(54) PROCESS FOR PREPARING SAPONIN COMPOUNDS

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(57) ABSTRACT

A process for preparing compounds of formula (1):

![Chemical Structure](image)

including the convergent steps as defined in the specification, and wherein R groups have any of the values defined in the specification. The invention also provides processes and intermediates useful for preparing compounds of formula (1).

22 Claims, No Drawings
OTHER PUBLICATIONS


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PROCESS FOR PREPARING SAPONIN COMPOUNDS

RELATED APPLICATION

This application claims priority under 35 U.S.C. 119(e) from U.S. Provisional Application No. 60/310,709 filed Aug. 7, 2001, which application is incorporated herein by reference.

FIELD OF THE INVENTION

The present invention provides processes for the preparation of saponin compounds, and more specifically, provides processes for the preparation of compounds of formula (1) and to intermediates leading thereto as described herein. The compounds of formula (1) are related to naturally occurring saponins such as OSW-1 and analogues thereof. The compounds are useful as anti-cancer drugs.

BACKGROUND OF THE INVENTION

Saponins are a large family of naturally occurring glycoconjugate compounds with considerable structural diversity. Saponin OSW-1, 3β,16β,17β,24-trihydroxycholest-5-en-22-one 16-O-[β-(2-O-(4-methoxybenzoyl)-β-D-xylopyranosyl)-(1-3)-2-O-acetyl-α-L-rabinopyranoside], is the major component of a small group of cholesterol saponins isolated by Sashida et al. (Phytochemistry, 31, 3936, 1992) from the bulbs of a species of the lily family. OSW-1 is highly toxic against a broad spectrum of malignant tumor cells (Bioorg. Med. Chem. Lett., 7, 633, 1997) with little toxicity to normal cells in vitro.

Saponins are glycosidic natural plant products, composed of a ring structure (the aglycone) to which is attached one or more sugar chains. The saponins are grouped together based on several common properties. In particular, saponins are surfactants which display hemolytic activity and form complexes with cholesterol. Although saponins share these properties, they are structurally diverse. In particular, the aglycone can be a steroid, triterpenoid or a steroidal alkaloid and the number of sugars attached to the glycosidic bonds vary greatly.

Saponins have been employed as absorption adjuvants in pharmaceutical compositions. For example, U.S. Pat. No. 4,501,734, describes the use of a triterpenoid saponin extract from Sapindus mukorossi Gaertn. to increase absorption of a coadministered beta-lactum antibiotic. Saponins have also been used as immunological adjuvants in vaccine compositions against a variety of diseases including protozoal infections and foot and mouth disease. The saponins typically used as immunological adjuvants are triterpene glycosides extracted from the South American tree, Quillaja saponaria, termed Quill A., see for example, U.S. Pat. No. 5,057,540.

Saponins have also been used in pharmaceutical compositions for a variety of other purposes. For example, U.S. Pat. No. 5,118,671, describes the use of aescin, a saponin obtained from Aesculus hippocastanum seeds, in pharmaceutical and cosmetic compositions as an anti-inflammatory. Similarly, U.S. Pat. No. 5,147,859, discusses the use of Glycyrrhiza glabra saponin/phospholipid complexes as anti-inflammatory and anti-ulcer agents and U.S. Pat. No. 5,166,139, describes the use of complexes of saponins and aglycons, obtained from Centella asiatica and Terminalia sp., with phospholipids in pharmaceutical compositions. International Publication No. WO 91/04052, published 4 Apr. 1991, discusses the use of solid Quillaja saponaria saponin/GnRH vaccine compositions for immunocastration and immunospaying.

The present invention also provides a process for preparing a saponin intermediate comprising:

reacting, in the presence of a 1,4-addition activating agent, an enone compound of the formula (9):
The preparative processes of the present invention can also further comprise:

a) converting the above vinyl ether of compound (18) at —OR₃ to a corresponding ketal;

b) generating a corresponding enolate at —OR⁴ of compound (18) wherein R⁴ is, for example, a metal counter ion; and

c) oxidizing the resulting enolate to an alpha-hydroxy ketone compound of the formula (20):

The foregoing preparative process of the present invention can further comprise: stereoselectively reducing the ketone of the formula (20) to a 1,2-diol compound of formula (7):

In other embodiments, the present invention provides a process for preparing the compound of formula (1):
wherein $R^2$ can be independently $-H$ or a hydroxyl protecting group, and $R^3$ can be independently $-C(=O)-Ar$ or $-C(=O)-CR_2=CR_3=CR_4=Ar$, wherein Ar can be independently aryl or heteroaryl, and $R_1$ and $R_2$ can independently each be $-H$, $C_{1-4}$ alkyl, $C_{2-4}$ alkanoyl, $C_{1-4}$ alkoxy carbonyl, aryl, (aryl)$C_{1-4}$ alkyl, arylecarbonyl, or aryl oxy carbonyl, and $R^{10}$ is as defined above, comprising:

a) coupling a compound of the formula (7) prepared in accordance with the above description and as illustrated herein:

with a compound of the formula (6):

wherein $R^6$, $R^8$ and $R^9$ are each independently a hydroxyl protecting group, and $-OR^7$ is a leaving group, that is, a displaceable group which can be substituted by another group or molecule, such as by the secondary alcohol ($-OH$) functional group of compound (7), and without inversion of the stereoisomerism on the sugar ring carbon to which $-OR^7$ is attached, to form a compound of the formula (36); and

b) deprotecting the compound of formula (36) to afford the compound of formula (1).

In embodiments, the aforementioned $R^1$ as a hydroxyl protecting group can be, for example, of the formula $-Si(R^{12})_3$, wherein each $R^{12}$ can be independently $C_{1-4}$ alkyl, such as $-Me$, $-Et$, and the like. The Ar of $-C(=O)-Ar$ can be independently an aryl or a heteroaryl group, optionally substituted with one or more substituents selected independently from, for example, halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-OCF_3$, methylene dioxy, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, phenyl, NR$_2$, $-C(=O)NR_2$, and wherein each $R_1$ and $R_2$ is independently $-H$, $C_{1-4}$ alkyl, $C_{2-6}$ alkanoyl, $C_{1-4}$ alkoxy carbonyl, aryl, (aryl)$C_{1-4}$ alkyl, arylecarbonyl, aryl oxy carbonyl, or like groups; or $R_1$ and $R_2$ together with a nitrogen to which they are attached form a pyrroldino, piperidino, morpholino, or thiomorpholino ring; or a pharmaceutically acceptable salt thereof.

