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(71) Applicant: **COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH** [IN/IN]; Anusandhan Bhawan, Rafi Marg, New Delhi 110001 (IN).

(72) Inventors: **REDDY, Dambala Srinivasa**; National Chemical Laboratory, Dr. Homi Bhabha Road, Pune (Maharashtra) 411008 (IN). **HANDORE, Kishore Laxman**; National Chemical Laboratory, Dr. Homi Bhabha Road, Pune (Maharashtra) 411008 (IN).

(74) Agents: **PHILLIPS, Prashant** et al.; Lakshmi Kumaran & Sridharan, B6/10, Safdarjung Enclave, New Delhi 110029 (IN).

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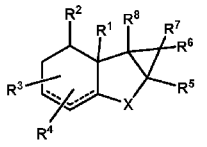
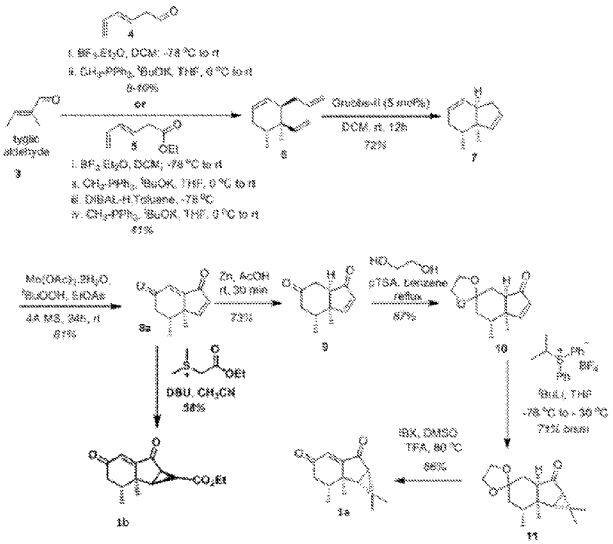
(54) Title: TRICYCLIC COMPOUNDS AND PROCESS FOR PREPARATION THEREOF



(I)



Scheme: 1

(57) Abstract: The present invention discloses tricyclic compounds of formula (I) or salt thereof and their process for synthesis. Further, the present invention relates to the use of these novel tricyclic compounds of formula (I) or salt thereof as insect repellents.

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TRICYCLIC COMPOUNDS AND PROCESS FOR PREPARATION THEREOF

FIELD OF THE INVENTION

The present invention relates to tricyclic compounds of formula (I) or salt thereof. Particularly, the present invention relates to process for synthesis of tricyclic compounds of formula (I) or salt thereof. More particularly, the present invention relates to the use of these tricyclic compounds of formula (I) or salt thereof as insect repellents.

BACKGROUND OF THE INVENTION

Nardoaristolones B is a terpenoid derived from aristolane-type sesquiterpenoid. Nardoaristolones B possesses a nor-aristolone sesquiterpenoid skeleton with an unusual 3/4/5 tricyclic ring system.

Repellent substances generally cause insects to be driven away from, or to reject, otherwise insect-acceptable food sources or habitats. Most known repellents are only mildly toxic. A few of the known repellents, in fact, are not active poisons at all but rather prevent damage to plants/animals or articles of manufacture by making insect food sources or living conditions unattractive or offensive. Most current commercial insect repellents contain the synthetic chemical N,N-diethyl-m-toluamide (DEET) as their primary active ingredient. For instance, repellents sold under the major commercial brand names such as Off!®, Deep Woods Off!®, and Cutter® are all DEET based products and comprise 85% of insect repellent sales (Consumer Reports Buying Guide, 1994 Special Year-End Issue).

Article titled "Nootkatone is a repellent for Formosan subterranean termite (Coptotermes formosanus)." By BC Zhu et al. published in *J Chem Ecol.*, 2001; 27(3); 523-31 first time reports nootkatone, a sesquiterpene ketone, isolated from vetiver oil as a strong repellent and toxicant to Formosan subterranean termites. The lowest effective concentration tested was 10 micrograms/g substrate.

Article titled "A General Approach toward Bakkanes: Short Synthesis of (±)-Bakkenolide-A (Fukinanolide)" by DS Reddy published in *Org. Lett.,* 2004, 6 (19), pp 3345–3347 reports an efficient, general, and fully stereo controlled approach to the family of bakkanes. This route highlights a highly diastereoselective Diels–Alder/aldol sequence to furnish the common hydrindane precursor for the synthesis of bakkanes.

Article titled "Ready Access to Functionally Embellished cis-Hydrindanes and cis-Decalins: Protecting Group-Free Total Syntheses of (±)-Nootkatone and (±)-Noreremophilane" by KL Handore et al. published in J. Org. Chem., 2013, 78 (16), pp 8149–8154 reports a simple and efficient synthesis of functionalized cis-hydrindanes and cis-decalins achieved using a sequential Diels–Alder/aldol approach in a highly diastereoselective manner. The article reports ready access to 13 new cis-hydrindanes/cis-decalins, a protecting group-free total synthesis of an insect repellent Nootkatone, and the first synthesis of a Noreremophilane using the shortest sequence.

As the existing repellents are developing resistance and have side effects. Hence, there is a need to identify and develop novel insect repellents to control the spread of various tropical diseases.

OBJECTIVE OF THE INVENTION

The main objective of present invention is to provide a tricyclic compound of formula (I) or salt thereof.

Another objective of present invention is to provide a process for the synthesis of tricyclic compound of formula (I).

Yet another object of present invention is to provide use of tricyclic compound of formula (I) or salt thereof as insect repellent.

BRIEF DISCRPTION OF THE DRAWING

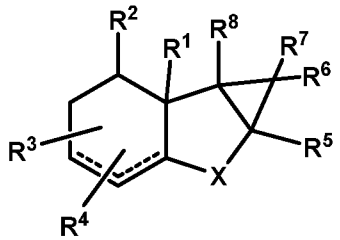
Scheme 1 represents process steps for the synthesis of 3/5/6 tricyclic compounds of formula (I).

Scheme 2 represents process steps for synthesis of 3/5/6 tricyclic compounds of formula (I) from compound of formula 14.

Scheme 3 represents process steps for the synthesis of Nardoaristolone B.

SUMMARY OF THE INVENTION

Accordingly, present invention provides a compound of formula (I)



Formula (I)

wherein,

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 is selected from group consisting of hydrogen, alkyl (C_1 to C_4), COOR, COOH COR, CONRR, CH_2OR, NRR wherein, any two of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 may form a 3 to 8 membered carbocyclic ring which may optionally be substituted or may contain a heteroatom selected from O or N;

X is selected from C=O; C=S or C-R-R;

R is selected from hydrogen, alkyl (C_1 to C_4);

wherein any two R may form a 3 to 8 membered carbocyclic ring which may optionally be substituted or may contain a heteroatom selected from O or N;

'.....' represents a single or double bond;

either of the ring in formula (I) may additionally contain at least one carbonyl group or salt thereof.

In an embodiment of the present invention, the said compounds are selected from the group consisting of:

i. (1aR,1bR,2R,6aS)-1,1,1b,2-Tetramethyl-1,1a,1b,2,3,6a-hexahydro - cyclopropa[a]indene-4,6-dione (1a),
ii. Ethyl(1R,1aS,1bR,2R,6aR)-1b,2-dimethyl-4,6-dioxo-1,1a,1b,2,3,4,6, 6a - octahydrocyclopropa[a]indene-1-carboxylate (1b),
iii. (1aR,6aR)-1,1-Dimethyl-1a,1b,2,3,6,6a-hexahydrocyclopropa[a]-inden-4(1H)-one (1c),
iv. (1aR,6aR)-1,1,5-trimethyl-1a,1b,2,3,6,6a hexahydrocyclopropa[a] inden-4(1H)-one (1d),
v. (1aR,1bS,6aR)-1,1,2-Trimethyl-1a,1b,2,3,6,6a-hexahydrocyclo pro pa[a]inden-4(1H)-one (1e),

vi. (1aR,1bS,6aR)-2-Ethyl-1,1-dimethyl-1a,1b,2,3,6,6a-hexahydrocyclo propa[a] inden-4(1H)-one (1f),

vii. (1aR,1bS,6aR)-1,1-Dimethyl-2-propyl-1a,1b,2,3,6,6a-hexahydrocyclo propa[a]inden-4(1H)-one (1g),

viii. (1aR,1bR,6aR)-1,1,2,2-Tetramethyl-1a,1b,2,3,6,6a-hexahydrocyclopropa[a] inden-4(1H)-one (1h).

