H) (2.6 g, 50%) as a yellow oil.
 1H -NMR ($CDCl_3$) δ 0.89 (3H, d, $J = 6.9$ Hz), 1.19 (3H, d, $J = 6.6$ Hz), 1.81 (1H, m), 3.70
15 (2H, m), 4.04 (1H, m); MS $[M-1]^+$ 103.5.

EXAMPLE 18

Synthesis of the Protected 1,3-Dihydroxy-2-methylbutane **12** (Z=TBDMS):

To a suspension of sodium hydride (424 mg, 10.6 mmol) in THF (30 mL) added **12**
20 (Z=H) (1.1 g, 10.6 mmol) and stirred at room temperature for 45 min, at which time a large amount of an opaque white precipitate had formed. The tert-butyldimethylsilyl chloride (1.59 g, 10.6 mmol) was added and the reaction mixture was allowed to stir at room temperature for 1.5 h. The reaction mixture was diluted with ether (300 mL) and washed with 10% aqueous potassium carbonate (90 mL), brine (75 mL). The organic
25 extracts were dried over sodium sulfate, concentrated under vacuum and purified by silica gel chromatography (8/1 hexane/ethyl acetate) to obtain **12** (Z=TBDMS) (2.3 g, 99%) as a colorless oil. 1H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.90 (12H, s,d), 1.16 (3H, d, $J = 6.3$ Hz), 3.72 (2H, m), 3.99 (1H, m); ^{13}C NMR ($CDCl_3$) δ -5.8 (2C), 10.5, 19.5, 25.7, 25.9, 39.8, 70.7; Anal. Calcd for $C_{11}H_{25}O_2Si$: C, 60.55; H, 11.93. Found C, 61.01; H, 11.84; IR (film):
30 3449, 2957, 2859, 1464, 1256 cm^{-1} ; MS $[M+1]^+$ 219.1.

Compound 14 (Z=TBDMS):

To monophenol **6** (900 mg, 3.14 mmol), triphenylphosphine (1.24 g, 4.73 mmol) and **12** (R=TBDMS) (1.1 g, 5.05 mmol) in THF (60 mL) added DEAD (800 μ L, 5.08 mmol) and stirred at room temperature under nitrogen overnight. The reaction mixture was concentrated under vacuum and purified by silica gel chromatography (3/1 hexane/ethyl acetate) to obtain **14** (Z=TBDMS) (1.53 g, 100%) as an oil. ^1H NMR (CDCl_3) δ -0.08 (6H, m), 0.88 (9H, s), 0.96 (3H, d, $J = 7.2$ Hz), 1.03 (3H, t, $J = 7.2$ Hz), 1.27 (3H, d, $J = 6.3$ Hz), 1.49 (6H, s), 1.66 (2H, m), 2.08 (1H, m), 2.88 (2H, t, $J = 7.6$ Hz), 3.56 (2H, m), 4.51 (1H, m), 5.52 (1H, d, $J = 9.9$ Hz), 5.94 (1H, s), 6.42 (1H, s), 6.64 (1H, d, $J = 9.9$ Hz); ^{13}C -NMR (CDCl_3) δ -5.7 (2C), 11.9, 14.0, 15.4, 18.1, 23.1, 25.8 (3C), 27.7 (2C), 38.3, 40.3, 64.6, 65.4, 75.2, 94.2, 103.7, 107.8, 110.8, 116.9, 126.7, 151.9, 156.3, 158.2, 161.4; Anal. Calcd for $\text{C}_{28}\text{H}_{42}\text{O}_5\text{Si}$: C, 69.03; H, 8.63. Found C, 69.33; H, 8.84; IR (film): 2928, 2857, 1738, 1605 cm^{-1} ; MS $[\text{M}+1]^+$ 487.2.

EXAMPLE 19

15 Compound **14** (Z=H):

To **14** (Z=TBDMS) (1.5 g, 3.08 mmol) in THF (45 mL) added TBAF (1.0 M soln in THF, 5 mL, 5 mmol) and stirred at room temperature overnight. The reaction mixture was acidified with 1M HCl and extracted with ethyl acetate. The organic extracts were then washed with water, brine, dried (sodium sulfate) and concentrated under vacuum. The crude product was purified by silica gel chromatography (1/1 hexane/ethyl acetate) to obtain **14** (Z=H) (800 mg, 70%) as an oil. ^1H -NMR (CDCl_3) δ 0.87 (3H, d, $J = 7.8$ Hz), 1.06 (3H, t, $J = 6.9$ Hz), 1.32 (3H, d, $J = 6.3$ Hz), 1.49 (6H, s), 1.65 (2H, m), 2.09 (1H, m), 2.88 (2H, t, $J = 7.6$ Hz), 3.68 (2H, d, $J = 5.7$ Hz), 4.50 (1H, m), 5.53 (1H, d, $J = 9.9$ Hz), 5.95 (1H, s), 6.4 (1H, s), 6.62 (1H, d, $J = 10.2$ Hz); ^{13}C -NMR (CDCl_3) δ 12.4, 13.9, 16.2, 23.1, 27.7 (2C), 38.3, 40.4, 65.0, 75.0, 94.2, 104.0, 107.8, 110.9, 116.6, 126.9, 151.9, 156.0, 156.5, 158.2, 161.4; Anal. Calcd for $\text{C}_{22}\text{H}_{28}\text{O}_5+0.7$ eq H_2O : C, 68.62; H, 7.70. Found C, 68.71; H, 7.85; IR (film): 3464, 2969, 2874, 1738, 1593 cm^{-1} ; MS $[\text{M}+1]^+$ 373.1.

EXAMPLE 20

30 Compound **13** (Y=H):

To CH_2Cl_2 (1 mL) at -78 $^\circ\text{C}$ added oxalyl chloride (20 μ L, 0.223 mmol), followed by DMSO (33 μ L, 0.459 mmol). After 5 minutes added alcohol **14** (R=H) (57 mg, 0.153

mmol) in CH₂Cl₂ (2 mL). The reaction mixture was stirred at -78 °C for 30 minutes. Triethylamine (107 μL, 0.765 mmol) was added to the reaction mixture and allowed to warm to room temperature over 2h. The reaction mixture was concentrated under vacuum and purified by silica gel chromatography to obtain **13** (Y=H) (46 mg, 82%) as an oil. ¹H-NMR (CDCl₃) δ 1.03 (3H, t, *J* = 7.2 Hz), 1.21 (3H, d, *J* = 6.9 Hz), 1.28 (3H, d, *J* = 6.9 Hz), 1.49 (6H, s), 1.55-1.70 (2H, m), 2.72-2.77 (1H, m), 2.89 (2H, t, *J* = 7.2 Hz), 4.72 (1H, m), 5.52 (1H, d, *J* = 10.2 Hz), 5.97 (1H, s), 6.42 (1H, s), 6.55 (1H, d, *J* = 10.2 Hz), 9.79 (1H, d, *J* = 2.4 Hz); MS [M+1]⁺ 371.2.

10 EXAMPLE 21

Compound **13** (Y=OH):

To aldehyde **13** (Y=H) (43 mg, 0.116 mmol) in acetone (4 mL) added 2-methyl-2-butene (1 mL, 2.0 M solution in THF). To the above reaction mixture added sodium chlorite (100 mg, 1.10 mmol) and sodium dihydrogenphosphate (96 mg, 0.800 mmol) in water (2 mL) and allowed to stir at room temperature overnight. The reaction mixture was diluted with water and extracted with ethyl acetate, dried (Na₂SO₄) and concentrated under vacuum to obtain **13** (Y=OH) (45 mg, 100%) as an oil. ¹H-NMR (CDCl₃) δ 1.04 (3H, t, *J* = 7.2 Hz), 1.22 (3H, d, *J* = 6.9 Hz), 1.27 (3H, d, *J* = 6.9 Hz), 1.49 (6H, s), 1.52-1.67 (2H, m), 2.86-2.93 (3H, m), 4.73 (1H, m), 5.52 (1H, d, *J* = 9.9 Hz), 5.97 (1H, s), 6.45 (1H, s), 6.61 (1H, d, *J* = 9.9 Hz); MS [M+1]⁺ 387.2.