The Ar of $-C(=O)-CR_2=CR_3=CR_4=Ar$ can independently be an aryl or a heteroaryl group and wherein any aryl or heteroaryl can be optionally substituted with one or more substituents independently selected from halo, $-OH$, $-CN$, $-NO_2$, $-CF_3$, $-OCF_3$, methylene dioxy, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy, phenyl, NR$_2$, $-C(=O)NR_2$, and like groups; wherein each $R_1$ and $R_2$ can be independently hydrogen, $C_{1-4}$ alkyl, $C_{2-6}$ alkanoyl, $C_{1-4}$ alkoxy carbonyl, aryl, (aryl)$C_{1-4}$ alkyl, arylecarbonyl, aryl oxy carbonyl, or like groups; or $R_1$ and $R_2$ together with the nitrogen to which they are attached form a pyrroldino, piperidino, morpholino, thiomorpholino ring, and like groups; or a pharmaceutically acceptable salt thereof. In embodiments, $R^2$ can be independently p-methoxybenzoyl, 3,4-dimethoxybenzoyl, ($E$)-cinnamoyl, or ($Z$)-cinnamoyl, and like groups.

Preferred $R^1$ and $R^2$ groups in the compound of the formula (1) are where $R^1$ is $-H$, and $R^2$ is p-methoxybenzoyl, and which compound corresponds to OSW-1 wherein $R^{10}$ is $-CH_2-CH_2(CH_2)_{2}$. The 1,4-addition activating agent can be, for example, a trialkylsilylchloride, such as trimethylsilyl chloride. The $R^3$ enolic hydroxy protecting group can be, for example, an alkyl group and like groups, and preferably a bulky alkyl or cycloalkyl group, such as, $C_4$, cycloalkyl, and the $R^4$ enolic hydroxy protecting group can be, for example, alkanoyl, such as acetyl, and like groups.

The selective deprotection of indicated hydroxyl groups to afford the compound of formula (1) can be accomplished by sequentially treating the compound of formula (36) with DDQ and thereafter bis-(acetoneitrile)dichloropalladium(II). The compound of the formula (9) can be prepared by the steps comprising, for example:

a) olefinating the ketone of the compound of formula (14), for example, with an appropriate Wittig reagent, like olefin producing ylid modification reagents, and like reagents or equivalent reagents which produce an olefin product being compatible with the $R^9$ protecting group.

b) allylicly oxidizing the resulting olefin compound to form an allylic alcohol compound of formula (15); and
c) oxidizing the allylic alcohol (15) to form a 1,4-enone compound of formula (9)

The compound of the formula (6):

can be prepared by the steps comprising:

a) glycosylating a compound of the formula (25)

wherein R^5 is a hydroxyl protecting group, that is, suitable for protection and deprotection of a secondary hydroxyl group in a simple sugar or a similarly substituted pyranose ring system, and X can be, for example, an SN$_1$ leaving group, that is for example, a group which is capable of selective substitution or conversion to an —OR$^7$ leaving group and without stereoelectronic inversion at the sugar ring carbon. For example, X can be —SAr wherein Ar is, for example, phenyl. Compound 25 can be glycosylated, for example, by reaction with a compound of the formula (34)

wherein —OR$^{11}$ is preferably a leaving group of the formula —OC(==NH)CCl$_3$, to afford a compound of the formula (35):

b) X is then converted into a leaving group —OR$^7$ of the formula, for example, —O—C(==NH)CCl$_3$ to afford the above compound of formula (6). The leaving group X can be, for example, —SAr wherein Ar is as defined above, such as phenyl, and like substituents.

The present invention also provides novel intermediates and processes as disclosed herein that are useful for preparing compounds of formula (1).

DETAILED DESCRIPTION OF THE INVENTION

Applicants have discovered a new and efficient convergent strategy for the total synthesis of OSW-1 and related saponin compounds including direct introduction of the complete carbon side chain of OSW-1 steroid precursors as shown in Scheme 1.

A retrosynthetic analysis is shown in Scheme 2. OSW-1 (1) was conceptually disconnected into the disaccharide 6 and the steroid aglycone 7. Compound 7 was viewed as obtainable by 1,4-addition of the R-alkoxy vinyl cuprate 8 to compound 9 which compound was prepared from commercially available 5-androsten-3β-ol-17-one 10.
Scheme 3 outlines the synthesis of the R-alkoxy vinyl cuprate 8. The acetylenic ether 11 was prepared according to the literature procedure. The α-bromo vinyl ether 13 was prepared regio- and stereoselectively according to literature procedures, which was in turn converted in situ to a high-order cuprate 8.

Scheme 3

a 1: R = H
12: R = iso-butyl
b

c

40. a. (i) n-BuLi, -20-0°C, 20 min; (ii) iso-butyl triflate, -30-25°C, 12 h, 85%
b. b. TMSBr, MeOH, CH₂Cl₂, -40-25°C, 15 min, 99% c. c. (i) t-BuLi (2 equiv), ether, -78°C, 30 min; (ii) Co₂CN, LICN, TiF₅, -78°C, 15 min.

Compound 15 was prepared from 10 according to literature procedure as shown in Scheme 4.

Scheme 4

a 10: R = H
14: R = TBS
Trost and co-workers have shown that selenium dioxide-mediated allylic oxidation can regio- and stereoselectively introduce a hydroxy group into the C-16 of the steroid 17(20)-en-16-ones. However, in their examples the double bond in the B ring was protected. The present invention achieves complete chemo-, regio-, and stereoselective allylic oxidation at C-16 under the same reaction conditions without the protection of the 5(6) double bond.