In another embodiment, present invention provides a process for the preparation of compound of formula (I) comprising the steps of:

a) adding boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$) to a solution of diene compounds of formula 4 and (*E*)-2-methylbut- 2-enal of formula 3 in Dichloromethane (CH_2Cl_2) followed by stirring the reaction for the period ranging from 10 to 12 h at temperature in the range of -78 °C to 30°C to afford compound of **formula 6**; or

b) adding Grubbs second-generation catalyst to a solution of compound of formula 6 of step (a) followed by stirring the mixture for 22 to 24 h temperature in the range of 25 to 30°C to afford compound of formula **7**;

c) adding Manganese triacetate dehydrate [$Mn(OAC)_3.2H_2O$] and tert-butyl hydroperoxide (^{t}BuOOH) to a solution of compound of formula 7 of step (b) in ethyl acetate (EtOAc) followed by stirring the reaction mixture for 22 to 24 h at temperature 25 to 30 °C to give compound of formula **8a;**

d) adding 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) to a suspension of (ethoxycarbonylmethyl)-dimethylsulfonium bromide in chloroform ($CHCl_3$) to obtain a mixture followed by addition of solution of compound of formula 8a of step (c) in $CHCl_3$ and stirring the reaction mixture to afford compound of formula **1b;**

e) adding zinc dust to a stirred solution of dienedione of formula 8a of step (c) in acetic acid followed by stirring for 20 to 30 min at temperature in the range of 25 to 30°C to afford enone compound of formula **9**;

f) adding ethylene glycol and p-Toluenesulfonic acid (PTSA) to a solution of compound of formula 9 of step (e) in benzene followed by refluxing for 50 to 60

minutes at temperature in the range of 80 to 85°C to afford compound of formula **10**;

g) adding the solution of ^{t}BuLi in pentane and isopropyldiphenylsulfonium tetrafluoroborate in THF to a solution of compound of formula 10 of step (f) followed by cooling the reaction mixture to (-)15 to (-)20 °C for 50 to 60 minutes quenching the reaction mixture to give compound of formula **11**;

h) adding 2-iodoxybenzoic acid (IBX) and trifluoroacetic acid (TFA) to a solution of ketone of formula 11 of step (f) in dimethyl sulfoxide (DMSO) followed by stirring the reaction mixture at 70 to 80 °C for 20 to 24 h to afford compound of formula (I).

In still another embodiment of the present invention, the step (c) is carried out under nitrogen atmosphere.

In yet another embodiment of the present invention, compound 6 of the step (a) may optionally be prepared by the process comprising the steps of:

a. adding $BF_3 \cdot OEt_2$ to a solution of diene of formula 5 and (E)-2-methylbut- 2-enal of formula 3 in CH_2Cl_2 followed by stirring the reaction mixture at 25 °C for 12 hrs to afford aldehyde S-I;

b. adding methyl triphenylphosphonium bromide in tetrahydrofuran (THF) and potassium tert-butoxide to aldehyde S-I of step (a) followed by stirring at 0 °C for 1 h to afford ester S-II;

c. adding diisobutylaluminium hydride (DIBAL)in toluene to a solution of compounds of step (b) in toluene at -78 °C with constant stirring to afford compound of formula aldehyde S-III;

d. Adding methyl triphenylphosphonium bromide in tetrahydrofuran (THF) and potassium tert-butoxide to aldehyde S-I of step (a) followed by stirring at 0 °C for 1 h to afford 6.

In yet another embodiment of the present invention, the process further comprises adding a solution of tert-Butyllithium (^{t}BuLi) in pentane and isopropyldiphenylsulfonium tetrafluoroborate in THF to a solution of compound of formula 8a of step (c) followed by cooling the mixture to -30 °C for 1 h to afford Nardoaristolone B.

In yet another embodiment, present invention provides a process for the preparation of compound of formula (I) comprises adding potassium tert-butoxide (KO^tBu) and ketone compound to a stirred solution of compound of formula 14 **((1R,5S)-6,6-dimethylbicyclo[3.1.0]hexan-3-one)** and sodium sulfate (Na_2SO_4) in tertiary butanol followed by stirring the reaction mixture for the period ranging from 0.5 h – 6 h at temperature 25 °C - 60 °C to afford compounds of formula (I).

In yet another embodiment, present invention provides a process for the preparation of compounds of formula (I), wherein ketone compounds is selected from methyl vinyl ketone, pent-1-en-3-one, (E)-pent-3-en-2-one, (E)-hex-3-en-2-one, (E)-hept-3-en-2-one, 4-methylpent-3-en-2-one.

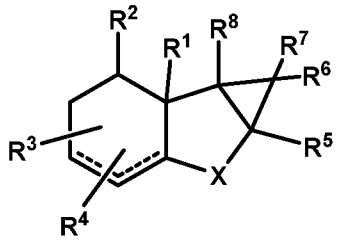
In yet another embodiment of the present invention, the compounds of formula (I) are useful as insect repellents.

In yet another embodiment of the present invention, the protection period of the compounds of formula (I) against mosquito bites is in the range of 1.23 h to 6.46 h at the concentration in the range of 0.25 to 0.50 mg/cm^2.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides tricyclic compounds of formula (I) and process of synthesis thereof which are useful as insect repellents.

The present invention provides 3/5/6 tricyclic compounds of formula (I),



Formula (I)

wherein,

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 is selected from the group consisting of hydrogen, alkyl (C_1-C_4), COOR, COOH, COR, CONRR, CH_2OR, NRR;

wherein any two of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 may form a 3 to 8 membered carbocyclic ring which may optionally be substituted or may contain a heteroatom selected from O or N;

X is selected from C=O; C=S or CRR;

R is selected from hydrogen, alkyl (C_1-C_4);

wherein any two R may form a 3 to 8 membered carbocyclic ring which may optionally be substituted or may contain a heteroatom selected from O or N;

'.....' represents a single or double bond;

Either of the ring in formula (I) may additionally contain at least one carbonyl group or salt thereof.

The tricyclic compounds of formula (I) are selected from the group consisting of:

(1aR,1bR,2R,6aS)-1,1,1b,2-Tetramethyl-1,1a,1b,2,3,6a-hexahydro -cyclopropa[a]indene-4,6-dione (1a),

Ethyl(1R,1aS,1bR,2R,6aR)-1b,2-dimethyl-4,6-dioxo-1,1a,1b,2,3,4,6, 6a - octahydrocyclopropa[a]indene-1-carboxylate (1b),

(1aR,6aR)-1,1-Dimethyl-1a,1b,2,3,6,6a-hexahydrocyclopropa[a]-inden-4(1H)-one (1c),

(1aR,6aR)-1,1,5-trimethyl-1a,1b,2,3,6,6a hexahydrocyclopropa[a] inden-4(1H)-one (1d),

(1aR,1bS,6aR)-1,1,2-Trimethyl-1a,1b,2,3,6,6a-hexahydrocyclo pro pa[a]inden-4(1H)-one (1e),

(1aR,1bS,6aR)-2-Ethyl-1,1-dimethyl-1a,1b,2,3,6,6a-hexahydrocyclo propa[a] inden-4(1H)-one (1f),

(1aR,1bS,6aR)-1,1-Dimethyl-2-propyl-1a,1b,2,3,6,6a-hexahydrocyclo propa[a]inden-4(1H)-one (1g),

(1aR,1bR,6aR)-1,1,2,2-Tetramethyl-1a,1b,2,3,6,6a-hexahydro cyclo propa[a]inden-4(1H)-one (1h).

The present invention provides a process for the synthesis of 3/5/6 tricyclic compounds formula (I) from tiglic aldehyde comprising the steps of:

a) adding boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$) to a solution of diene compounds of formula 4 and (*E*)-2-methylbut- 2-enal of formula 3 in Dichloromethane (CH_2Cl_2) to afford compound of formula 6; or

Adding $BF_3 \cdot OEt_2$ to a solution of diene of formula 5 and (*E*)-2-methylbut- 2-enal of formula 3 in CH_2Cl_2 followed by addition of methyl triphenylphosphonium bromide in dry tetrahydrofuran (THF) and potassium tert-butoxide to the reaction mixture followed by addition of diisobutylaluminium hydride (DIBAL-H) to afford compound of formula 6;

b) adding Grubbs second-generation catalyst to a solution of compound of formula 6 of step (a) to afford compound of formula 7;

c) Adding Manganese triacetate dehydrate $[Mn(OAC)_3.2H_2O]$ and tert-butyl hydroperoxide (^{t}BuOOH) to a solution of compound of formula 7 of step (b) in ethyl acetate (EtOAc) followed by stirring the reaction mixture to give compound of formula 8a;

d) adding 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) to a suspension of (ethoxycarbonylmethyl)-dimethylsulfonium bromide in chloroform ($CHCl_3$) to obtain a mixture followed by addition of solution of compound of formula 8a of step (c) in $CHCl_3$ and stirring the reaction mixture to give compound of formula **1b;**

e) adding zinc dust to a stirred solution of dienedione of formula 8a of step (c) in acetic acid to give compound of formula **9**;

f) adding ethylene glycol and p-Toluenesulfonic acid (PTSA) to a solution of compound of formula 9 of step (d) followed by refluxing and quenching to give compound of formula **10**;

g) adding the solution of ^{t}BuLi in pentane and isopropyldiphenylsulfonium tetrafluoroborate in THF to a solution of compound of formula 10 of step (e) and quenching the reaction mixture to give compound of formula **11**;

h) adding 2-iodoxybenzoic acid (IBX) and TFA to a solution of ketone of formula 11 of step (f) in dimethyl sulfoxide (DMSO) and stirring the reaction mixture followed by quenching to give compound of formula (I).

The above process for the synthesis of 3/5/6 tricyclic compounds of formula (I) is shown in scheme 1.