EXAMPLE 22

12-Oxocalanolide **A** (**10**) from **13** (Y=OH):

To acid **13** (Y=OH) (120 mg, 0.31 mmol) in benzene (3 mL) added thionyl chloride (90 μL, 1.24 mmol) and refluxed under nitrogen for 1 h. The reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was dissolved in CH₂Cl₂ and concentrated under vacuum. This process was repeated twice. The reaction mixture was then dissolved in xylene (3 mL). Nafion NR-50 (50 mg) was added to the reaction mixture and refluxed for 22 h. Cooled to room temperature, filtered the resin, diluted with ethyl acetate and washed with aqueous saturated sodium bicarbonate solution and brine. The organic extracts were dried over sodium sulfate and concentrated under vacuum. The crude product was then purified by preparative TLC (10% ethyl acetate in hexanes) to obtain **10** (20 mg, 18%).

EXAMPLE 23**Compound 19** ($R_6=R_8=R_9=H$, $R_7=Me$, $X=OTs$):

A solution of methyl acetoacetate (20 g, 0.17 mol) in MeOH (100 ml) was added dropwise to a stirred solution of $NaBH_4$ (2 g, 0.05 mmol) in MeOH (200 ml) at room temperature. The reaction was monitored by TLC. After 1 hour of stirring, no reaction occurred. An additional 1 g (0.03 mol) of $NaBH_4$ was added into the reaction mixture, and another portion of $NaBH_4$ (1 g, 0.03 mol) after 0.5 h of stirring. Stirring was continued for 0.5 hour, and no starting compound was detected by TLC. The MeOH was removed to afford a residue as a clear oil. The residue was washed with 1N HCl (150 ml), then extracted into EtOAc (3 x 200 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 , and concentrated to afford 13 g of crude product methyl 3-hydroxybutyrate as a light-yellow oil which was used for the following tosylation without further purification.

To a solution of methyl 3-hydroxybutyrate (13 g, 110 mmol) in anhydrous pyridine (100 ml) was added *p*-toluenesulfonyl chloride (31.5 g, 165 mmol) at $0^\circ C$ under N_2 . After two days of stirring at $0^\circ C$, the reaction mixture was cooled to $-5^\circ C$ followed by the dropwise addition of water (100 ml) while maintaining the temperature $< 0^\circ C$. After an additional 10 min of stirring, more water (200 ml) was added slowly. Crystallization occurred immediately. The temperature was maintained at $0^\circ C$ for 1 h, and the crystalline product was filtered, washed with water (5 x 100 ml), and dried to give 20.6 g (70%) of **19** ($R_6=R_8=R_9=H$, $R_7=Me$, $X=OTs$) as a white solid: mp. $45-47^\circ C$; 1H NMR (d_6 -DMSO) δ 1.27 (3H, d, $J = 6.6$ Hz), 2.43 (3H, s), 2.61 (1H, dd, $J = 15.0, 7.5$ Hz), 2.69 (1H, dd, $J = 15.0, 5.4$ Hz), 3.48 (3H, s), 4.86 (1H, m), 7.48 (2H, d, $J = 8.1$ Hz), 7.78 (2H, d, $J = 8.1$ Hz); ^{13}C NMR ($CDCl_3$) δ 20.4, 21.1, 40.5, 51.6, 76.8, 127.6, 130.3, 133.6, 145.0, 169.7; IR 1750 cm^{-1} . Anal. Calcd for $C_{12}H_{16}O_5S$: C, 52.94; H, 5.88. Found: C 53.10; H 5.95.

EXAMPLE 24**Compound 20** ($R_1=n$ -propyl, $R_2=R_5=R_6=R_7=H$, $R_3=R_4=R_8=R_9=Me$, $Y=OH$):

To monophenol **6** (430 mg, 1.50 mmol), triphenylphosphine (590 mg, 2.25 mmol) and **19** ($R_6=R_7=H$, $R_8=R_9=Me$, $X=OH$) (396 mg, 3 mmol) in dioxane (34 mL) added DEAD (360 μL , 2.25 mmol) and stirred at reflux under nitrogen for 2 h. The reaction mixture was cooled and concentrated under vacuum. The residue was dissolved in ethyl

acetate (100 mL) and washed with water (80 mL), dried (sodium sulfate), concentrated under vacuum and purified by silica gel chromatography (3/1 hexane/ethyl acetate) to obtain the corresponding methyl ester of **20** (445 mg, 74%) as a white solid. Mp: 100-101 °C; ¹H NMR (DMSO-d₆) δ 0.99 (3H, t, *J* = 7.5 Hz), 1.26 (6H, s), 1.45 (6H, s), 2.39 (2H, m), 2.86 (2H, t, *J* = 7.5 Hz), 3.63 (3H, s), 4.09 (2H, s), 5.73 (1H, d, *J* = 10.2 Hz), 6.02 (1H, s), 6.45 (1H, d, *J* = 9.6 Hz), 6.63 (1H, s); ¹³C-NMR (CDCl₃) δ 13.8, 22.3, 23.0, 27.7, 38.3, 43.2, 52.1, 74.8, 77.7, 93.3, 104.3, 107.2, 111.2, 116.3, 127.1, 151.7, 156.4, 156.7, 158.1, 161.3, 176.2; MS [M+1]⁺ 401.1; Anal. Calcd for C₂₃H₂₈O₆: C, 69.0; H, 7.0. Found C, 69.16; H, 7.12; IR (film): 1726, 1605 cm⁻¹.

To the methyl ester of **20** obtained above (40 mg, 0.1 mmol) in methanol (2 mL) added KOH (25 mg, 0.45 mmol) in water (1 mL) and stirred at room temperature for 3 h. The reaction mixture was concentrated under vacuum. Water was added to the residue, acidified with 1M HCl and extracted with ethyl acetate. The organic extracts were washed with brine, dried (sodium sulfate) and concentrated under vacuum to obtain **20** (R₁=n-propyl, R₂=R₅=R₆=R₇=H, R₃=R₄=R₈=R₉=Me, Y=OH) (30 mg, 78 %) as a white solid. Mp: 140-142 °C ¹H NMR (DMSO-d₆) δ 0.99 (3H, t, *J* = 7.6 Hz), 1.23 (6H, s), 1.45 (6H, s), 1.59 (2H, m), 2.86 (2H, t, *J* = 8.0 Hz), 4.06 (2H, s), 5.72 (1H, d, *J* = 9.9 Hz), 6.02 (1H, s), 6.50 (1H, d, *J* = 10.2 Hz), 6.63 (1H, s); ¹³C-NMR (CDCl₃) δ 13.8, 22.1, 23.0, 27.7, 38.3, 43.1, 74.4, 77.7, 93.3, 104.3, 107.3, 111.2, 116.4, 127.1, 151.8, 156.4, 156.6, 158.2, 161.4, 181.4; MS [M+1]⁺ 387.2; Anal. Calcd for C₂₂H₂₆O₆+0.2 eq H₂O: C, 67.75; H, 6.92. Found C, 67.7; H, 6.8; IR (film): 3381, 2750, 1740, 1605 cm⁻¹.

EXAMPLE 25

Compound 21 (R₁=n-propyl, R₂=R₅=R₆=R₇=H, R₃=R₄=R₈=R₉=Me):

To acid **20** (R₁=n-propyl, R₂=R₅=R₆=R₇=H, R₃=R₄=R₈=R₉=Me, Y=OH) (120 mg, 0.31 mmol) in benzene (3 mL) added thionyl chloride (90 μL, 1.24 mmol) and refluxed under nitrogen for 1 h. The reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was dissolved in CH₂Cl₂ and concentrated under vacuum. This process was repeated twice. The reaction mixture was then dissolved in xylene (3 mL). Nafion NR-50 (50 mg) was added to the reaction mixture and refluxed for 22 h. Cooled to room temperature, filtered the resin, diluted with ethyl acetate and washed with aqueous saturated sodium bicarbonate solution and brine. The organic extracts were

dried over sodium sulfate and concentrated under vacuum. The crude product was then purified by preparative TLC (10% ethyl acetate in hexanes) to obtain **21** ($R_1=n$ -propyl, $R_2=R_5=R_6=R_7=H$, $R_3=R_4=R_8=R_9=Me$) (15 mg, 13%). 1H -NMR ($CDCl_3$) δ 1.03 (3H, t, $J = 7.4$ Hz), 1.21 (6H, s), 1.54 (6H, s), 1.67 (2H, m), 2.88 (2H, t, $J = 7.6$ Hz), 4.21 (2H, s),
5 5.60 (1H, d, $J = 9.9$ Hz), 6.05 (1H, s), 6.65 (1H, d, $J = 10.2$ Hz); MS $[M+1]^+$ 369.2.