Swern oxidation of 16 afforded enone 9 in nearly quantitative yield. TMSCl-activated 1,4-addition of R-alkoxy vinyl cuprate 8 to enone 9 gave silyl enol ether intermediate 17, which was converted to enol acetate 18 in a single operation without the isolation of 17. The conversion of silyl enol ether 17 to enol acetate 18 enabled chemoselective transformation of the enol ether to cyclic acetel 19. Generation of the enolate from 19 by potassium ethoxide or potassium tert-butoxide followed by in situ oxidation by Davis reagent stereoselectively gave R-hydroxy ketone 20 in 76% yield. Stereoselective reduction of compound 20 by LiAlH₄ at -78°C provided the requisite trans-16β,17α-diol 7 in 97% yield. Thus, the protected aglycon of OSW-1 (1) was synthesized with eight operations in 48.4% overall yield.

Synthesis of the disaccharide 6 is outlined in Schemes 5, 6, and 7. Thioglycoside 22 was prepared from tetraacetyl-L-arabinose 21 as shown in Scheme 5.

Regioselective protection of the cis-diol 22 followed by protection of the C-2 hydroxy group gave 23 in 90% yield. Deprotection of the acetonephorid affixed 24. Although it is known that the equatorial C-3 hydroxy group in many sugars is more reactive than C-4 axial hydroxy group, surprisingly high selectivity at the C-4 hydroxy group was observed when 24 was treated with TESOTf and lutidine at low temperature affording the desired product 25 in 90% yield.
The thio ortho ester 28 was prepared from tetraacetyl-D-xylose 26 as shown in Scheme 6.\(^{21}\)

![Chemical structures](image)

Protecting-group manipulations followed by zinc chloride promoted intramolecular ring-opening of the thio ortho ester 30 gave thioglycoside 31 in excellent yield. After deacetylation, the p-methoxy benzyol group was introduced, and 33 was converted to 34 in 84%.\(^{21}\)

Glycosylation of 25 with 34 afforded the β-disaccharide 35 which was converted to 6 as shown in Scheme 7.

![Chemical structures](image)

Coupling of 6 with the steroid aglycone 7 under standard conditions\(^{22}\) gave compound 36 in 71% yield. Removal of all of the protecting groups by sequential treatment of compound 36 with DDQ and bis-(acetonitrile) dichloropalladium(II) in one operation afforded OSW-1 (1) in 81% yield. The physical data of synthetic OSW-1 (1) were identical to those reported by Sashida.\(^{10}\)

The new strategy provides stereoselective introduction of the steroid side chain via 1,4-addition of an α-alkoxy vinyl cuprate to 17(20)-en-16-one steroids. On the basis of the strategy, the highly potent anti-tumor natural product OSW-1 (1) was synthesized in 10 linear operations from 10 in 28% overall yield.

Additional supporting experimental information, such as spectral characterizations, is available at [http://pubs.acs.org](http://pubs.acs.org). The foregoing literature references of this section are listed below.
The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, that is, the prefix C_{n,m} indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus, for example, C_{1,3}alkyl refers to alkyl of one to six carbon atoms, inclusive.

The compounds of the present invention are generally named according to the IUPAC or CAS nomenclature system. Abbreviations which are well known to one of ordinary skill in the art may be used, for example, “Ph” for phenyl, “Me” for methyl, “Et” for ethyl, “h” for hour or hours and “r” for room temperature.

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

Specifically, C_{1,3}alkyl may be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, and all isomers thereof; C_{1,8}alkyl may be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, hexyl, and all isomers thereof; C_{1,3}alkoxycarbonyl can be, for example, acetoxy, propanoato, butanoyl, pentanoyl, 4-methylpentanoyl, hexanoyl, and all isomers thereof; C_{1,3}alkoxycarbonyl can be, for example, acetoxy, propanoato, butanoyl, pentanoyl, 4-methylpentanoyl, hexanoyl, and all isomers thereof; C_{1,3}alkoxy can be, for example, acetoxyl, propanoyloxy, butanoyloxy, isobutanoxy, pentanoyloxy, hexanoyloxy, and all isomers thereof; aryl can be, for example, phenyl, indenyl, or naphthyl; and heteroaryl can be furyl, imidazolyl, triazolyl, triazinyl, oxazolyl, isoxazolyl, thiiazolyl, isothiazolyl, pyrazolyl, pyrrolidinyl, pyrazinyl, tetrazolyl, pyridyl or its N-oxide, thiophenyl, pyrimidinyl or its N-oxide, indolyl, isoquinolyl or its N-oxide, or quinolyl or its N-oxide, and all isomers thereof.

A specific value for R^1 is —H. Another specific value for R^1 is a hydroxyl protecting group. A specific value for R^1 is the formula —Si(R^1)^3 wherein each R^1 may be independently C_{1,8}alkyl. A specific value for R^1 is —Si(C_3H_3)_3; another specific value for R^2 is —Si(C_3H_3)_3, a specific value for R^2 is hydroxyl protecting group. A specific value for R^2 is aroyl of the formula —C(==O)Ar. A specific value for R^2 is p-methoxybenzoyl. Another value for R^2 is —C(==O)Ar. A specific value for R^2 is (E)-cinnamoyl. Another specific value for R^2 is (Z)-cinnamoyl. A specific value for R^2 is a hydroxyl protecting group. A specific value for R^2 is alkyl. Another specific value for R^2 is cycloalkyl. Another specific value for R^2 is C_{6}cycloalkyl, that is, cyclohexyl. A specific value for R^2 is an enolic hydroxyl protecting group. A specific value for R^2 is an alkanyl. Another specific value for R^2 is acetyl. Another specific value for R^2 is propanoyl. Another specific value for R^2 is butanoyl. A specific value for R^2 is a hydroxyl protecting group. A specific value for R^2 is an —C(==O)Ar. Another specific value for R^2 is a benzoyl. Another specific value for R^2 is a mono-methoxy substituted benzoyl.
Another more specific value for R² is a di-methoxy substituted benzyol.
Another more specific value for R³ is p-methoxy substituted benzyol.
A specific value for X is a leaving group
A more specific value for X is —SO₂
Another more specific value for X is —SPh.
A specific value for —OR₁ is a leaving group.
A more specific value for —OR₁ is an acetimidate.
Another more specific value for —OR₁ is —OC(NH)CCl₃.
A specific value for R₈ or R₉ is a hydroxyl protecting group.
A more specific value for R₈ or R₉ is an —C(=O)—Ar.
Another more specific value for R₈ or R₉ is a benzoyl.
Another more specific value for R₈ or R₉ is a mono-methoxy substituted benzyol.
Another more specific value for R₈ or R₉ is a di-methoxy substituted benzyol.
Another more specific value for R₈ or R₉ is p-methoxy substituted benzyol.
A specific value for R₁₀ is C₆H₄-Rₐ alkyl.
A more specific value for R₁₀ is —CH₂—CH(CH₃)₂.
A specific value for —OR₂ is a leaving group.
A more specific value for —OR₂ is an acetimidate.
Another more specific value for —OR₂ is —OC(NH)CCl₃.