The present invention provides the process for synthesis of 3/5/6 tricyclic compounds of formula (I) from compound of formula 14

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comprising the steps of:

a) adding potassium tert-butoxide (KO^tBu) and ketone compound to a stirred solution of compound of formula 14 and sodium sulfate (Na_2SO_4) in dry tertiary butanol to obtain the reaction mixture;

b) stirring the reaction mixture for the period ranging from 0.5 h – 6 h at temperature 25 °C - 60 °C followed by quenching to give compound of formula (I).

c) The ketone compound is selected from methyl vinyl ketone, pent-1-en-3-one, (E)-pent-3-en-2-one, (E)-hex-3-en-2-one, (E)-hept-3-en-2-one, 4-methylpent-3-en-2-one.

The above process for synthesis of 3/5/6 tricyclic compounds is as shown in Scheme 2.

The present invention provides a process for the synthesis of Nardoaristolone B comprising the steps of:

a) Adding boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) to a solution of diene compounds of formula 4 and (*E*)-2-methylbut- 2-enal of formula 3 in dry CH_2Cl_2 to give compound of formula 6; or

b) Adding $BF_3{\cdot}OEt_2$ to a solution of diene of formula 5 and (*E*)-2-methylbut- 2-enal of formula 3 in dry Dichloromethane (CH_2Cl_2) followed by addition of suspension of methyl triphenylphosphonium bromide in dry THF and potassium tert-butoxide to the reaction mixture followed by addition of Diisobutylaluminium hydride (DIBAL) to give compound of formula **6**;

c) Adding Grubbs' second-generation catalyst to a solution of compound of formula 6 of step (a) to give compound of formula **7**;

d) Adding molecular sieves, Manganese triacetate dehydrate [$Mn(OAC)_3.2H_2O$] and tert-butyl hydroperoxide (^{t}BuOOH) to a solution of compound of formula 7 of step (b) in ethyl acetate (EtOAc) followed by stirring the reaction mixture to give compound of formula **8a;**

e) Adding a solution of tert-Butyllithium (^{t}BuLi) in pentane and isopropyldiphenylsulfonium tetrafluoroborate in THF to a solution of compound of formula 8a and quenching the resulting mixture to give desired product Nardoaristolone B.

The above process is shown in Scheme 3.

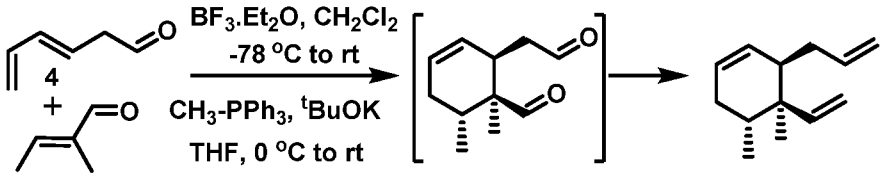
The tricyclic compounds of present invention are used as insect repellents.

Examples

Following examples are given by way of illustration and therefore should not be construed to limit the scope of the invention.

Example 1

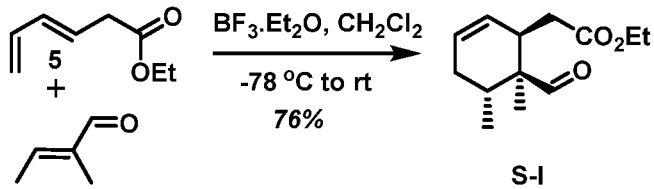
1a) Synthesis of (3*R*,4*S*,5*R*)-3-allyl-4,5-dimethyl-4-vinylcyclohex-1-ene (6)



To a solution of diene **4** (100 mg, 0.892 mmol) and (*E*)-2-methylbut- 2-enal (0.18 mL, 1.78 mmol) in dry CH_2Cl_2 (20 mL) was added $BF_3{\cdot}OEt_2$ (0.16 mL, 0.16 mmol) dropwise at –78 °C. The mixture was allowed to warm to 25 °C and was stirred for 10 h at same temperature. The CH_2Cl_2 layer was washed with saturated $NaHCO_3$ (3 X 10 mL) followed by H_2O (5 mL) and brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material obtained after the removal of solvent was immediately used for next step. To a suspension of methyl triphenylphosphonium bromide (640 mg, 1.78 mmol) in dry THF (10 mL) was added potassium tert-butoxide (200 mg, 1.78 mmol) at 0 °C. After 30 minutes, the solution became canary yellow color, to that above crude bis-aldehyde in THF (10 mL) was added and allowed to stirr at 0 °C for 1 h. The reaction was quenched with NH_4Cl (5.0 ml) and extracted with petroleum ether (2 X 30 mL). Combined organic layer was washed with water (15 mL), brine (15 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel 100–200, petroleum ether) afforded **6** (15 mg, 10%) as colorless oil. ^{1}H NMR

(400 MHz, $CDCl_3$) δ 6.01–5.94 (m, 1 H), 5.86–5.77 (m, 1 H), 5.62–5.61 (m, 2 H), 5.05–4.99 (m, 4 H), 2.31–2.19 (m, 2 H), 1.91–1.84 (m, 2 H), 1.72–1.64 (m, 2 H), 1.03 (s, 3 H), 0.86 (d , *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 138.3, 129.1, 125.1, 115.7, 112.3, 43.9, 40.9, 35.8, 35.1, 31.6, 19.3, 16.4; HRMS (ESI) calcd for $C_{13}H_{20}$[M-H] 175.1481, found 175.1480.

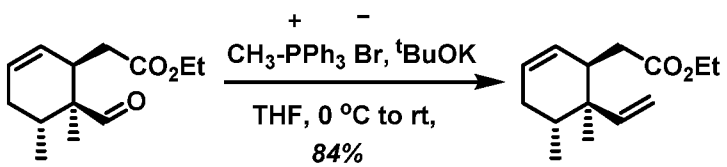
1b) Synthesis of Ethyl 2-((1*R*,5*R*,6*S*)-6-formyl-5,6-dimethylcyclohex-2-en-1-yl) acetate (S-I):



S-I

To a solution of diene **5** (6.0 g, 0.042 mol) and (*E*)-2-methylbut- 2-enal (10.3 mL, 0.107 mmol) in dry CH_2Cl_2 (200 mL) was added $BF_3{\cdot}OEt_2$ (10.6 mL, 0.085 mol) dropwise at –78 °C. The mixture was allowed to warm to 25 °C and was stirred for 12 h at same temperature. The CH_2Cl_2 layer was washed with saturated $NaHCO_3$ (3 X 50 mL) followed by H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude material obtained after the removal of solvent was purified by column chromatography (silica gel 100–200, 1.0:9.0 ethyl acetate: petroleum ether) to afford **S-I** (7.3 g, 76%) as light yellow oil. IR (neat, cm^{-1}) 2978, 1732, 1174; ^1H NMR (400 MHz, $CDCl_3$) δ = 9.60 (s, 1H), 5.71–5.66 (m, 1H), 5.64–5.97 (m 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 2.65–2.59 (m, 1H), 2.45 (dd, *J* = 5.4 Hz, 15.8 Hz, 1H), 2.37–2.30 (m, 1H), 2.25–2.18 (m, 1H), 2.17–2.05 (m, 1H), 1.79–1.72 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.08 (s, 3H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 206.6, 172.6, 127.4, 126.1, 60.4, 49.6, 37.6, 35.6, 30.65, 29.5, 15.7, 15.6, 13.9;

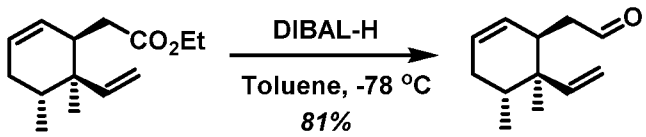
1c) Synthesis of Ethyl 2-((1*R*,5*R*,6*S*)-5,6-dimethyl-6-vinylcyclohex-2-en-1-yl) acetate (S-II):



S-I S-II

To a suspension of methyl triphenylphosphonium bromide (26.8 g, 0.075 mol) in dry THF (60 mL) was added potassium tert-butoxide (7.6 g, 0.068 mol) at 0 °C. After 30 minutes, the solution became canary yellow color, to that aldehyde **S-I** (5.1g, 0.022 mol) in THF (30 mL) was added and allowed to stirred at 0 °C for 1 h. The reaction was quenched with brine (30 ml) and extracted with ethyl acetate (2 X 50 mL). Combined organic layer was washed with water (30 mL), brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel 100–200, 0.5:9.5 ethyl acetate:petroleum ether) afforded **S-II** (4.2 g, 84%) as light brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.86 (dd, J = 11.0 Hz, 18.3 Hz, 1 H), 5.65–5.53 (m, 2 H), 5.06–5.05 (m, 1 H), 5.03–5.02 (m, 1 H), 4.15–4.09 (q, 2 H), 2.48–2.39 (m, 2 H), 2.23–2.18 (m, 1 H), 2.12–2.07 (m, 1 H), 1.82–1.73 (m, 2 H), 1.25 (t, J = 7.3 Hz, 3 H), 1.02 (s, 3 H), 0.87 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.7, 145.2, 128.6, 126.2, 113.3, 60.4, 41.2, 40.5, 36.7, 34.4, 31.5, 18.8, 16. 4, 14.4. HRMS (ESI) calcd for $C_{14}H_{22}O_2Na^+$ 245.1512, found 245.1508.