EXAMPLE 26

Compound 23 ($R_6=R_8=R_9=H$, $R_7=Me$, $Z=TBDMS$):

To a suspension of sodium hydride (4 g, 0.1 mol) in THF (200 mL) added 1,3-
10 dihydroxybutane (9 mL, 0.1 mol) and stirred at room temperature for 45 min, at which time a large amount of an opaque white precipitate had formed. The tert-butyltrimethylsilyl chloride (15.1 g, 0.1 mol) was added and the reaction mixture was allowed to stir at room temperature overnight. The mixture was diluted with ether (500 mL) and washed with 10% aqueous potassium carbonate (150 mL), brine (100 mL). The
15 organic extracts were dried over sodium sulfate and concentrated under vacuum to obtain a colorless oil (20 g). A portion of the crude product (1 g) was purified by silica gel chromatography (8/1 hexane/ethyl acetate) to obtain **23** ($R_6=R_8=R_9=H$, $R_7=Me$, $Z=TBDMS$) (700 mg) as a colorless oil. 1H NMR ($CDCl_3$) δ 0.08 (6H, s), 0.90 (9H, s), 1.19 (3H, d, $J = 6.3$ Hz), 1.62-1.70 (2H, m), 3.23 (1H, br s), 3.77-3.99 (2H, m), 4.02-4.07
20 (1H, m); ^{13}C NMR ($CDCl_3$) δ -5.7 (2C), 23.2, 25.6, 25.7 (3C), 39.8, 62.7, 68.2; MS $[M+1]^+$ 204.9.

EXAMPLE 27

Compound 24 ($R_1=n$ -propyl, $R_2=R_5=R_6=R_8=R_9=H$, $R_3=R_4=R_7=Me$, $Z=TBDMS$):

To monophenol **6** (72 mg, 0.25 mmol), triphenylphosphine (98.4 mg, 0.375 mmol)
25 and **23** ($R_6=R_8=R_9=H$, $R_7=Me$, $Z=TBDMS$) (77 mg, 0.375 mmol) in THF (5 mL) added DEAD (60 μ L, 0.375 mmol) and stirred at room temperature under nitrogen for 1.5h. The reaction mixture was concentrated under vacuum and purified by silica gel chromatography (3/1 hexane/ethyl acetate) to obtain **24** ($R_1=n$ -propyl, $R_2=R_5=R_6=R_8=R_9=H$, $R_3=R_4=R_7=Me$, $Z=TBDMS$) (111 mg, 94%) as an oil. 1H NMR ($CDCl_3$) δ -
30 0.02 (6H, s), 0.89 (9H, s), 1.03 (3H, t, $J = 7.2$ Hz), 1.19 (3H, d, $J = 6.3$ Hz), 1.49 (6H, s), 1.63-1.73 (2H, m), 1.79-2.02 (2H, m), 2.88 (2H, t, $J = 6.0$ Hz), 3.71-3.76 (2H, m), 4.59-4.65 (1H, m), 5.52 (1H, d, $J = 9.9$ Hz), 5.95 (1H, s), 6.44 (1H, s), 6.64 (1H, d, $J = 9.9$

Hz); ^{13}C -NMR (CDCl_3) δ -5.6(2C), 13.8, 18.4, 19.6, 23.1, 25.7 (3C), 27.7, 38.3, 39.4, 59.1, 71.7, 94.2, 103.8, 106.3, 107.8, 110.8, 116.9, 126.7, 151.8, 156.3, 156.5, 158.2, 161.5; Anal. Calcd for $\text{C}_{27}\text{H}_{40}\text{O}_5\text{Si}$: C, 68.6; H, 8.53. Found C, 68.9; H, 8.6; IR (film): 2959, 2872, 1736, 1605 cm^{-1} ; MS $[\text{M}+1]^+$ 473.2.

5

EXAMPLE 28**Compound 24** (R_1 =n-propyl, $\text{R}=\text{R}_2=\text{R}_5=\text{R}_6=\text{R}_8=\text{R}_9=\text{H}$, $\text{R}_3=\text{R}_4=\text{R}_7=\text{Me}$):

To **24** (R_1 =n-propyl, $\text{R}_2=\text{R}_5=\text{R}_6=\text{R}_8=\text{R}_9=\text{H}$, $\text{R}_3=\text{R}_4=\text{R}_7=\text{Me}$, $\text{Z}=\text{TBDMS}$) (176 mg, 0.372 mmol) in THF (8 mL) added TBAF (1.0 M soln in THF, 560 μL) and stirred at
10 room temperature overnight. The reaction mixture was acidified with 1M HCl and extracted with ethyl acetate. The organic extracts were then washed with water, brine, dried (sodium sulfate) and concentrated under vacuum. The crude product was purified by silica gel chromatography (1/1 hexane/ethyl acetate) to obtain **24** (R_1 =n-propyl, $\text{R}=\text{R}_2=\text{R}_5=\text{R}_6=\text{R}_8=\text{R}_9=\text{H}$, $\text{R}_3=\text{R}_4=\text{R}_7=\text{Me}$) (133 mg, 100%) as an oil. ^1H NMR (CDCl_3) δ
15 1.03 (3H, t, $J = 7.5$ Hz), 1.38 (3H, d, $J = 6.0$ Hz), 1.49 (6H, s), 1.65-1.79 (2H, m), 1.94-2.05 (2H, m), 2.88 (2H, t, $J = 6.0$ Hz), 3.81 (2H, t, $J = 5.7$ Hz), 4.65-4.67 (1H, m), 5.52 (1H, d, $J = 9.9$ Hz), 5.95 (1H, s), 6.46 (1H, s), 6.62 (1H, $J = 10.2$ Hz); ^{13}C -NM(CDCl_3) δ
13.9, 15.1, 19.7, 23.1, 27.7, 38.3, 38.9, 59.3, 72.4, 77.6, 94.2, 104.1, 107.8, 110.9, 116.7, 126.9, 151.9, 156.0, 156.4, 158.2, 161.4; $\text{C}_{21}\text{H}_{26}\text{O}_5+0.3$ eq H_2O : C, 69.32; H, 7.37. Found
20 C, 69.25; H, 7.39; IR (film): 3474, 2971, 1738, 1593 cm^{-1} ; MS $[\text{M}+1]^+$ 359.1.

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WHAT WE CLAIM:

1. 2,2-Dimethyl-5-acyloxy-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one.
- 5 2. 2,2-Dimethyl-5-propionyloxy-10-propyl-2*H*, 8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one.
3. 2,2-Dimethyl-5-pivaloyloxy-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one.
4. A method for preparing 2,2-dimethyl-5-acyloxy-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one comprising reacting 5-hydroxy-7-acyloxy-4-propylcoumarin with 3-chloro-3-methyl-1-butyne.
10
5. The method according to claim 4 wherein said 2,2-dimethyl-5-acyloxy-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one comprises 2,2-dimethyl-5-propionyloxy-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one or 2,2-dimethyl-5-pivaloyloxy-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one.
15
6. A method for preparing 2,2-dimethyl-5-hydroxy-6-propionyl-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one **4** comprising heating a solution of 2,2-dimethyl-5-propionyloxy-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one **5a** in the presence of an anhydrous Lewis acid.
20
7. The method according to claim 6 wherein said anhydrous Lewis acid comprises anhydrous aluminum chloride.
8. A method for preparing 2,2-dimethyl-5-hydroxy-6-propionyl-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one **4** comprising reacting 2,2-dimethyl-5-hydroxy-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyran-8-one **6** with propionyl acylating agent.
25
9. The method according to claim 8 wherein said propionyl acylating agent comprises propionyl anhydride.
30
10. The method according to claim 9 further comprising a Lewis acid.