The invention also provides processes and intermediates useful for preparing compounds of formula (1). For example, intermediates useful for preparing a compound of the formula (1) wherein R₁₀ is hydrogen and R₉ is an aryl or a cinnamoyl group, or a corresponding compound of the formula (1) wherein R₁₀ is a suitable protecting group, such as trialkylsilane. Thus the invention provides a compound of formula (1) wherein R₂ is both a suitable protecting group and is also desired in the final product such as an aryl or a cinnamoyl group. Suitable protecting groups as used herein, as well as methods for their preparation and removal, are well known in the art, for example, see Greene, T. W.; Wutz, P. G. M. “Protecting Groups In Organic Synthesis” 3rd edition, 1999, New York, John Wiley & sons, Inc.

The invention also provides intermediate compounds, for example, of the formulas 6, 7, 9, 15, 18, 20, 25, 34, 35, and 36, among others, and as shown in accompanying preparative schemes hereinafter.

The invention also provides intermediate salts that are useful for preparing or purifying compounds of formula (1). Suitable methods for preparing salts are known in the art and are disclosed herein. As will be apparent to one skilled in the art, such salts can be converted to the corresponding free-base or to another salt using known methods.

The invention also provides a method for preparing a compound of formula (1) wherein R₁₀ is hydrogen comprising deprotecting a corresponding compound of formula (1) in the presence of a second protecting group R₉ wherein both R⁸ and R₉ are suitable protecting groups, and as illustrated herein.

Compounds of the invention can generally be prepared using the illustrated synthetic schemes. Starting materials can be prepared by procedures described in these schemes, the accompanying experimental examples, or by procedures well known to one of ordinary skill in organic chemistry. The variables used in the schemes are as defined below or as in the claims.

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartrate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal, for example, sodium, potassium or lithium, or alkaline earth metal, for example calcium, salts of carboxylic acids can also be made.

Useful dosages of the compounds of formula (1) can be determined by comparing their in vitro activity, and in vivo activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

DESCRIPTION OF PREFERRED EMBODIMENTS

The following examples in conjunction with the accompanying schemes and references provide illustrative and representative synthetic procedures for preparing compounds of the formula (1) and intermediate compounds leading thereto.

EXAMPLE I
Preparation of Compound 12
To a solution of 11 (4.20 g, 33.46 mmol) in dry THF (50 mL) was added n-BuLi (1.38 M, 27.4 mL, 37.8 mmol) at 0° C. The reaction was stirred at 0° C. for 20 min, then was cooled to −60° C. Isobutyl triflate (7.64 g, 37.06 mmol) in CH₂Cl₂ (10 mL) was added drop-wise. The reaction was allowed to gradually warmed up to 25° C. over 2 hours and stirred at 25° C. for 10 hours. Then 30 mL aqueous NaHCO₃ was added and THF was removed. The water layer was extracted with 30 mL hexane 4 times. The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed and the product was purified with Et₃N deactivated silica gel column chromatography to afford 12 (5.13 g, 85%).

EXAMPLE II
Preparation of Compound 13
To the solution of 12 (3.31 g, 21.80 mmol) and anhydrous methanol (0.706 mL, 17.44 mmol) in CH₂Cl₂ (50 mL) was added trimethylsilyl bromide (2.30 mL, 17.44 mmol) drop-wise at −40° C. The reaction solution was stirred at −40° C. for 10 min, then gradually warmed up to room temperature. The solvent was removed to afford 13 which was used without further purification.

EXAMPLE III
Preparation of Compound 14
To a solution of 10 (10 g, 34.7 mmol) and imidazole (2.83 g, 41.6 mmol) in CH₂Cl₂ (100 mL) was added tert-butylsilyl chloride (5.49 g, 36.4 mmol) at 25° C. The reaction solution was stirred at 25° C. for 12 hours and then quenched with saturated aqueous NaHCO₃. The organic layer was separated and the water layer was extracted with 50 mL CH₂Cl₂ three times. The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed and the product was purified by silica gel column chromatography to afford 14 (14.42 g, 99%).
EXAMPLE IV
Preparation of Compound 19
A mixture of ethyltriphenylphosphonium bromide (10 g, 27 mmol) and potassium tert-butoxide (1M in THF, 24.2 mL, 24.2 mmol) in anhydrous THF (30 mL) was stirred at 25° C. for 20 hours. Then 14 (3.95 g, 9.8 mmol) in anhydrous THF (10 mL) was added. After the reaction was stirred at 25° C. for two days, hexane (60 mL) and aqueous methanol (50%, 100 mL) was added. The organic layer was separated and the aqueous layer was extracted with 30 mL of hexane three times. The hexane layer was combined and the solvent was removed. The residue was dissolved in methanol (25 mL) and methyl iodide (1 mL, 16 mmol) was added. The solution was stirred at 25° C. for two hours. The solvent and excess methyl iodide were removed. The residue was partitioned between hexane (100 mL) and water (100 mL). The water layer was extracted with hexane (50 mL) twice and the combined hexane layer was dried with N,N-dimethylformamide. The solvent was removed. The crude product was purified by silica gel column chromatography to afford 15 (3.98 g, 95%).