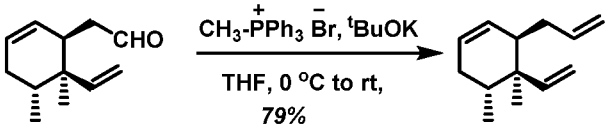
1d) Synthesis of 2-((1*R*,5*R*,6*S*)-5,6-Dimethyl-6-vinylcyclohex-2-en-1-yl) acetaldehyde (S-III):



S-II S-III

To a solution of ester **S-II** (0.5 g, 2.27 mmol) in dry distilled toluene (15 mL) was added DIBAL (1.0 M in toluene, 1.36 mL, 1.36 mmol) at -78 °C dropwise. Stirred at this temperature for 10 min and then added DIBAL (1.0 M in toluene, 1.13 mL, 1.13 mmol) at -78 °C dropwise. After stirring at the same temperature for 0.5 h, the reaction was quenched with methanol (3 mL), diluted with Et_2O (20 mL) and sat. Na/K tartrate (15 mL). The solution was stirred at 25 °C for 2 h. Extracted the solution with ethyl acetate (3 x 20 mL), and the combined extracts were dried over Na_2SO_4. The crude mixture was passed through small bed of silica gel and eluted with 20% ethyl acetate: petroleum ether. The eluent was concentrated *in vacuo* to give the aldehyde **S-III** (0.33 g, 81 %) as a colorless oil which is immediately used for next step.

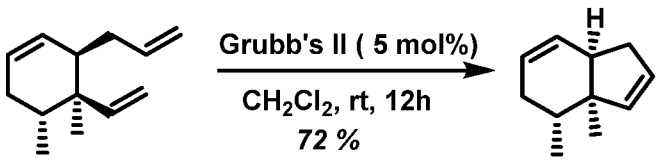
1e) Synthesis of (3*R*,4*S*,5*R*)-3-allyl-4,5-dimethyl-4-vinylcyclohex-1-ene (6)



S-III 6

To a suspension of methyl triphenylphosphonium bromide (14.5 g, 0.040 mol) in dry THF (40 mL) was added potassium tert-butoxide (4.1 g, 0.037 mol) at 0 °C. After 30 minutes, the solution became canary yellow color, to that aldehyde **S-III** (2.2 g, 0.012 mol) in THF (20 mL) was added and allowed to stirred at 0 °C for 1 h. The reaction was quenched with NH_4Cl (20 ml) and extracted with petroleum ether (2 X 60 mL). Combined organic layer was washed with water (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel 100–200, petroleum ether) afforded **6** (1.7 g, 79%) as colorless oil. Spectral data was identical with that of above compound **6.**

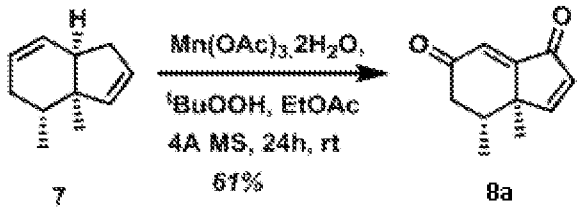
1f) Synthesis of (3a*R*, 4R, 7aR)-3a, 4-Dimethyl-3a,4,5,7a-tetrahydro-1H-indene (7)



6 7

To a solution of **6** (2.0 g, 0.011 mol) in dry CH_2Cl_2 (100 mL) was added Grubbs' second-generation catalyst (480 mg, 5 mol %) at 25 °C . After stirring for 24 h, reaction mixture was filtered through celite and filtrate was concentrated *in vacuo*. The crude material obtained after the removal of solvent was purified by column chromatography (silica gel 100–200, petroleum ether) to afford **7** (1.2 g, 72%) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 5.79–5.72 (m, 2 H), 5.69–5.66 (m, 2 H), 2.56–2.49 (m, 1 H), 2.25–2.20 (m, 1 H), 2.11–2.04 (m, 1 H), 1.93–1.87 (m, 1 H), 1.78–1.69 (m, 1 H), 1.63–1.56 (m, 1 H), 0.92 (s, 3 H), 0.90 (d , J = 6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 129.3, 128.5, 125.9, 48.0, 47.7, 38.9, 34.1, 31.05, 18.7, 15.8;

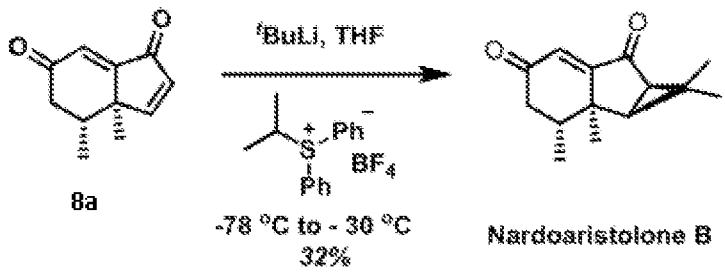
1g) Synthesis of (3aR, 4R)-3a, 4-dimethyl-1, 6-dioxo-3a, 4, 5, 6-tetrahydro-1H-inden-2-ylium (8a)



7 8a

To a solution of diene **7** (1 g, 6.75 mmol) in EtOAc (100 mL) were added 4Å molecular sieves (2 g) and ^{t}BuOOH (5.0 M in decane, 6.7 mL, 33.7 mmol) at room temperature. The reaction mixture was stirred for 30 min before $Mn(OAc)_3.2H_2O$ (905 mg, 3.37 mmol) was added at 25 °C . The resulting mixture was stirred at room temperature (25-30 °C) an under nitrogen atmosphere for 24 h before it was filtered through celite, eluted with EtOAc (30 mL) and concentrated in *vacuo*. The crude material obtained after the removal of solvent was purified by column chromatography (silica gel 100–200, 2: 8 ethyl acetate: petroleum ether) to afford **8a** and mono oxidised mixture which was again oxidised using similar reaction condition to give the **9** (725 mg, 61%) as yellow solid. Mp: 70–72 °C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 5.9 Hz, 1 H), 6.35 (d, J = 5.9 Hz, 1 H), 6.27 (s, 1 H), 2.50–2.46 (m, 2 H), 2.27–2.21 (m, 1 H), 1.22 (s, 3 H), 1.13 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 195.8, 165.0, 160.4, 133.6, 121.8, 46.5, 42.8, 36.3, 18.4, 15.0 ; HRMS (ESI) calcd for $C_{11}H_{13}O_2[M+H]^+$ 177.0910, found 177.0909.

1h) Synthesis of (1a*S*,1b*R*,2*R*,6a*R*)-1,1,1b,2-Tetramethyl-1,1a,1b,2,3,6a-hexahydrocyclopropa[a]indene-4,6-dione (Nardoaristolone B)



8a Nardoaristolone B

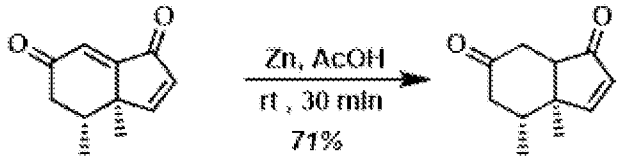
A 1.6 M solution of ^{t}BuLi in pentane (0.55 mL, 0.852 mmol) was added dropwise to a suspension of isopropyldiphenylsulfonium tetrafluoroborate (296 mg, 0.937 mmol) in THF (4 mL) at -78 °C. After 30 min, **8a** (50 mg, 0.284 mmol) was added as a solution in THF (2 mL). The resulting mixture was maintained at -30 °C for 1 h, quenched with

saturated aqueous NH_4Cl (2 mL), and allowed to warm to 25 ^oC . The reaction mixture was then extracted with ethyl acetate (3 X 5 mL). Combined organic layer was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel 100–200, 1.5:8.5 ethyl acetate: petroleum ether) afforded **1a Nardoaristolone B** (20 mg, 32%) as yellow solid.

^1H NMR (400 MHz, $CDCl_3$) δ 6.18 (s, 1 H), 2.40–2.23 (m, 3 H), 1.94 (d, *J* =5.6 Hz, 1 H), 1.77 (d, *J* =5.6 Hz, 1 H), 1.17 (s, 3 H), 1.13 (s, 3 H), 1.09 (s, 3 H), 1.06 (d , *J* =6.6 Hz, 3 H); ^{13}C NMR (100 MHz,$CDCl_3$) δ 201.5, 200.0, 165.1, 123.6, 44.3, 42.3, 42.2, 40.3, 35.5, 32.1, 28.8, 20.8, 17.8, 15.8 ; HRMS (ESI) calcd for $C_{14}H_{19}O_2[M+H]^+$ 219.1380, found 219.1377.