11. A method for preparing (\pm)-calanolide A comprising the steps of:

(a) heating a solution of 2,2-dimethyl-5-propionyloxy-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyrans-8-one **5a** in the presence of an anhydrous Lewis acid to produce 2,2-dimethyl-5-hydroxy-6-propionyl-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyrans-8-one **4**;

5 (b) converting 2,2-dimethyl-5-hydroxy-6-propionyl-10-propyl-2*H*,8*H*-benzo[1,2-*b*:3,4-*b'*]dipyrans-8-one **4** to 12-oxocalanolide **10**; and

(c) reducing 12-oxocalanolide **10** so as to form (\pm)-calanolide A.

12. The method according to claim 11, wherein step (b) conversion is
10 performed by a chlorotitanium-mediated aldol reaction with acetaldehyde followed by a Mitsunobu reaction.

13. The method according to claim 11, wherein step (b) conversion is performed with paraaldehyde or CH₃CH(OEt)₂.

15

14. The method according to claim 11, wherein step(c) reduction is performed with NaBH₄.

15. The method according to claim 11, wherein said anhydrous Lewis acid
20 comprises AlCl₃.

16. A method for preparing (\pm)-calanolide A comprising the steps of:

(a) reacting **6** with a propionyl acylating agent in the presence of a Lewis acid to produce 2,2-dimethyl-5-hydroxy-6-propionyl-10-propyl-2*H*,8*H*-benzo [1,2-*b*:3,4-*b'*]dipyrans-8-one
25 **4**;

(b) converting 2,2-dimethyl-5-hydroxy-6-propionyl-10-propyl-2*H*,8*H*-benzo [1,2-*b*:3,4-*b'*]dipyrans-8-one **4** to 12-oxocalanolide **10**; and

(c) reducing 12-oxocalanolide **10** so as to form (+)-calanolide A.

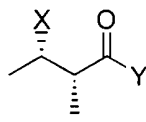
30 17. The method according to claim 16, wherein step (b) conversion is performed by a chlorotitanium-mediated aldol reaction with acetaldehyde followed by a Mitsunobu reaction.

18. The method according to claim 16, wherein step (b) conversion is performed with paraaldehyde or $\text{CH}_3\text{CH}(\text{OEt})_2$.

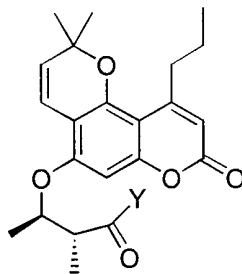
19. The method according to claim 16, wherein step(c) reduction is performed
5 with NaBH_4 .

20. The method according to claim 16, wherein said anhydrous Lewis acid comprises AlCl_3 , TiCl_4 or BF_3 .

10 21. A method for preparing (+)-calanolide A comprising the steps of:
(a) coupling **6** with compound **11**

**11**

15 to produce compound **13**:

**13**

wherein Y represents -OMe, -OEt, or amino;

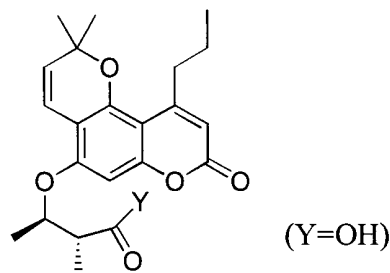
20 (b) hydrolyzing compound **13**;
(c) cyclizing the product of step (b) in the presence of a Lewis acid to produce
12-oxocalanolide **10**; and
(d) reducing 12-oxocalanolide **10** to produce (+)-calanolide A.

25 22. The method according to claim 21, wherein step (c) Lewis acid comprises AlCl_3 , TiCl_4 or BF_3 .

23. The method according to claim 21 wherein said step (d) reduction is performed with sodium borohydride in the presence of cerium chloride.

24. A method for preparing a compound having a structure:

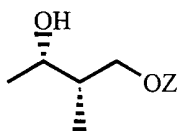
5



said method comprising the steps of:

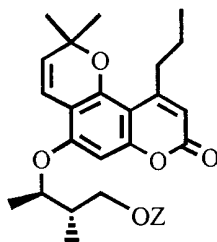
(a) coupling **6** with compound **12**

10



12

wherein Z represents TBDMS, THP and Ts to produce compound **14**:



14

15

wherein Z is the same as described above;

- (b) deprotecting compound **14** to produce compound **14** (Z=H);
- (b) oxidizing compound **14** (Z=H) to produce compound **13** (Y=H); and
- (c) oxidizing compound **13** (Y=H) to produce compound **13** (Y=OH).

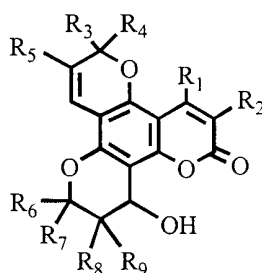
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25. The method according to claim 24, wherein step (a) coupling is performed by a Mitsunobu reaction.

26. The method according to claim 24, wherein step (b) oxidation is performed by Swern oxidation using oxalyl chloride and DMSO.

27. The method according to claim 24, wherein step (c) oxidation is performed in the presence NaClO₂ and NaH₂PO₄.

28. A method for preparing a calanolide analogue having the structure **22**:



22

10

wherein R₁ is H, halogen, hydroxyl, amino, C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, hydroxy-C₁₋₆ alkyl, C₁₋₆ alkoxy, amino-C₁₋₈ alkyl, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, C₁₋₈ alkylamino-C₁₋₈ alkyl, di(C₁₋₆ alkyl) amino-C₁₋₈ alkyl, cyclohexyl, aryl, or heterocycle, wherein aryl or heterocycle may each be unsubstituted or substituted with one or more of the following: C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy-C₁₋₄ alkyl, hydroxyl, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, amino-C₁₋₈ alkyl, C₁₋₈ alkylamino-C₁₋₈ alkyl, di(C₁₋₆ alkyl-amino-C₁₋₈ alkyl, nitro, azido or halogene;

15

R₂ is H, halogen, hydroxyl, C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, aryl or heterocycle:

20

R₃ and R₄ are independently selected from the group consisting of H, C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, aryl or heterocycle; or

R₃ and R₄ together form a 5-7 membered saturated cycle ring or heterocycle ring;

R₅ is H, halogen, methyl, ethyl;

25

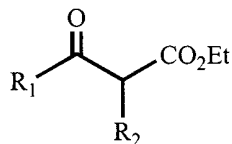
R₆, R₇, R₈ and R₉ are independently selected from the group consisting of H, halogen, hydroxy, amino, mono- or dialkylamino-C₁₋₆ alkyl, hydroxy-C₁₋₆ alkyl, amino-C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, aryl or heterocycle; or

R₆ and R₇ together form a 5-7 membered saturated cycle ring or heterocycle ring; or

R₈ and R₉ together form a 5-7 membered saturated cycle ring or heterocycle ring;

said method comprising the steps of:

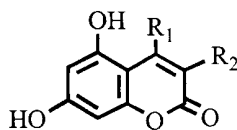
- (a) coupling 1,3,5-trihydroxybenzene with β -ketoester **25**:



5

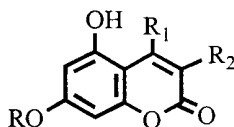
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to produce compound **15**:

**15**

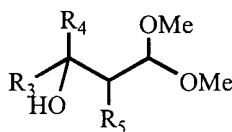
wherein R_1 and R_2 as the same as described above;

- 10 (b) acylating compound **15** with $(RCO)_2O$ wherein R represents C_{1-6} alkyl, aryl- C_{1-6} alkyl, mono- or poly- fluorinated C_{1-6} alkyl, aryl or heterocycle to produce compound **16**

**16**

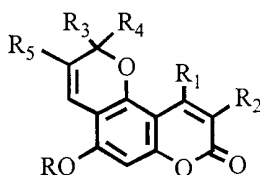
15 wherein R, R_1 and R_2 are the same as described above;