EXAMPLE V
Preparation of Compound 16
A solution of selenium dioxide (13 mg, 0.12 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was added tert-ButOH (5M, 0.051 mL, 0.237 mmol) at 0° C. The solution was stirred at 0° C. for 15 min until the solid disappeared. 15 (99 mg, 0.234 mmol) was added in one portion. The reaction solution was stirred at 0° C. for 5 hours. The reaction was diluted with 2 mL CH<sub>2</sub>Cl<sub>2</sub> and then quenched with 2 mL aqueous NaOH. The organic layer was separated and the water layer was extracted with 3 mL CH<sub>2</sub>Cl<sub>2</sub>, three times. The combined organic layer was washed with brine and dried with Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed and the product was purified by silica gel column chromatography to afford 16 (100.5 mg, 99%).

EXAMPLE VI
Preparation of Compound 9
A solution of DMF (0.016 mL, 0.23 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL) was added oxaly chloride (0.01 mL, 0.115 mmol) in −50° C., and the solution was stirred at −50° C. for 3 min. 16 (41.1 mg, 0.095 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (0.3 mL) was added. The flask was washed with CH<sub>2</sub>Cl<sub>2</sub> once. The reaction was stirred at −50° C. for 30 min, then Et<sub>3</sub>N (0.066 mL, 0.48 mmol) was added. The reaction was stirred at −50° C. for 10 min, then was allowed to warm up to 25° C. Water (2 mL) was added and the organic layer was separated. The water layer was extracted with 3 mL CH<sub>2</sub>Cl<sub>2</sub> for three times. The combined organic layer was washed with brine and dried with Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed and the product was purified by silica gel column chromatography to afford 9 (40.4 mg, 99%).

EXAMPLE VII
Preparation of Compounds 17, 18, 19
A solution of 13 (17.44 mmol) in dry ether (60 mL) and dry THF (10 mL) was cooled to −78° C., then tert-ButLi (1.71M, 20.4 mL, 34.88 mmol) was added drop-wise. The reaction was stirred at −78° C. for 30 min, and was then cannulated to a clear solution of CuCN (781 mg, 8.72 mmol) and LiCl (740 mg, 17.44 mmol) in THF (20 mL, CuCN and LiCl was stirred for 10 min at 25° C.) at −78° C. After the solution was stirred at −78° C. for 20 min, a solution of 9 (1.22 g, 2.85 mmol) and trimethylsilyl chloride (redistilled, 1.8 mL, 14.25 mmol) in THF (5 mL) was cannulated to the cuprate solution in −78° C. The reaction solution was stirred at −78° C. for 30 min, then was allowed to gradually warmed up to 25° C. To the reaction was added 1 mL triethylamine and diluted with 50 mL hexane. The solution was passed through a short silica gel pad which was precipitated with 5% triethylamine-hexane. The silica gel was washed with ether (10 mL) three times. The solvent was removed to afford crude product 17. Crude 17 was dissolved in 10 mL anhydrous benzene and the benzene was removed. The operation was repeated three times. The reaction mixture was vacuumed for 30 min and then it was dissolved in anhydrous THF (20 mL). Potassium tert-butoxide (1M, 3.42 mL, 3.42 mmol) was added at 0° C. The reaction solution was stirred at 0° C. for 10 min, then was cooled to −30° C. Acetyl chloride (redistilled, 0.3 mL, 4.28 mmol) was added drop-wise. The reaction was stirred at −30° C. for 30 min, and was then allowed to warm up to 25° C. Saturated aqueous NaHCO<sub>3</sub> (20 mL) and ethyl acetate (20 mL) were added. The organic layer was separated and the water layer was extracted with 10 mL ethyl acetate three times. The combined organic layer was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed and the product was purified by silica gel column chromatography to afford 18 (1.274 g, 75% from 9).

EXAMPLE VIII
Preparation of Compound 20
A solution of 19 (118.9 mg, 0.193 mmol) in anhydrous THF (1 mL) was added potassium tert-butoxide (1M, 0.3 mL, 0.3 mmol) at 0° C. After the reaction was stirred at 0° C. for 10 min and cooled to −78° C., it was cannulated to a solution of Davis reagent (87 mg, 0.325 mmol) in anhydrous THF (0.5 mL) in −78° C. The flask was rinsed with THF (0.3 mL) once. The reaction was stirred at −78° C. for 30 min, then 30 mg silica gel was added in −78° C. before it was warmed up to 25° C. The silica gel was filtered and solvent was removed. The product was purified by silica gel chromatography to give 20 (86 mg, 76%).

EXAMPLE IX
Preparation of Compound 7
A solution of 20 (83.4 mg, 0.142 mmol) in anhydrous THF (1 mL) was added LiAlH<sub>4</sub> (1M, 0.071 mL, 0.071 mmol) at −78° C. The reaction solution was stirred at −78° C. for 1 hour and was quenched with ethyl acetate. Saturated aqueous potassium sodium tartrate (3 mL) was added. The organic layer was separated and the water layer was extracted with ethyl acetate (3 mL) for three times. The combined organic layer was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was removed and the product was purified by silica gel column chromatography to afford 7 (84.1 mg, 99%).