Example 2

2a) Synthesis of (3a*R*,4*R*)-3a,4-Dimethyl-4,5,7,7a-tetrahydro-1H-indene-1,6(3aH)-dione (9):

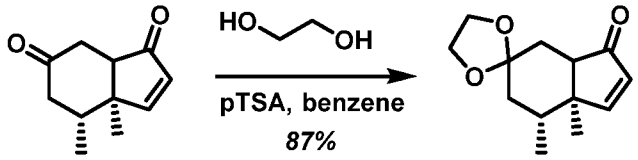


8a 9

To a stirred solution of dienedione **8a** (200 mg, 1.13 mmol) in CH_3COOH (10 mL) at 25 ^oC was added zinc dust (436 mg, 6.81 mmol). The resulting mixture was stirred for 30 min before being filtered on a short pad of Celite and washed with EtOAc (30 mL). The resulting organic layer was concentrated *in vacuo* and the crude obtained was purified on column chromatography (silica gel 100–200, 2.5:7.5 ethyl acetate: petroleum ether) to afford enone **9** (143 mg, 71%) as white solid. Mp: 68–70 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 5.8 Hz, 1 H), 6.17 (d, *J* = 5.8 Hz, 1 H), 2.67–2.62 (m, 1 H), 2.53–2.48 (m, 1 H), 2.32–2.26 (m, 2 H), 2.20–2.14 (m, 1 H), 2.07–2.04 (m, 1 H), 1.16 (s, 3 H), 1.07 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.0, 209.5, 170.5, 131.2, 51.5, 47.0, 43.1, 38.7, 35.1, 19.8, 15.5 ; HRMS (ESI) calcd for $C_{11}H_{14}O_2Na^+$ 201.0886, found 201.0885.

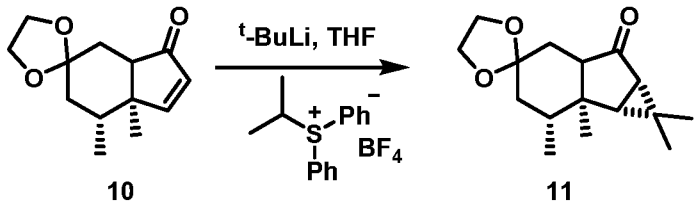
2b) Synthesis of (7*R*,7a*R*)-7,7a-Dimethyl-3a,6,7,7a-tetrahydrospiro[indene-5,2'-[1,3]dioxolan]-3(4H)-one (10)



9 10

To a solution of the **9** (120 mg, 0.674 mmol) in benzene (10 mL) was added ethylene glycol (86 mg, 1.34 mmol) and *p*TSA (12 mg, 0.067 mmol) at room temperature. The reaction was reflux (80-85 °C) for 1 h then quenched by saturated $NaHCO_3$ (3 ml) and extracted with ethyl acetate (3 X 5 mL). Combined organic layer was washed with water (5 mL), brine (5 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel 100–200, 2.0 :8.0 ethyl acetate: petroleum ether) afforded **10** (130 mg, 87%) as white solid.; Mp: 62–64 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 5.8 Hz, 1 H), 6.07 (d, *J* = 5.8 Hz, 1 H), 3.98–3.87 (m, 4 H), 2.21–2.12 (m, 2 H), 1.81–1.77 (m, 1 H), 1.74–1.70 (m, 1 H), 1.66–1.56 (m, 2 H), 1.15 (s, 3 H), 0.96 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 171.1, 130.5, 108.8, 64.4, 64.1, 54.6, 46.6, 39.5, 37.3, 30.1, 18.0, 16.4; HRMS (ESI) calcd for $C_{13}H_{18}O_3Na^+$ 245.1148, found 245.1143.

2c) Synthesis of (1a*R*,1b*R*,2*R*,6a*S*)-1,1,1b,2-Tetramethyloctahydro-6H-spiro[cyclopropa[a]indene-4,2'-[1,3]dioxolan]-6-one (11)



10 11

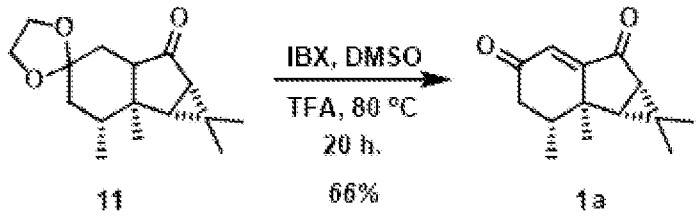
-78 °C, 1h

50%, 71% brsm

A 1.6 M solution of ^{t}BuLi in pentane (0.84 mL, 1.34 mmol) was added dropwise to a suspension of isopropyldiphenylsulfonium tetrafluoroborate (465 mg, 1.47 mmol) in THF (6 mL) at -78 °C. After 30 min, **10** (100 mg, 0.446 mmol) was added as a solution in THF (4 mL). The resulting mixture was maintained at -20 °C for 1 h, quenched with saturated aqueous NH_4Cl (2 mL), and allowed to warm to 25 °C . The reaction mixture was then

extracted with ethyl acetate (3 X 10 mL). Combined organic layer was washed with water (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel 100–200, 1.5 :8.5 ethyl acetate:petroleum ether) afforded **11** (59 mg, 50%, 71% brsm) as white solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99–3.83 (m, 4 H), Hz, 1 H), 2.32–2.28 (m, 1 H), 2.19–2.17 (m, 1 H), 1.94–1.89 (m, 1 H), 1.76 (d, *J* = 5.8 Hz, 1 H), 1.68 (d, *J* = 5.8 Hz, 1 H), 1.50–1.42, (m, 3 H), 1.34 (s, 3 H), 1.12 (s, 3 H), 1.09 (s, 3 H), 0.97 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.8, 107.8, 64.3, 63.9, 53.4, 43.7, 40.5, 40.2, 38.7, 37.2, 29.9, 28.9, 28.2, 18.0, 16.9, 16.4; HRMS (ESI) calcd for $C_{16}H_{24}O_3Na^+$ 287.1618, found 287.1614

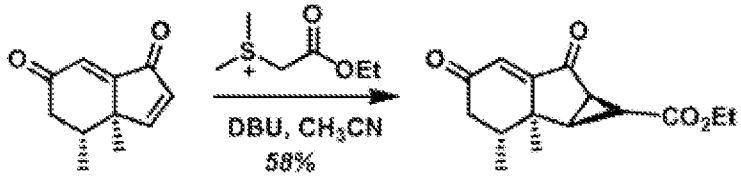
2d) Synthesis of (1a*R*,1b*R*,2*R*,6a*S*)-1,1,1b,2-Tetramethyl-1,1a,1b,2,3,6a-hexahydro -cyclopropa[a]indene-4,6-dione (1a)



To a solution of ketone **11** (40 mg, 0.151 mmol) in DMSO (5 mL) were added IBX (128 mg, 0.454 mmol) and TFA (~1 drop) at 0 °C. After being stirred at 80 °C for 24 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL). The aqueous layer was extracted with EtOAc (3 X 5 mL), the organic layer was washed with saturated aqueous $NaHCO_3$, water (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by column chromatography (silica gel 100–200, 1.5 :8.5 ethyl acetate:petroleum ether) afforded **12** (22 mg, 66%) as yellow solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (s, 1 H), 2.46–2.31 (m, 2 H), 2.19–2.14 (m, 1 H), 2.01 (d, *J* =5.6 Hz, 1 H), 1.94 (d, *J* =5.6 Hz, 1 H), 1.33 (s, 3 H), 1.23 (s, 3 H), 1.22 (s, 3 H), 1.15 (d , *J* =6.6 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 200.1, 165.0, 122.1, 42.5, 41.8, 41.5, 41.4, 40.0, 31.5, 29.1, 20.6, 16.4, 15.0; HRMS (ESI) calcd for $C_{14}H_{19}O_2[M+H]^+$ 219.1380, found 219.1378.

Example 3

Synthesis of Ethyl(1*R*,1a*S*,1b*R*,2*R*,6a*R*)-1b,2-dimethyl-4,6-dioxo-1,1a,1b,2,3,4,6, 6a -octahydrocyclopropa[a]indene-1-carboxylate (1b)

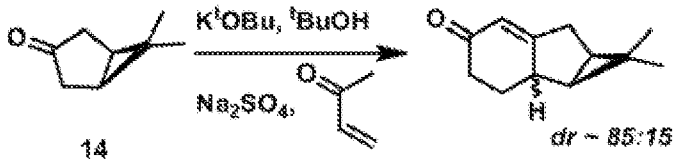


8a 1b

DBU (0.06 mL, 0.426 mmol) was added to a suspension of (ethoxycarbonylmethyl)-dimethylsulfonium bromide (97 mg, 0.426 mmol) in $CHCl_3$ (5.0 mL) at room temperature. After 30 min, compound **8a** (50 mg, 0.284 mmol) in $CHCl_3$ (2.0 mL) was added and the solution was allowed to stir for 16 h at 25 °C. The organic solvents were evaporated and then partitioned between CH_2Cl_2 (10 mL) and water (5 mL). The organic layer was washed with brine, dried over MgSO4, filtered, and concentrated. The residue was purified using silica gel chromatography (silica gel 100–200, 2.5 :7.5 ethyl acetate : petroleum ether) afforded **1b** (43 mg, 58%) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (s, 1 H), 4.09–4.02 (m, 2 H), 2.52–2.48 (m, 1 H), 2.42–2.31 (m, 4 H), 2.28–2.24 (m, 1 H), 1.26 (s, 3 H), 1.19 (t, *J* = 7.0 Hz, 3 H), 1.15 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (100 MHz,$CDCl_3$) δ 199.9, 199.6, 168.8, 161.6, 124.2, 61.9, 43.5, 42.2, 35.4, 35.1, 31.5, 31.0, 21.3, 15.5, 14.0; HRMS (ESI) calcd for $C_{15}H_{18}O_4Na^+$ 285.1097, found 285.1094.