- (c) coupling compound **16** with compound **26**

**26**

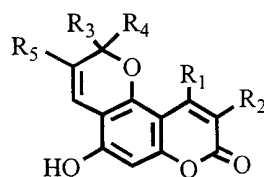
20

to provide compound **17**

**17**

wherein R, R₁, R₂, R₃, R₄, and R₅ are the same as described above;

(d) hydrolyzing compound **17** to produce compound **18**

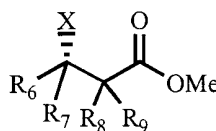


18

5

wherein R₁, R₂, R₃, R₄, and R₅ are the same as described above;

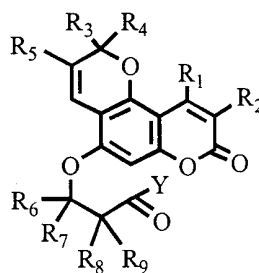
(e) coupling compound **18** with compound **19**



19

10

to produce compound **20**

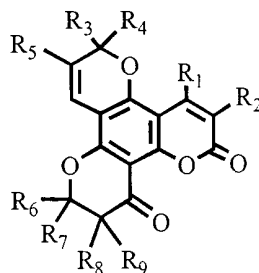


20

15 wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, and R₉ are the same as described above, Y=OH
OMe;

(f) hydrolyzing compound **20** (Y=OMe) to form **20** (Y=OH)

(g) cyclizing compound **20** (Y=OH) in the presence of a Lewis acid to produce
compound **21**



48

20

21

wherein R₁, R₂, R₃, R₄, R₅, R₆, R₇, R₈, and R₉ are the same as described above; and

(h) reducing compound **21** to produce compound **22**.

5 29. The method according to claim 28, wherein step (a) coupling is performed in the presence of an acid catalyst.

30. The method according to claim 28, wherein step (b) acylation is performed in the presence of a Lewis acid.

10

31. The method according to claim 28, wherein step (c) coupling is performed in the presence of a base.

32. The method according to claim 28, wherein step (d) hydrolysis is performed in the presence of a base in aqueous solution.

15

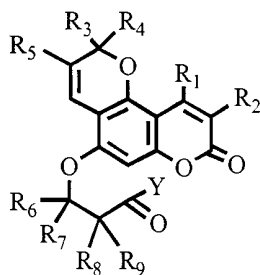
33. The method according to claim 28, wherein step (e) coupling is performed under Mitsunobu or nucleophilic displacement condition.

20 34. The method according to claim 28, wherein the Lewis acid of step (g) is AlCl₃, TiCl₄ or BF₃.

35. The method according to claim 28, wherein step (h) reduction is performed in the presence of sodium borohydride and cerium chloride.

25

36. A method for preparing a compound having the structure **20**:



wherein R₁ is H, halogen, hydroxyl, amino, C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, hydroxy-C₁₋₆ alkyl, C₁₋₆ alkoxy, amino-C₁₋₈ alkyl, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, C₁₋₈ alkylamino-C₁₋₈ alkyl, di(C₁₋₆ alkyl) amino-C₁₋₈ alkyl, cyclohexyl, aryl, or heterocycle, wherein aryl or heterocycle may each be unsubstituted or substituted
 5 with one or more of the following: C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy-C₁₋₄ alkyl, hydroxyl, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, amino-C₁₋₈ alkyl, C₁₋₈ alkylamino-C₁₋₈ alkyl, di(C₁₋₆ alkyl-amino-C₁₋₈ alkyl, nitro, azido or halogene;

R₂ is H, halogen, hydroxyl, C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, aryl or heterocycle;

10 R₃ and R₄ are independently selected from the group consisting of H, C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, aryl or heterocycle; or

R₃ and R₄ together form a 5-7 membered saturated cycle ring or heterocycle ring; and

R₅ is H, halogen, methyl or ethyl;

R₆, R₇, R₈ and R₉ are independently selected from the group consisting of H, halogen,
 15 hydroxy, amino, mono- or dialkylamino-C₁₋₆ alkyl, hydroxy-C₁₋₆ alkyl, amino-C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, aryl or heterocycle; or

R₆ and R₇ together form a 5-7 membered saturated cycle ring or heterocycle ring; or

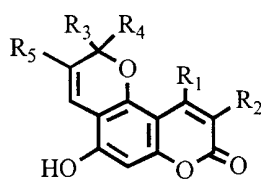
R₈ and R₉ together form a 5-7 membered saturated cycle ring or heterocycle ring;

Y is H, OH, OMe, or amino group;

20

said method comprising the steps of:

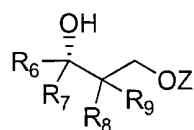
(a) coupling compound **18**



18

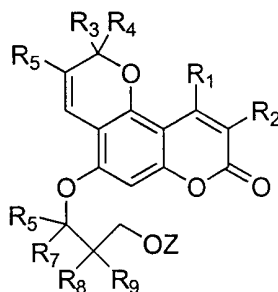
25

wherein R₁, R₂, R₃, R₄, and R₅ are the same as described above, with compound **23**



23

wherein R_6 , R_7 , R_8 , and R_9 are the same as described above and Z represents TBDMS, THP, Ts, or COR, wherein R can be C_{1-6} alkyl, aryl- C_{1-6} alkyl, mono- or poly- fluorinated C_{1-6} alkyl, aryl or heterocycle to produce compound **24**

**24**

wherein Z, R_1 to R_9 are the same as described above;

(b) deprotecting compound **24** to form **24** ($Z=H$)

(c) oxidizing compound **24** ($Z=H$); and

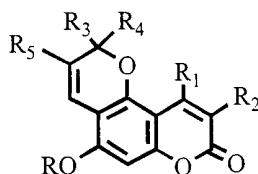
(d) oxidizing the product of step (b) to produce compound **20**.

37. The method according to claim 36, wherein step (a) coupling is performed in the presence of under Mitsunobu or nucleophilic displacement condition.

38. The method according to claim 36, wherein step (c) oxidation is performed by Swern oxidation using oxalyl chloride and DMSO.

39. The method according to claim 36, wherein step (d) oxidation is performed with $NaClO_2$ and NaH_2PO_4 .

40. A compound having the formula **17**:

**17**

wherein R_1 is H, halogen, hydroxyl, amino, C_{1-6} alkyl, aryl- C_{1-6} alkyl, mono- or poly- fluorinated C_{1-6} alkyl, hydroxy- C_{1-6} alkyl, C_{1-6} alkoxy, amino- C_{1-8} alkyl, C_{1-6} alkylamino,

di(C₁₋₆ alkyl)amino, C₁₋₈ alkylamino-C₁₋₈ alkyl, di(C₁₋₆ alkyl) amino-C₁₋₈ alkyl, cyclohexyl, aryl, or heterocycle, wherein aryl or heterocycle may each be unsubstituted or substituted with one or more of the following: C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy-C₁₋₄ alkyl, hydroxyl, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, amino-C₁₋₈ alkyl, C₁₋₈ alkylamino-C₁₋₈ alkyl, di(C₁₋₆ alkyl-amino-C₁₋₈ alkyl, nitro, azido or halogen;

R₂ is H, halogen, hydroxyl, C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, aryl or heterocycle such as;

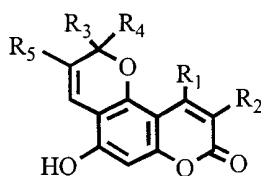
R₃ and R₄ are independently selected from the group consisting of H, C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, aryl or heterocycle; or

R₃ and R₄ together form a 5-7 membered saturated cycle ring or heterocycle ring; and

R₅ is H, halogen, methyl, and ethyl; and

R is C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly- fluorinated C₁₋₆ alkyl, aryl or heterocycle.