EXAMPLE X
Preparation of Compound 22
Dry 1,2,3,4-O-tetraaethyl-L-arabinose (18.3 g, 57.5 mmol) was dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (200 mL) and was
cooled to −78 °C. Thiophenol (6.5 mL, 63.3 mmol) was added followed by addition of SnCl₄ (1M, 17.3 mL, 17.3 mmol). The reaction solution was stirred at −78 °C for 6 hours until the disappearance of the starting material in TLC. Saturated aqueous NaHCO₃ (100 mL) was added. The organic layer was separated and the water layer was extracted with CH₂Cl₂ (30 mL) three times. The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed and the product was purified by silica gel column chromatography to afford thiophenyl-2,3,4-O-triacetyl-L-arabinose (16.95 g, 80%). Thiophenyl-2,3,4-O-triacetyl-L-arabinose (8.88 g, 24.1 mmol) was dissolved in MeOH (120 mL) followed by the addition of sodium methoxide (65 mg, 2 mmol). The reaction solution was stirred at 25 °C for three hours, then saturated aqueous NH₄Cl was added. The organic layer was separated and the water layer was extracted with CH₂Cl₂ (30 mL) three times. The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed and the product was purified by silica gel column chromatography to afford 22 (5.53 g, 22.9 mmol, 95%).

EXAMPLE XI
Preparation of Compounds 23, 24
A solution of 22 (4.85 g, 20.04 mmol) in CH₂Cl₂ (100 mL) was added 2,2-dimethoxypropane (2.96 mL, 24.05 mmol) and CSA (camphor sulfonic acid) (30 mg) at 25 °C. The reaction solution was stirred at 25 °C for 30 min and was quenched with saturated aqueous NaHCO₃ (30 mL). The organic layer was separated and the water layer was extracted with CH₂Cl₂ (20 mL) three times. The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed and the reaction mixture was carefully dried and was dissolved in CH₂Cl₂ (100 mL). Triethylamine (4.2 mL, 30 mmol), acetyl anhydride (2.62 mL, 24 mmol), and DMAP (50 mg) were added. The reaction was stirred at 25 °C for two hours, then was quenched with saturated aqueous NaHCO₃ (30 mL). The organic layer was separated and the water layer was extracted with CH₂Cl₂ (30 mL) for three times. The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed and the product was dissolved in methanol (100 mL) followed by addition of AMBERLITE IR-118H (4 g). The reaction solution was stirred at 25°C for 12 hours and the solid was filtered. The solvent was removed and the product was purified by silica gel column chromatography to afford 24 (5.1 g, 90% from 22).

EXAMPLE XII
Preparation of Compound 25
A solution of 24 (2.22 g, 7.81 mmol) and 2,6-lutidine (1.8 mL, 15.62 mmol) in anhydrous CH₂Cl₂ (200 mL) was cooled to −60 °C. Triethylsilyl triflate (2.1 mL, 9.37 mmol) was added drop-wise. The reaction was stirred at −60 °C for one hour and at −70 °C for another one hour. The reaction was quenched with saturated aqueous NaHCO₃ (50 mL) at −70 °C and was allowed to warm up to 25°C. The organic layer was separated and the water layer was extracted with CH₂Cl₂ (30 mL) for three times. The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed and the product was purified by silica gel column chromatography to afford 25 (2.8 g, 90%).

EXAMPLE XIII
Preparation of Compound 27
Dry 1,2,3,4-O-tetraacetyl-D-xylose (33.4 g, 104.9 mmol) was dissolved in dry CH₂Cl₂ and was cooled to 0 °C. HBr (30% in MeOH, 80 mL) was added slowly by addition funnel. The reaction was stirred at 0 °C for one hour and at 25°C for three hours. The reaction solution was washed first with water (50 mL), then the organic layer was poured into cold saturated aqueous NaHCO₃ with stirring. The organic layer was separated and the water layer was extracted with CH₂Cl₂ (50 mL) three times. The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed to afford 27 (33.088 g, 93%).

EXAMPLE XIV
Preparation of Compound 28
Carefully dried 27 (8.5 g, 23.94 mmol) was dissolved in dry nitromethane (30 mL, distilled over CaH₂) and thiophenol (3.55 mL, 47.89 mmol) and 2,6-lutidine (4.2 mL, 35.91 mmol, distilled over CaH₂) was added. The reaction solution was stirred under nitrogen at 25 °C for 12 hours. The reaction was quenched with saturated aqueous NaHCO₃. The organic layer was separated and the water layer was extracted with CH₂Cl₂ (30 mL) for three times. The combined organic layer was washed with brine and dried with Na₂SO₄. The solvent was removed and the product was purified by silica gel column chromatography to afford 28 (6.29 g, 82%).

EXAMPLE XV
Preparation of Compound 29
To a solution of 28 (3.679 g, 11.48 mmol) in methanol (60 mL) was added sodium methoxide (30 mg, 0.57 mmol). The reaction solution was stirred at 25 °C for 1 hour and methanol was removed to afford 29 (2.750 g, 99%) which was used in the next step without further purification.

EXAMPLE XVI
Preparation of Compound 30
To a solution of 29 (2.714 g, 11.48 mmol) in dry THF (100 mL) was added NaH (60% in mineral oil, 1.45 g, 36 mmol) at 0°C. The reaction solution was stirred at 25°C for 10 min and p-methoxybenzyl chloride (3.3 mL, 24.3 mmol) and tetrabutylammonium iodide (100 mg, 0.27 mmol) were added. The reaction was stirred under reflux for 4 hours and quenched with saturated aqueous NaHCO₃. The organic layer was separated and the water layer was extracted with ethyl acetate (30 mL) three times. The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed and the product was purified by silica gel column chromatography to afford 30 (5.14 g, 98%).

EXAMPLE XVII
Preparation of Compounds 31, 32
To a solution of carefully dried 30 (3.73 g, 8.17 mmol) in dry CH₂Cl₂ (20 mL) was added zinc chloride (1M in ether, 0.5 mL, 0.5 mmol) at −60 °C. The reaction was stirred at −60 °C for 30 min and was warmed up to 0 °C in 30 min. The reaction was quenched with saturated aqueous NaHCO₃. The organic layer was separated and the water layer was extracted with CH₂Cl₂ (15 mL) three times. The combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed to afford crude product 31. The crude 31 was dissolved in methanol (40 mL) and sodium methoxide (22 mg, 0.4 mmol) was added. The reaction was stirred at 25°C for 4 hours. The solvent was removed and the product was purified by silica gel column chromatography to afford 32 (3.4 g, 96% from 30).