Example 4

Synthesis of (1a*R*,6a*R*)-1,1-Dimethyl-1a,1b,2,3,6,6a-hexahydrocyclopropa[a]-inden-4(1H)-one (1c)



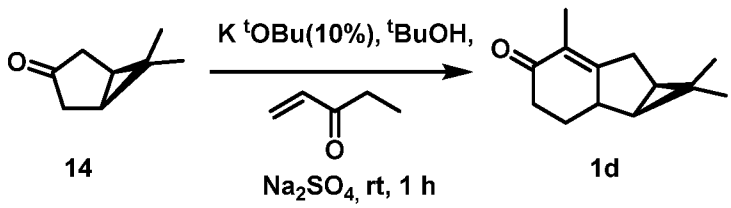
14 1c

To a stirred solution of compound **14** (300 mg, 2.42 mmol) and Na_2SO_4 (1.5 g) in dry *tert* butanol (15 mL) at 25 °C was added catalytic amount of KO^{t}Bu (27 mg, 0.24 mmol) and then methyl vinyl ketone (0.25 mL, 2.90 mmol) slowly in drop wise manner. Stirring was continued for 30 min. Reaction was quenched by the addition of saturated aq.NH_4Cl (5 mL). Organic solvent was evaporated, water (10 mL) and ethyl acetate (15 mL) were added, organic solvent was separated and aqueous layer was extracted with ethyl acetate

(3 X 10 mL), combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. Purification by column chromatography (silica gel 100–200, 1.0:9.0 ethyl acetate : petroleum ether) afforded **1c** (275 mg, 65%) as colourless oil.^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (s, 1 H), 2.70–2.63 (m, 1 H), 2.45–2.34 (m, 3 H), 2.30–2.25 (m, 1 H), 2.21–2.17 (m, 1 H), 2.03–1.98 (m, 1 H), 1.82–1.73 (m, 1 H), 1.33–1.29 (m, 1 H), 1.04 (s, 3 H), 0.99 (s, 3 H); ^{13}C NMR (100 MHz,$CDCl_3$) δ 199.5, 181.1, 120.8, 40.8, 37.8, 34.4, 32.3, 30.4, 29.0, 27.1, 22.8, 14.2. MS: 177.

Example 5

Synthesis of (1aR,6aR)-1,1,5-trimethyl-1a,1b,2,3,6,6a hexahydrocyclopropa[a] inden-4(1H)-one (1d)



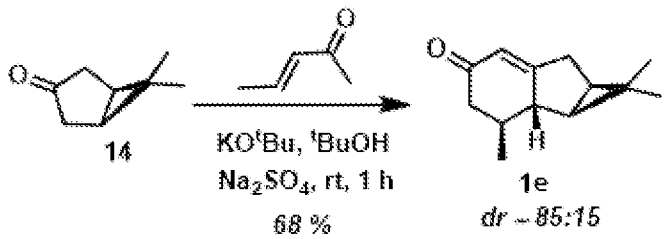
78%

The compound 1d prepared by using similar procedure given in example 3.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.77–2.71 (m, 1 H), 2.51–2.38 (m, 2 H), 2.34–2.24 (m, 2 H), 2.13–2.10 (m, 1 H), 1.78–1.69 (m, 1 H), 1.65 (m, 3 H), 1.31–1.28 (m, 2 H), 1.03 (s, 3 H), 0.97 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 174.2, 126.7, 41.4, 38.4, 34.9, 31.4, 30.3, 29.3, 27.2, 22.1, 14.3, 11.6.

Example: 6

Synthesis of (1a*R*,1b*S*,6a*R*)-1,1,2-Trimethyl-1a,1b,2,3,6,6a-hexahydrocyclo pro pa[a]inden-4(1H)-one (1e)



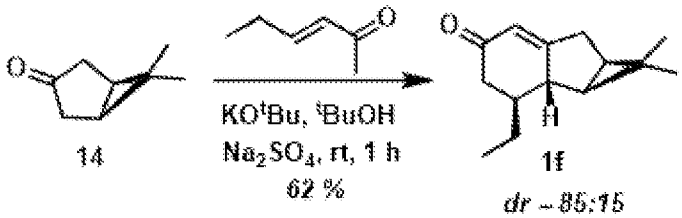
The compound 1d prepared by using similar procedure given in example 3.

IR (film) νmax 1667, 1373, 1236 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (s, 1H), 2.70–2.64 (m, 1H), 2.42–2.34 (m, 2H), 2.03–1.96 (m, 2H), 1.29–1.25 (m, 1H), 1.14–1.12 (m, 1H), 1.11 (d, *J* = 5.9 Hz, 3H), 1.08–1.06 (m, 1H), 1.06 (s, 3H), 0.98 (s, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 200.0, 180.3, 121.2, 48.1, 46.3, 37.0, 32.8, 32.3, 28.6, 27.2, 22.8, 20.7, 14.4; HRMS (ESI) calcd for $C_{13}H_{19}O[M+H]^+$ 191.1430, found 191.1429.

Example 7

Synthesis of (1a*R*,1b*S*,6a*R*)-2-Ethyl-1,1-dimethyl-1a,1b,2,3,6,6ahexahydrocyclo propa[a] inden-4(1H)-one (1f)

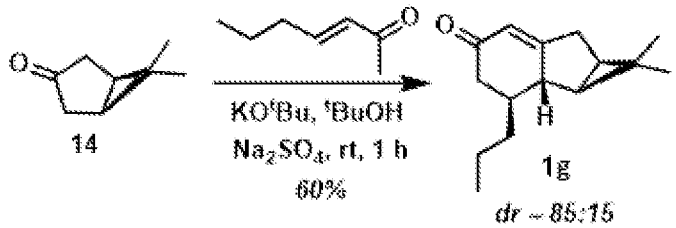


The compound 1d prepared by using similar procedure given in example 3.

IR (film) νmax 1668, 1368, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.71 (s, 1H), 2.70–2.64 (m, 1H), 2.53–2.49 (m, 1H), 2.38–2.34 (m, 1H), 2.11–2.08 (m, 1H), 1.97–1.90 (m, 1H), 1.87–1.82 (m, 1H), 1.77–1.71 (m, 1H), 1.36–1.25 (m, 2H), 1.15–1.13 (m, 1H), 1.06 (s, 3H), 0.98 (s, 3H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.2, 180.6, 121.0, 46.1, 43.1, 42.8, 32.7, 32.3, 28.7, 27.4, 27.3, 22.9, 14.4, 10.6; HRMS (ESI) calcd for $C_{14}H_{21}O[M+H]^+$ 205.1587, found 205.1584.

Example 8

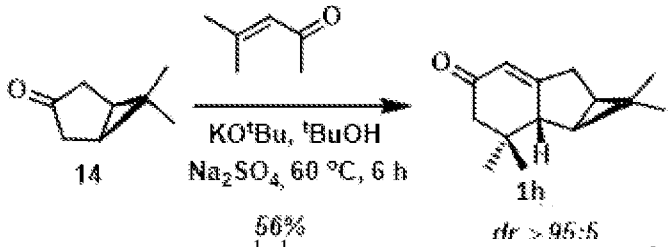
Synthesis of (1a*R*,1b*S*,6a*R*)-1,1-Dimethyl-2-propyl-1a,1b,2,3,6,6a-hexahydrocyclo propa[a]inden-4(1H)-one (1g)



IR(film) νmax 1669, 1351, 1233 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.67 (s, 1H), 2.65–2.60 (m, 1H), 2.49–2.47 (m, 1H), 2.35–2.30 (m, 1H), 2.17–2.10 (m, 1H), 2.06–2.04 (m, 1H), 1.91–1.86 (m, 2H), 1.63–1.59 (m, 1H), 1.43–1.35 (m, 1H), 1.25–1.19 (m, 2H), 1.12–1.10 (m, 1H), 1.03 (s, 3H), 0.95 (s, 3H), 0.89 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.1, 180.5, 121.0, 46.5, 43.4, 41.5, 37.2, 32.8, 32.3, 28.6, 27.3, 22.9, 19.4, 14.4, 14.3; HRMS (ESI) calcd for $C_{15}H_{23}O[M+H]^+$ 219.1743, found 219.1739.

Example 9

Synthesis of (1a*R*,1b*R*,6a*R*)-1,1,2,2-Tetramethyl-1a,1b,2,3,6,6a-hexahydro cyclo propa[a]inden-4(1H)-one (1h)



IR (film) νmax 1668, 1367, 1246 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (s, 1H), 2.71–2.64 (m, 1H), 2.44–2.36 (m, 2H), 2.18 (s, 2H), 1.28–1.26 (m, 1H), 1.13 (s, 3H), 1.11–1.09 (m, 1H), 1.07 (s, 3H), 0.97 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.7, 178.3, 121.4, 53.1, 51.6, 38.5, 32.6, 30.4, 30.0, 28.7, 27.3, 21.8, 19.9, 14.3; HRMS (ESI) calcd for $C_{14}H_{21}O[M+H]^+$ 205.1587, found 205.1583.