41. A compound having the formula **18**:



18

wherein R₁ is H, halogen, hydroxyl, amino, C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, hydroxy-C₁₋₆ alkyl, C₁₋₆ alkoxy, amino-C₁₋₈ alkyl, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, C₁₋₈ alkylamino-C₁₋₈ alkyl, di(C₁₋₆ alkyl) amino-C₁₋₈ alkyl, cyclohexyl, aryl, or heterocycle, wherein aryl or heterocycle may each be unsubstituted or substituted with one or more of the following: C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy-C₁₋₄ alkyl, hydroxyl, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, amino-C₁₋₈ alkyl, C₁₋₈ alkylamino-C₁₋₈ alkyl, di(C₁₋₆ alkyl-amino-C₁₋₈ alkyl, nitro, azido or halogen;

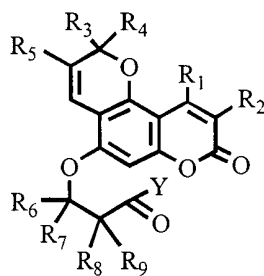
R₂ is H, halogen, hydroxyl, C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, aryl or heterocycle;

R₃ and R₄ are independently selected from the group consisting of H, C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, aryl or heterocycle; or

R₃ and R₄ together form a 5-7 membered saturated cycle ring or heterocycle ring; and

R₅ is H, halogen, methyl, and ethyl.

42. A compound having the formula:



20

wherein R₁ is H, halogen, hydroxyl, amino, C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, hydroxy-C₁₋₆ alkyl, C₁₋₆ alkoxy, amino-C₁₋₈ alkyl, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, C₁₋₈ alkylamino-C₁₋₈ alkyl, di(C₁₋₆ alkyl) amino-C₁₋₈ alkyl, cyclohexyl, aryl, or heterocycle, wherein aryl or heterocycle may each be unsubstituted or substituted with one or more of the following: C₁₋₆ alkyl, C₁₋₆ alkoxy, hydroxy-C₁₋₄ alkyl, hydroxyl, amino, C₁₋₆ alkylamino, di(C₁₋₆ alkyl)amino, amino-C₁₋₈ alkyl, C₁₋₈ alkylamino-C₁₋₈ alkyl, di(C₁₋₆ alkyl-amino-C₁₋₈ alkyl, nitro, azido or halogen;

R₂ is H, halogen, hydroxyl, C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, aryl or heterocycle;

R₃ and R₄ are independently selected from the group consisting of H, C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, aryl or heterocycle; or

R₃ and R₄ together form a 5-7 membered saturated cycle ring or heterocycle ring; and

R₅ is H, halogen, methyl, and ethyl; and

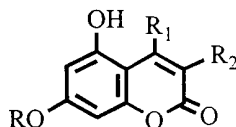
R₆, R₇, R₈ and R₉ are independently selected from the group consisting of H, halogen, hydroxy, amino, mono- or dialkylamino-C₁₋₆ alkyl, hydroxy-C₁₋₆ alkyl, amino-C₁₋₆ alkyl, aryl-C₁₋₆ alkyl, mono- or poly-fluorinated C₁₋₆ alkyl, aryl or heterocycle; or

R₆ and R₇ together form a 5-7 membered saturated cycle ring or heterocycle ring; or

R₈ and R₉ together form a 5-7 membered saturated cycle ring or heterocycle ring;

Y is H, OH, OMe, or amino group.

43. A compound having the formula:



16

wherein R_1 is H, halogen, hydroxyl, amino, C_{1-6} alkyl, aryl- C_{1-6} alkyl, mono- or poly-fluorinated C_{1-6} alkyl, hydroxy- C_{1-6} alkyl, C_{1-6} alkoxy, amino- C_{1-8} alkyl, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{1-8} alkylamino- C_{1-8} alkyl, di(C_{1-6} alkyl) amino- C_{1-8} alkyl, cyclohexyl, aryl, or heterocycle, wherein aryl or heterocycle may each be unsubstituted or substituted with one or more of the following: C_{1-6} alkyl, C_{1-6} alkoxy, hydroxy- C_{1-4} alkyl, hydroxyl, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, amino- C_{1-8} alkyl, C_{1-8} alkylamino- C_{1-8} alkyl, di(C_{1-6} alkyl-amino- C_{1-8} alkyl, nitro, azido or halogene;

10 R_2 is H, halogen, hydroxyl, C_{1-6} alkyl, aryl- C_{1-6} alkyl, mono- or poly-fluorinated C_{1-6} alkyl, aryl or heterocycle; and

R is C_{1-6} alkyl, aryl- C_{1-6} alkyl, mono- or poly- fluorinated C_{1-6} alkyl, aryl or heterocycle.