EXAMPLE XVIII
Preparation of Compound 33
To a solution of 32 (3.2 g, 7.36 mmol) and triethylamine (1.54 mL, 11.04 mmol) in CH₂Cl₂ (20 mL) was added
23
4-methoxybenzoyl chloride (1.33 mL, 9.57 mmol) and DMAP (45 mg, 0.37 mmol). The reaction was stirred at 25°
C. for 48 hours. A small amount of reaction solution was taken out, quenched with saturated aqueous NaHCO₃ and
diluted with 1 mL CH₂Cl₂. The organic layer was separated and the solvent was removed. The crude mixture was
checked with ¹H-NMR. When the NMR signal of 32 disappeared, the reaction was quenched with saturated aqueous
NaHCO₃. The organic layer was separated and the water layer was extracted with CH₂Cl₂ (30 mL) three times. The
combined organic layer was washed with brine and dried over Na₂SO₄. The solvent was removed and the product was
purified with silica gel column chromatography to afford 33 (4.06 g, 97%).

EXAMPLE XIX
Preparation of Compound 34
To a solution of 33 (2.31 g, 4.06 mmol) in CH₂Cl₂ (25 mL) and water (3 mL) was added NBS (7.95 g, 4.46 mmol) in
one portion. After the reaction was stirred at 25° C. for 1 hour, saturated aqueous Na₂SO₄ was added. The organic
layer was separated and the water layer was extracted with CH₂Cl₂ (15 mL) three times. The combined organic layer
was washed with brine and dried with Na₂SO₄. The solvent was removed and the product was purified with silica gel
column chromatography to afford 34 (555 mg, 95%).

EXAMPLE XX
Preparation of Compound 35
A solution of carefully dried 25 (339 mg, 0.718 mmol), 34 (941 mg, 1.407 mmol) and molecular sieve 4Å powder (150
mg) in dry CH₂Cl₂ (3 mL) was stirred at 25° C. for 15 min, then was cooled to –78° C. BF₃·Et₂O (0.1 mL in CH₂Cl₂, 0.7
mL, 0.07 mmol) was added. The reaction was gradually warmed up to -40° C. and was stirred at -40° C. for 2 hours.
Et₃N (0.1 mL) was added and the reaction solution was filtered. The solvent was removed and the product was
purified by silica gel column chromatography to afford 35 (602 mg, 93%).

EXAMPLE XXI
Preparation of Compound 6
To a solution of 35 (129 mg, 0.143 mmol) in CH₂Cl₂—
H₂O (2 mL, 10:1) was added NBS (31 mg, 0.172 mmol).
The reaction was stirred at 25° C. for two hours and then was quenched with saturated aqueous Na₂SO₄. The organic layer
was separated and the water layer was extracted with CH₂Cl₂ (3 mL) three times. The combined organic layer was
washed with brine and dried over Na₂SO₄. The solvent was removed and the product was purified with silica gel column
chromatography to afford 2-O-acetyl-3-O-(3,4-di-O-(4-
methoxybenzyl)-2-O-(4-methoxybenzyl)-β-D-
D-xylopyranosyl)-4-O-(triethylsilyl)-β-L-arabinopyranose
(93.4 mg, 81%). To a solution of 2-O-acetyl-3-O-(3,4-di-O-(4-
methoxybenzyl)-2-O-(4-methoxybenzyl)-β-D-
D-xylopyranosyl)-4-O-(triethylsilyl)-β-L-arabinopyranose in
dry CH₂Cl₂ (2 mL) was added trichloroacetonitrile (0.068
mL, 0.575 mmol) and DBU (1 drop). The reaction was stirred at 25° C. for 12 hours and the solvent was then
removed. The product was purified by Et₃N deactivated silica gel column chromatography to afford 6 (96.8 mg, 88%).

EXAMPLE XXII
Preparation of Compound 36
A solution of 6 (15.3 mg, 0.026 mmol), 7 (58 mg, 0.061 mmol) and dry molecular sieve 4Å powder (about 30 mg)
in dry CH₂Cl₂ (0.7 mL) was stirred at 25° C. for 15 min, then
was cooled to –20° C. TMSOTf (0.02 M in CH₂Cl₂, 0.16
mL, 0.0032 mmol) was added. The reaction was stirred at
–20° C. for 5 hours and was quenched with 0.1 mL Et₃N.
The solid was filtered and the solvent was removed. The
product was purified with Et₃N deactivated silica gel column
chromatography to afford 36 (30.1 mg, 89%).

EXAMPLE XXIII
Preparation of OSW-1(1)
To a solution of 36 (16.5 mg, 0.012 mmol) in CH₂Cl₂—
H₂O (1 mL, 10:1) was added DDO (8.1 mg, 0.036 mmol).
The reaction mixture was stirred at 25° C. for 12 hours, then
the CH₂Cl₂ was removed and acetone (1 mL) and Pd(CN)₂Cl₂
(0.5 mg) was added. After the reaction was stirred at 25° C. for 2 hours, the solvent was removed and the product was
purified by preparative TLC to afford 1 (8.5 mg, 81%).
All cited publications, patents, and patent documents are
incorporated by reference herein in their entirety. The invention
has been described with reference to various specific
and preferred embodiments and techniques. However, it
should be understood that many variations and modifica-
tions may be made while remaining within the spirit and
scope of the invention.

What is claimed is:
1. A process for preparing a saponin intermediate comprising:

reac[...]

wherein R' is independently —H or a hydroxyl protecting

...
wherein R^4 is an enolic hydroxyl protecting group.