Example 10

Protocol adopted for the mosquito repellence bioassay

Methodology

Mosquito repellence activity was assessed on the basis of protection period (hr) offered by various analogues of Nootkatone against Mosquito bites. The protection period was measured on the basis of the concept" time until the first bite" pioneered by Granette (Comparison of mosquito repellency test under laboratory and field conditions. Granett, P. *Proc Ann Meet NJ Mosq Assoc,* 1938, vol. 25, 51,). Repellence tests were carried out against 3-5 days old, blood starved but sucrose fed (0.5M solution), *Ae. aegypti* females mosquitoes , drawn from well-established laboratory colony maintained at 27±1°CTemperatureand 70 ± 5% Relative humidity. The light intensity was regulated at 300-500 lux for testing against laboratory, colonized Ae. aegypti, a day biting mosquito. Human volunteer's hand covered with polythene disposable gloves was introduced in the cage containing about 200 hungry mosquitoes. Mosquitoes were

allowed to bite on the back of the hand through muslin screen stuck over a small window (2cmx2cm) cutout in the polythene bag. Various analogues of Nootkatone were loaded on the muslin cloth screen instead of direct skin application so as to avoid the potential risk involved in the evaluation of natural products of unknown mammalian toxicity. All the test solutions were made in Analar grade Acetone The muslin cloth screen was first

treated with the analogue taking two doses @0.25 mg/cm^2 and 0.5mg/cm^2 and the solvent was evaporated before use. Control muslin screen was treated with solvent alone. After introduction of the hand covered with the polythene glove with the treated muslin screen into the mosquito cage, number of mosquito bites received in subsequent 5 minutes were counted. In the event of no bites in the initial 5 minutes exposure, the test hand was exposed repeatedly after every consecutive ½ hr for 5 minutes test till the time a confirmed bite was received. Number of hours before the receipt of a confirmed bite (Techniques for the evaluation of insect repellents. A critical review (Schreck, C.E, *Ann Rev Entomol,* 1977, vol 22, 101) represented the protection period offered by the test compound. In control rate of mosquito bite was 10-12 bites/ min. Above test were repeated with both male and female human volunteers using different mosquito batches. All the tests were carried out at 27±1 ^{o}C temperature between 9.00 -17.00 hrs.

Protection time offered by Nardoaristolone and its various analogues

Sample	Protection period in hrs @dose 0.25 mg/cm^2	Protection period in hrs @dose 0.50 mg/cm^2
Recemic nardoaristolone B	3.30 ± 0.0708	5.63 ± 0.1778
1a	4.13 ± 0.0626	5.35 ± 0.0868
1b	1.23 ± 0.040	1.40 ± 0.0549
1c	3.60 ± 0.0791	5.30 ± 0.088
1d	5.64±0.1984	6.29 ±0.0844
1e	5.22 ±0.0720	6.46 ±0.1507
1f	1.53 ±0.1223	3.48±0.1396
1g	1.8 ±0.1490	1.99±0.11366
1h	2.19 ±0.0716	2.38±0.07567
Recemic nootkatone	3.12±0.07	5.06±0.06
Natural nootkatone	5.58 ± 0.171	> 7 hrs

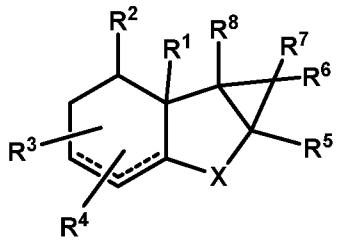
ADVANTAGES OF THE INVENTION

Compounds possess improved efficacy,

Simple processes for synthesis of natural compounds provided

WE CLAIM

1. A compound of formula (I)



Formula (I)

wherein,

R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 is selected from group consisting of hydrogen, alkyl (C_1 to C_4), COOR, COOH COR, CONRR, CH_2OR, NRR wherein, any two of R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8 may form a 3 to 8 membered carbocyclic ring which may optionally be substituted or may contain a heteroatom selected from O or N;

X is selected from C=O; C=S or C-R-R;

R is selected from hydrogen, alkyl (C_1 to C_4);

wherein any two R may form a 3 to 8 membered carbocyclic ring which may optionally be substituted or may contain a heteroatom selected from O or N;

'.....' represents a single or double bond;

either of the ring in formula (I) may additionally contain at least one carbonyl group or salt thereof.

2. The compound as claimed in claim 1, wherein the compounds of formula (I) are selected from the group consisting of:
   i. (1aR,1bR,2R,6aS)-1,1,1b,2-Tetramethyl-1,1a,1b,2,3,6a-hexahydro - cyclopropa[a]indene-4,6-dione (1a),
   ii. Ethyl(1R,1aS,1bR,2R,6aR)-1b,2-dimethyl-4,6-dioxo-1,1a,1b,2,3,4,6, 6a - octahydrocyclopropa[a]indene-1-carboxylate (1b),
   iii. (1aR,6aR)-1,1-Dimethyl-1a,1b,2,3,6,6a-hexahydrocyclopropa[a]-inden-4(1H)-one (1c),
   iv. (1aR,6aR)-1,1,5-trimethyl-1a,1b,2,3,6,6a hexahydrocyclopropa[a] inden-4(1H)-one (1d),

v. (1aR,1bS,6aR)-1,1,2-Trimethyl-1a,1b,2,3,6,6a-hexahydrocyclo pro pa[a]inden-4(1H)-one (1e),

vi. (1aR,1bS,6aR)-2-Ethyl-1,1-dimethyl-1a,1b,2,3,6,6a-hexahydrocyclo propa[a] inden-4(1H)-one (1f),

vii. (1aR,1bS,6aR)-1,1-Dimethyl-2-propyl-1a,1b,2,3,6,6a-hexahydrocyclo propa[a]inden-4(1H)-one (1g),

viii. (1aR,1bR,6aR)-1,1,2,2-Tetramethyl-1a,1b,2,3,6,6a-hexahydrocyclopropa[a] inden-4(1H)-one (1h).

3. The process for the preparation of compounds of formula (I) as claimed in claim 1, wherein said process comprising the steps of:

a) adding boron trifluoride diethyl etherate ($BF_3 \cdot OEt_2$) to a solution of diene compounds of formula 4 and (*E*)-2-methylbut- 2-enal of formula 3 in Dichloromethane (CH_2Cl_2) followed by stirring the reaction for the period ranging from 10 to 12 h at temperature in the range of -78 °C to 30°C to afford compound of **formula 6**; or

b) adding Grubbs second-generation catalyst to a solution of compound of formula 6 of step (a) followed by stirring the mixture for 22 to 24 h temperature in the range of 25 to 30°C to afford compound of formula **7**;

c) adding Manganese triacetate dehydrate [$Mn(OAC)_3.2H_2O$] and tert-butyl hydroperoxide (^{t}BuOOH) to a solution of compound of formula 7 of step (b) in ethyl acetate (EtOAc) followed by stirring the reaction mixture for 22 to 24 h at temperature 25 to 30 °C to give compound of formula **8a;**

d) adding 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) to a suspension of (ethoxycarbonylmethyl)-dimethylsulfonium bromide in chloroform ($CHCl_3$) to obtain a mixture followed by addition of solution of compound of formula 8a of step (c) in $CHCl_3$ and stirring the reaction mixture to afford compound of formula **1b;**

e) adding zinc dust to a stirred solution of dienedione of formula 8a of step (c) in acetic acid followed by stirring for 20 to 30 min at temperature in the range of 25 to 30°C to afford enone compound of formula **9**;

f) adding ethylene glycol and p-Toluenesulfonic acid (PTSA) to a solution of compound of formula 9 of step (e) in benzene followed by refluxing for 50 to 60 minutes at temperature in the range of 80 to 85°C to afford compound of formula **10**;