FIGURE 1

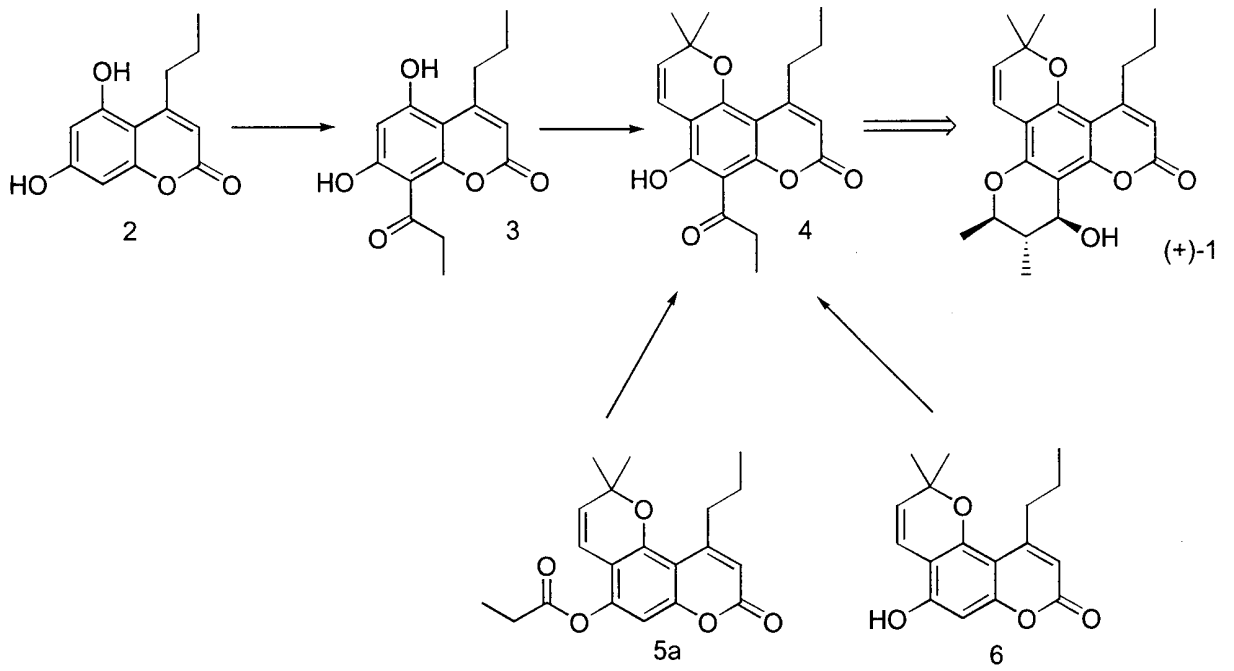


FIGURE 2

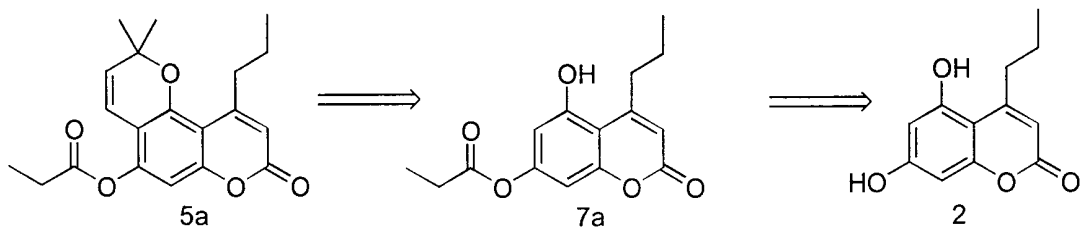


FIGURE 3

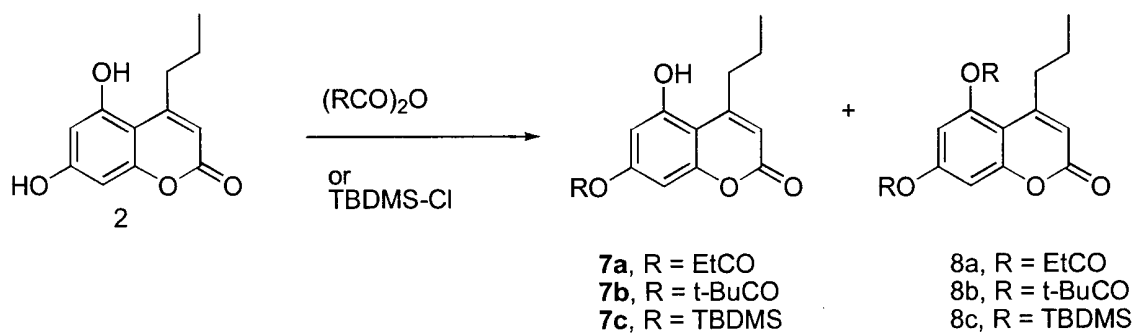
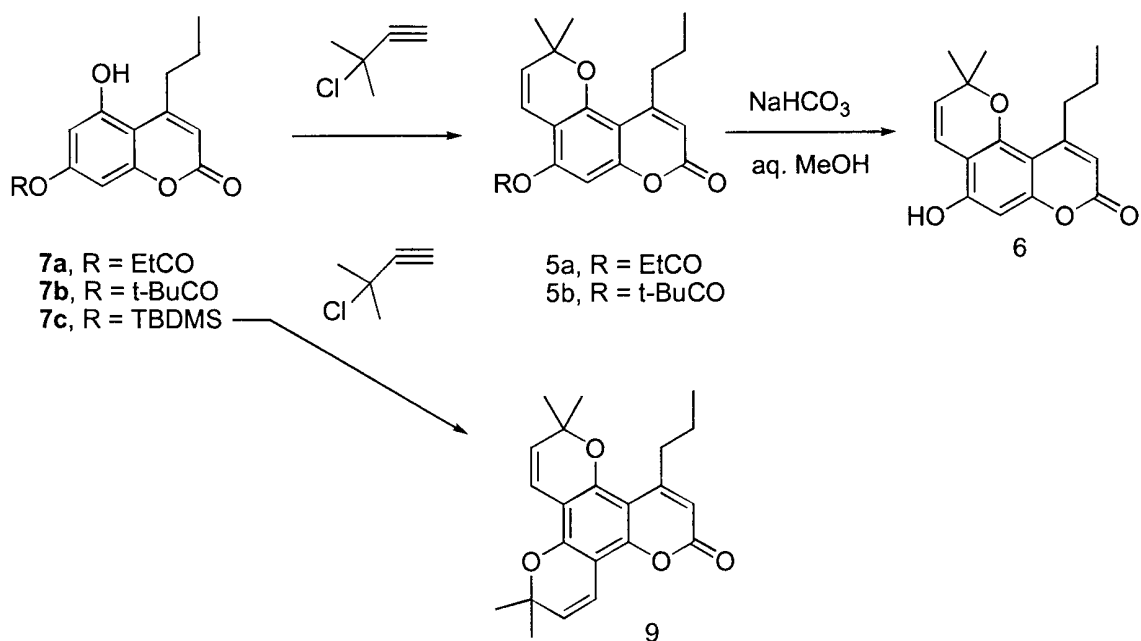
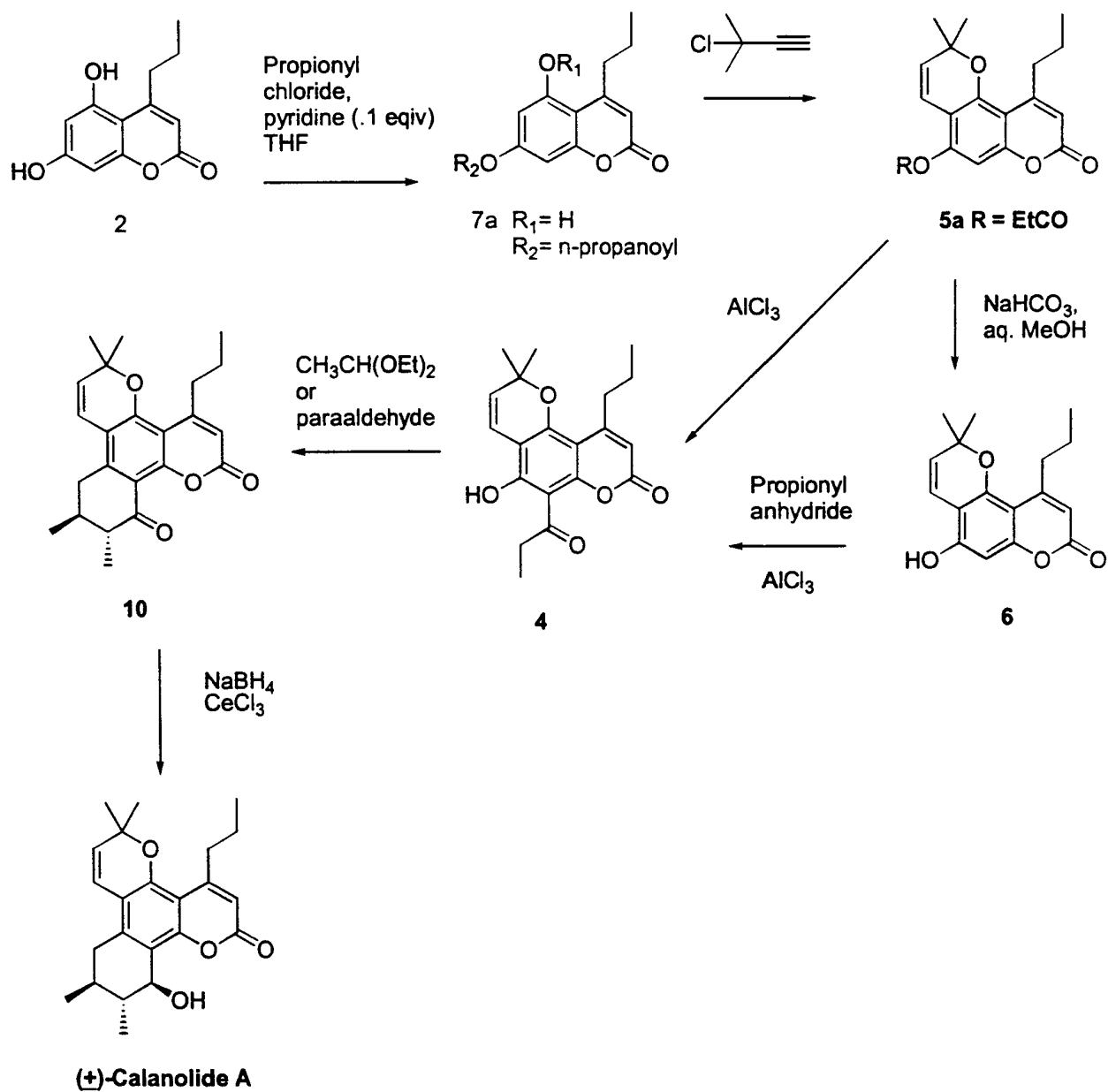