2. The process of claim 1, wherein R^{10} is C_{2-6}alkyl.

3. The process of claim 2, wherein R^{10} is CH\_2-CH(CH\_3)\_2.

4. The process of claim 1, further comprising:
   a) converting the vinyl ether of compound (18) at OR^3 to a corresponding ketal;
   b) generating a corresponding enolate at R^4 of compound (18) wherein R^3 is a metal counter ion; and
   c) oxidizing the resulting enolate to an alpha-hydroxy ketone compound of the formula (20):

5. The process of claim 4, wherein R^{10} is C_{2-6}alkyl.

6. The process of claim 5, wherein R^{10} is CH\_2-CH(CH\_3)\_2.

7. The process of claim 1, further comprising: stereoselectively reducing the ketone of the formula (20) to a diol compound of formula (7):

8. The process of claim 7, wherein R^{10} is C_{2-6}alkyl.

9. The process of claim 8, wherein R^{10} is CH\_2-CH(CH\_3)\_2.

10. A process of claim 7, further comprising preparing a compound of formula (1):

wherein R^2 is independently H or a hydroxyl protecting group, and R^2 is independently —C(==O)—Ar or —C(==O)—CR_1=CR_2=Ar, wherein Ar is independently aryl or heteroaryl, and R_1 and R_2 are each independently —H, C_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxycarbonyl, aryl, (aryl)C_{1-6}alkyl, arykehrbonyl, or aryloxy carbonyl, and R^{10} is C_{2-12}alkyl, comprising:
   a) coupling a compound of the formula (7):

with a compound of the formula (6):

wherein R^6, R^8, and R^9 are each independently a hydroxyl protecting group, and —OR^2 is a leaving group; to form a compound of the formula (36); and

b) deprotecting the compound of formula (36) to afford the compound of formula (1).
11. The process of claim 10, wherein R² is \(-\text{C}_2\text{-alkyl}\).

12. The process of claim 11, wherein R⁰ is \(-\text{CH}_2\text{-CH(CH}_3\text{)}_2\).

13. The process of claim 10, wherein R¹ as a hydroxyl protecting group is of the formula \(-\text{Si(R')}_2\text{O}_3\), wherein each R' is independently \text{C}_1\text{-alkyl}.

14. The process of claim 10, wherein the Ar of \(-\text{C}(\equiv\text{O})\text{-Ar}\) is independently aryl or heteroaryl, optionally substituted with one or more substituents independently selected from halo, \(-\text{OH}, -\text{CN}, -\text{NO}_2, -\text{CF}_3, -\text{OCF}_3, \text{methylene dioxy, C}_1\text{-alkyl, C}_1\text{-alkoxy, phenyl, NR}_2\text{R}, \text{or } -\text{C}(\equiv\text{O})\text{NR}_2\text{R}'\), wherein each R and R' is independently hydrogen, \text{C}_1\text{-alkyl, C}_1\text{-alkanoyl, C}_1\text{-alkoxycarbonyl, aryl, (aryl)C}_1\text{-alkyl, arylcarboxyl, or arylcarboxyl}, or R and R' together with the nitrogen to which they are attached form a pyrrolidino, piperidino, morpholino, or thiomorpholino ring, or a pharmaceutically acceptable salt thereof.

15. The process of claim 10, wherein the Ar of \(-\text{C}(\equiv\text{O})\text{-CR}_2\text{=CR}_2\text{-Ar}\) is independently aryl or heteroaryl, optionally substituted with one or more substituents independently selected from halo, \(-\text{OH}, -\text{CN}, -\text{NO}_2, -\text{CF}_3, -\text{OCF}_3, \text{methylene dioxy, C}_1\text{-alkyl, C}_1\text{-alkoxy, phenyl, NR}_2\text{R}, \text{or } -\text{C}(\equiv\text{O})\text{NR}_2\text{R}'\), wherein each R and R' is independently hydrogen, \text{C}_1\text{-alkyl, C}_1\text{-alkanoyl, C}_1\text{-alkoxycarbonyl, aryl, (aryl)C}_1\text{-alkyl, arylcarboxyl, or arylcarboxyl}, or R and R' together with the nitrogen to which they are attached form a pyrrolidino, piperidino, morpholino, or thiomorpholino ring, or a pharmaceutically acceptable salt thereof.

16. The process of claim 10, wherein R² is independently \text{p-methoxybenzoyl, 3,4-dimethoxybenzoyl, (E)-cinnamoyl, or (Z)-cinnamoyl.}

17. The process of claim 10, wherein R¹ is H, and R² is \text{p-methoxybenzoyl.}

18. The process of claim 1, wherein the 1,4-addition activating agent is trimethylsilylchloride, the R³ enolic hydroxyl protecting group is \(-\text{C}_5\text{-cycloalkyl, and the R⁴ enolic hydroxy protecting group is alkanoyl.}

19. The process of claim 10, wherein the deprotecting to afford the compound of formula (1) comprises sequentially treating the compound of formula (36) with DDQ and bis-(acetonitrile)dichloropalladium(II).

20. The process of claim 1, wherein the compound of the formula (9) is prepared by the steps comprising:

   a) olefinating the ketone of the compound of formula (14); wherein R³ is independently \(-\text{H} \text{ or a hydroxyl protecting group,}

   b) allylic oxidizing the resulting olefin compound to form an allylic alcohol compound of formula (15); and

21. The process of claim 10, wherein the compound of the formula (6) is prepared by the steps comprising:

   a) glycosylating a compound of the formula (25)

   b) oxidizing the allylic alcohol (15) to form a 1,4-enone compound of formula (9):
b) converting X into a leaving group —OR7 of the formula —O—C(==NH)CCl3 to afford the compound of formula (6).

22. The process of claim 21, wherein the leaving group X is —SAr.

* * * * *
It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In column 5, line 36, after “$R^a$” insert --, --.

In column 8, lines 1-9, formula 35, delete “" and insert

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-- , therefor.

In column 10, line 41, delete “99%:” and insert -- 99%: --, therefor.

In column 12, formula 7, delete “" and insert

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-- , therefor.
It is certified that error appears in the above-identifed patent and that said Letters Patent is hereby corrected as shown below:

In columns 11-12, formula 20, delete “

and insert

In column 11, line 31, delete “0.5 h.” and insert -- 0.5 h, --, therefor.

In column 26, line 48, after “R^8” insert --, --.

Signed and Sealed this Twenty-ninth Day of July, 2008

Jon W. Dudas
Director of the United States Patent and Trademark Office