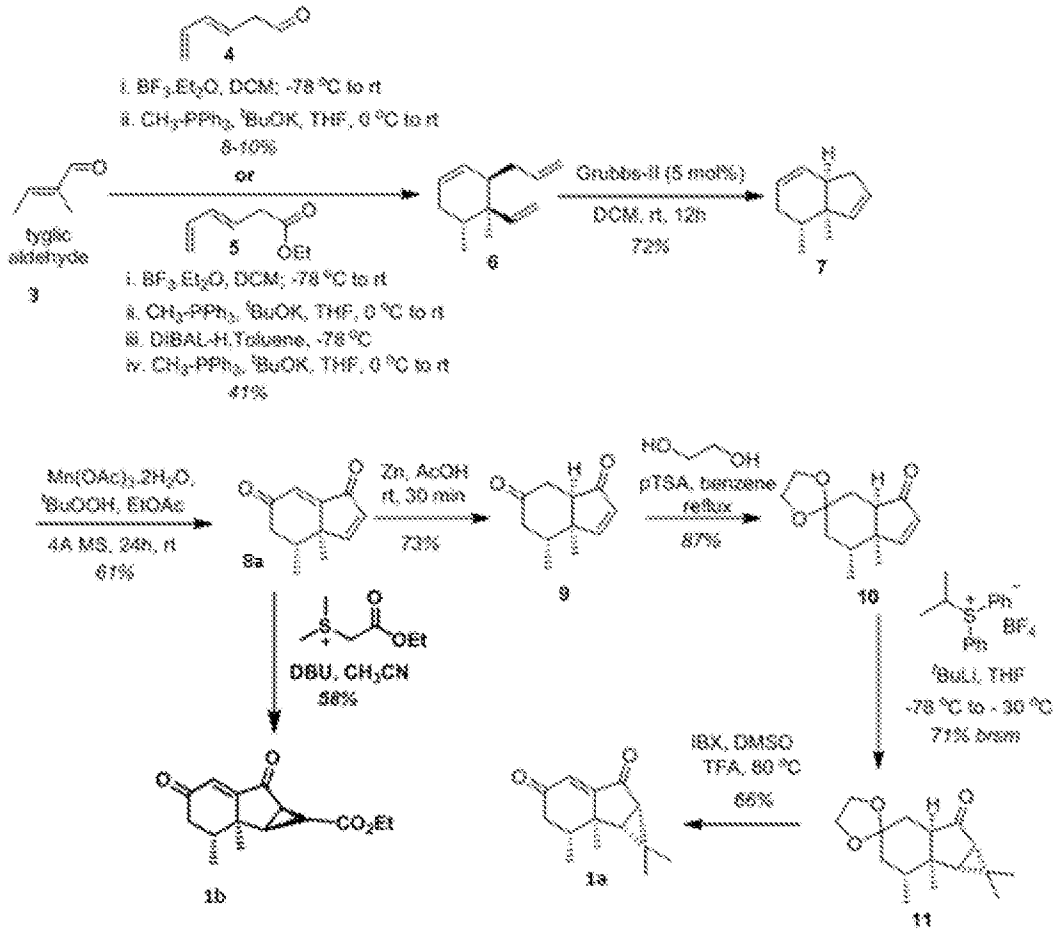
g) adding the solution of ^{t}BuLi in pentane and isopropyldiphenylsulfonium tetrafluoroborate in THF to a solution of compound of formula 10 of step (f) followed by cooling the reaction mixture to (-)15 to (-)20 °C for 50 to 60 minutes quenching the reaction mixture to give compound of formula **11**;

h) adding 2-iodoxybenzoic acid (IBX) and trifluoroacetic acid (TFA) to a solution of ketone of formula 11 of step (f) in dimethyl sulfoxide (DMSO) followed by stirring the reaction mixture at 70 to 80 °C for 20 to 24 h to afford compound of formula (I).

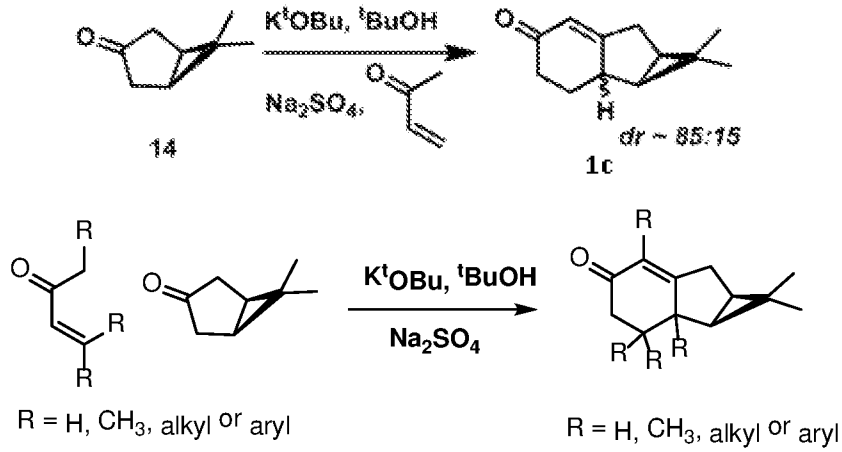
4. The process for the preparation of compounds of formula (I) as claimed in claim 3, wherein the step (c) is carried out under nitrogen atmosphere.
5. The process for the preparation of compounds of formula (I) as claimed in claim 3, wherein the process further comprises adding a solution of tert-Butyllithium (^{t}BuLi) in pentane and isopropyldiphenylsulfonium tetrafluoroborate in THF to a solution of compound of formula 8a of step (c) followed by cooling the mixture to -30 °C for 1 h to afford Nardoaristolone B.
6. The process for the preparation of compounds of formula (I) as claimed in claim 1, wherein said process comprises adding potassium tert-butoxide (KO^{t}Bu) and ketone compound to a stirred solution of compound of formula 14 ((1R,5S)-6,6-dimethylbicyclo[3.1.0]hexan-3-one) and sodium sulfate (Na_2SO_4) in tertiary butanol followed by stirring the reaction mixture for the period ranging from 0.5 h – 6 h at temperature 25 °C - 60 °C to afford compounds of formula (I).

7. The process for the preparation of compounds of formula (I) as claimed in claim 7, wherein ketone compounds is selected from methyl vinyl ketone, pent-1-en-3-one, (E)-pent-3-en-2-one, (E)-hex-3-en-2-one, (E)-hept-3-en-2-one, 4-methylpent-3-en-2-one.
8. The compound as claimed in claim 1, wherein the compounds are used as insect repellents.

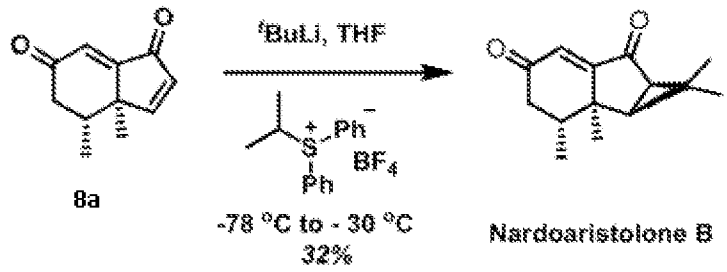
9. The compound as claimed in claim 1, wherein protection period of the compounds of formula (I) against mosquito bites is in the range of 1.23 h to 6.46 h at the concentration in the range of 0.25 to 0.50 mg/cm^2.


4
i. $BF_3.Et_2O$, DCM; -78 °C to rt
ii. CH_3-PPh_3, ^tBuOK, THF, 0 °C to rt
8-10%
or
5
OEt
i. $BF_3.Et_2O$, DCM; -78 °C to rt
ii. CH_3-PPh_3, ^tBuOK, THF, 0 °C to rt
iii. DIBAL-H,Toluene, -78 °C
iv. CH_3-PPh_3, ^tBuOK, THF, 0 °C to rt
41%
cyclic aldehyde
3
6
Grubbs-II (5 mol%)
DCM, rt, 12h
72%
7
$Mn(OAc)_3.2H_2O$,
^tBuOOH, EtOAc
4A MS, 24h, rt
61%
8a
Zn, AcOH
rt, 30 min
73%
9
pTSA, benzene
reflux
87%
10
DBU, CH_3CN
98%
1b
CO_2Et
IBX, DMSO
TFA, 80 °C
66%
1a
^tBuLi, THF
-78 °C to - 30 °C
77% brsm
11

Scheme: 1



Scheme: 2



Scheme: 3

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2015/050074

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C231/12 C07C229/50
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KUTNEY JAMES P ET AL: "THE CHEMISTRY OF THUJONE. XVII. THE SYNTHESIS OF AMBERGRIS FRAGRANCES AND RELATED ANALOGS", CANADIAN JOURNAL OF CHEMISTRY, NRC RESEARCH PRESS, CA, vol. 72, no. 6, 1 January 1994 (1994-01-01), pages 1570-1581, XP009078835, ISSN: 0008-4042, DOI: 10.1139/V94-196 page 1572, compounds 9-12, 14 ----- -/--	1

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search	Date of mailing of the international search report
20 November 2015	30/11/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Beyss-Kahana, Ellen

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KUTNEY, JAMES P.; PIOTROWSKA, KRYSTYNA; CHEN, YONG HUANG; CHENG, KWOK PING, NORMAN; GAO, ZHENYONG; RETTIG, STEVEN J.: "The chemistry of thujone. XV. A versatile route to antifeedants of the polygodial family", CANADIAN JOURNAL OF CHEMISTRY, vol. 68, no. 10, 1990, pages 1698-1708, XP002750933, ISSN: 0008-4042, DOI: 10.1139/v90-264 compounds 6, 12-14, 26	1
X	YUE GUIZHOU ET AL: "Total syntheses of lindenane-type sesquiterpenoids: (+-)-chloranthalactones A, B, F, (+-)-9-hydroxy heterogorgiolide, and (+-)-shizukanolide E", TETRAHEDRON, vol. 68, no. 47, 18 September 2010 (2010-09-18), - 18 September 2012 (2012-09-18), pages 9624-9637, XP028945123, ISSN: 0040-4020, DOI: 10.1016/J.TET.2012.09.053 page 9624, figure 1	1
X	QIAN SHAN ET AL: "Enantioselective total synthesis of (+)-sarcandralactone A", TETRAHEDRON, vol. 69, no. 52, 8 November 2013 (2013-11-08), pages 11169-11173, XP028793507, ISSN: 0040-4020, DOI: 10.1016/J.TET.2013.10.083 page 11170, compound 6	1
X	MOSER, W. H. ET AL.: "Photoreactions of gamma,delta-Unsaturated Chromium CarbeneComplexes", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 118, no. 34, 28 August 1996 (1996-08-28), pages 7873-7880, XP002750934, page 7876, compound 21	1