FIGURE 4



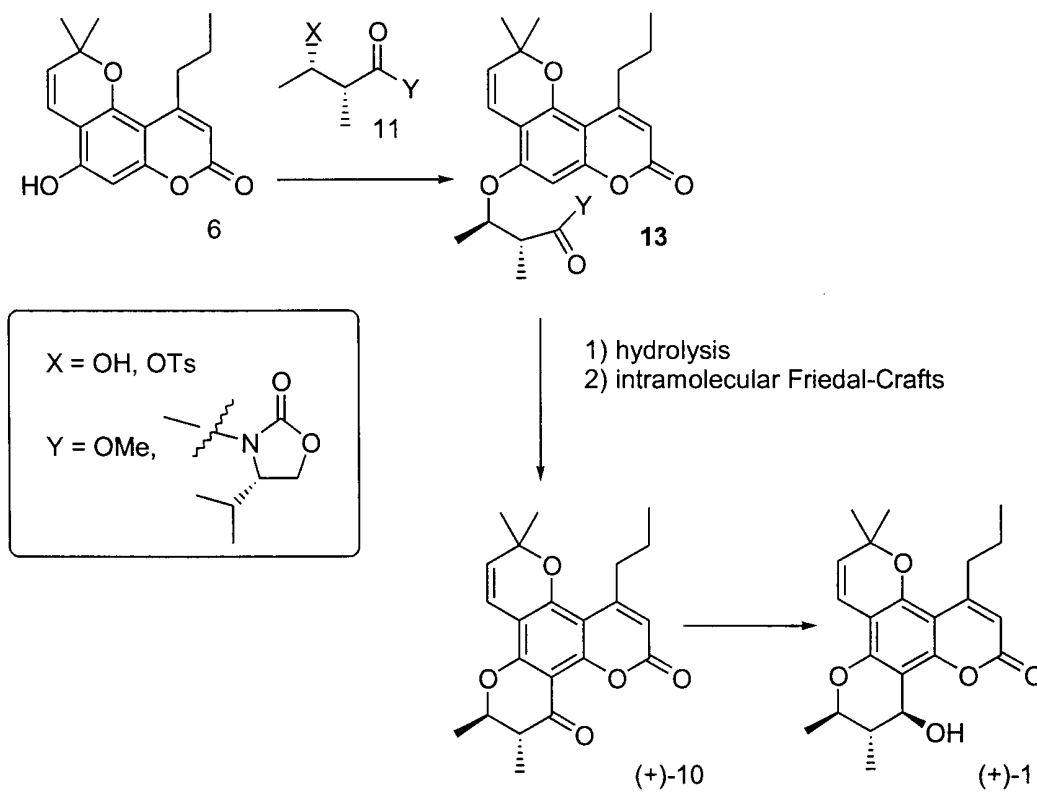
3/7

FIGURE 5



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FIGURE 6



5/7

FIGURE 7

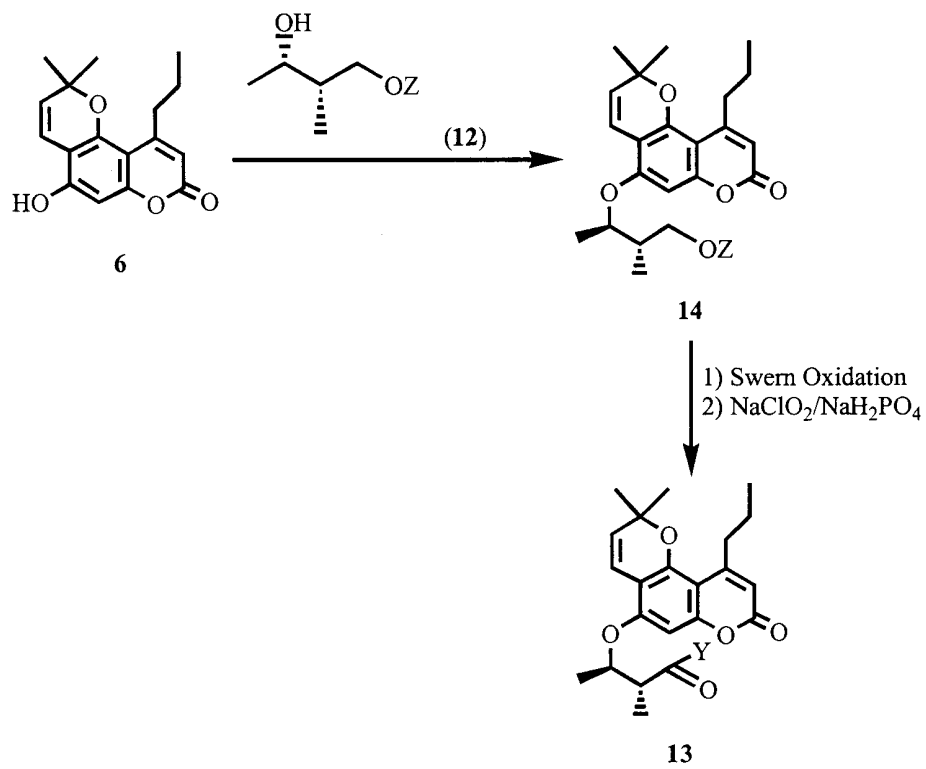


FIGURE 8

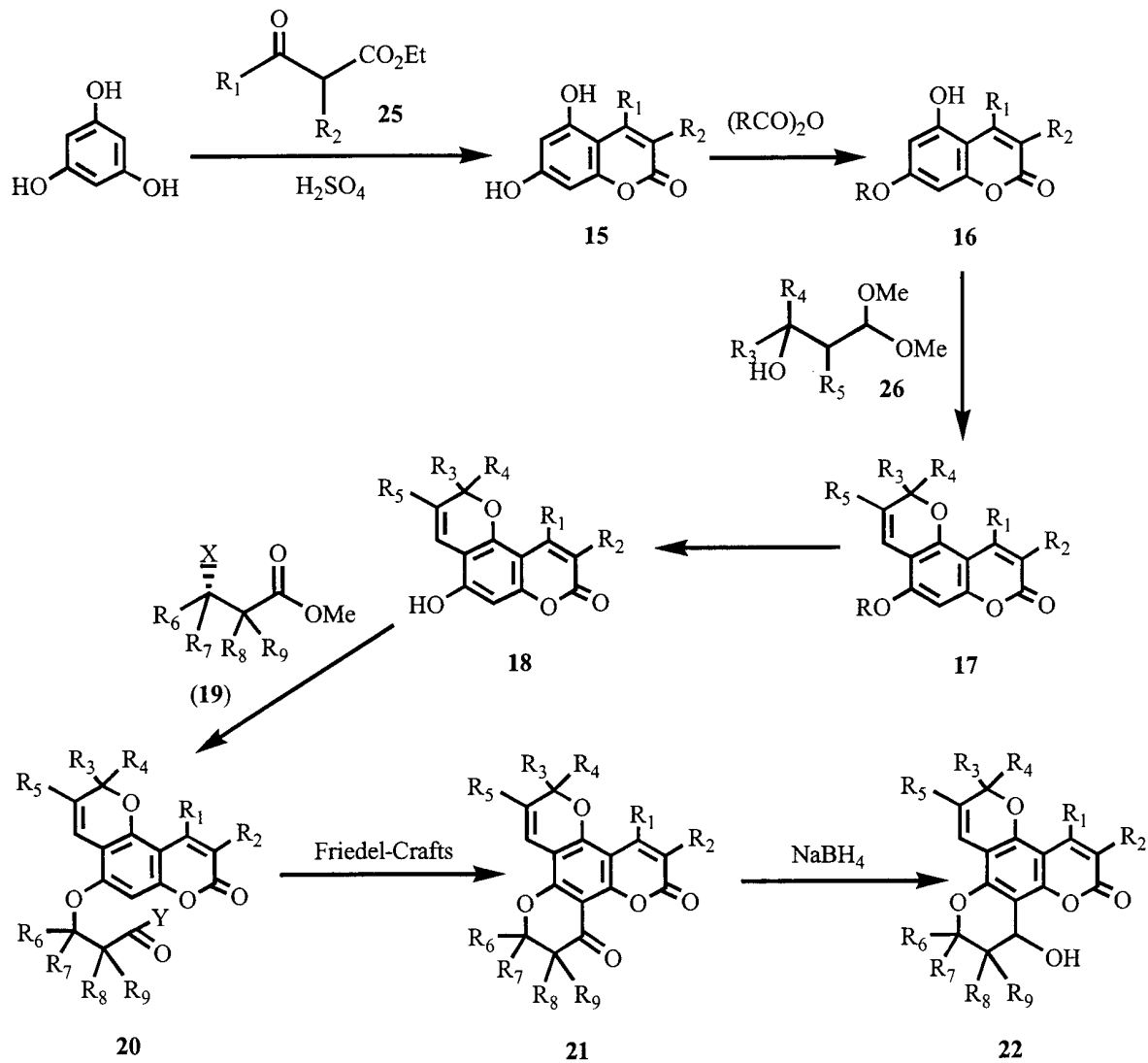


FIGURE 9

