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Total synthesis of the proposed structure of Anti-TMV active tabasesquiterpene A

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ABSTRACT

The proposed structure of Tabasesquiterpene A, an illudalane type of sesquiterpene has been synthesized in twelve steps from 2-methoxy-4-methylbenzaldehyde in 40% overall yield. Triflic acid mediated intramolecular Freidel-Crafts acylation allows to develop the critical indanone moiety, a key intermediate of this synthesis. A careful *ortho*-selective formylation and subsequent Knoevenagel condensation to incorporate three carbon side chain, followed by reduction, formation of tricyclic lactone and DIBAL-H supported reduction of lactone to target were other key transformation involved. The NMR spectroscopic data of the synthetic sample differ from those of natural tabasesquiterpene A.

1. Introduction

Nicotiana tabacum of the genus *Nicotiana*, native to the tropical Americas is a commercial crop of tobacco [1]. Apart from a stimulating agent, the herbs of *N. tabacum* have been used as an insecticide, anesthetic, diaphoretic, sedative, and emetic agent in Chinese folk medicine [2–4]. This herbaceous plant constitutes of diverse molecular scaffolds with remarkable biological activities, including anti-HIV-1, anti-TMV, and cytotoxicity [5]. In 2015, Shang et al. isolated a new sesquiterpene tabasesquiterpene A **1** (Fig. 1) with unprecedented structure from *Nicotiana tabacum* [6]. The architecture of **1** is similar to illudalane sesquiterpene, which is commonly found in fungi and ferns [7,8]. Unlikely, tabasesquiterpene A **1** has a *gem*-dimethylated indane core with hydroxy propyl side chain, whereas the illudalanes comprise of hydroxy ethyl side chain. Additionally, **1** exhibited potential anti-TMV activity with good inhibition rates. Shang et al. proposed the structure of **1** based on an extensive spectroscopic studies such as UV, HRMS, 1D NMR and 2D NMR (^{1}H–^{1}H COSY, HMBC). Apart from the biological activity, the polysubstituted benzene core represents tabasesquiterpene A **1** as a synthetic target for studies. In addition, the interesting part of **1** is a methyl group at C-6, hydroxypropyl side chain at C-5 of *gem*-dimethylated indane core. Generating this indane core from aromatic compound with poor directing groups and propyl chain regioselectively would be a challenging part associated with this synthesis. In the last two decades, remarkable works have been reported in the synthesis of illudalane sesquiterpenes [9]. In our ongoing endeavour to synthesize new biologically active natural products, we herein discuss our effort to synthesize target **1**.

2. Results and discussion

Retrosynthetic plan for synthesis of **1** is briefly outlined in Scheme 1. After careful evaluation of the structural features, we envisaged that the final compound could be obtained from the tricyclic lactone **2** by DIBAL-H mediated reduction. The precursor **2** could be easily developed from the intermediate **3** via *ortho*-formylation, methylation, Knoevenagel condensation followed hydrogenation and demethylation. Phenolic indane **3** could be accessible from the indanone **4** by the sequence of methylation, reduction of ketone to alkane followed by deprotection. The synthesis of challenging indanone **4** was imagined from readily available aldehyde **5** via Knoevenagel condensation, reduction of C=C bond and acid mediated intramolecular cyclization.

As outlined in Scheme 2, the synthesis of **1** started with the *ortho*-formylation of commercially available phenol **6** by treatment with $MgCl_2$, Et_3N, $(HCHO)_n$ in dry acetonitrile to give the aldehyde **7** in 72% yield [10]. The phenolic group in **7** was protected with MeI, K_2CO_3 in DMF to give the desired aldehyde **5** in 92% yield [11], which was subjected to Knoevenagel condensation with malonic acid to deliver the cinnamic acid **8** in 93% yield [12] (see Scheme 2).

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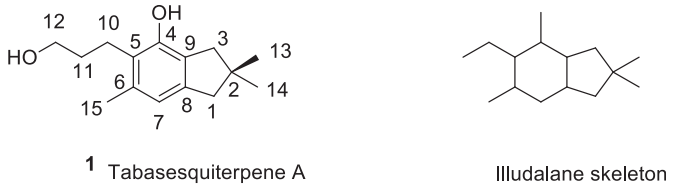
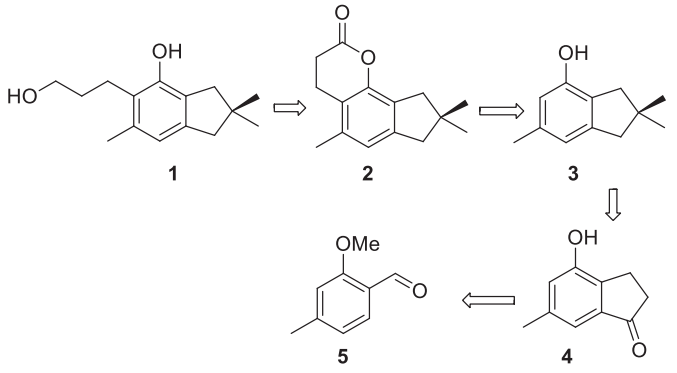


Fig. 1. Structure of tabasesquiterpene A

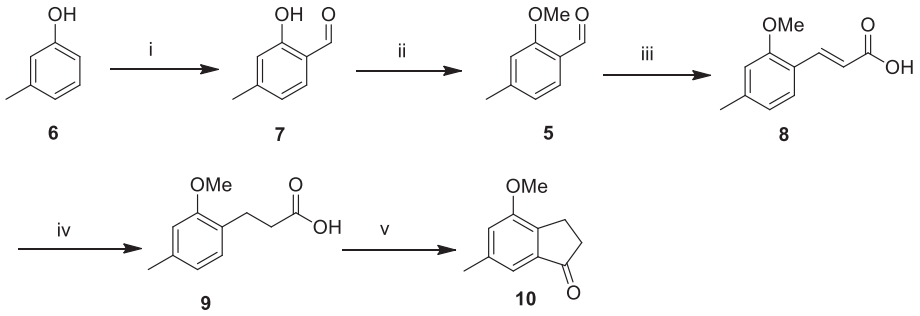


Scheme 1. Retrosynthetic analysis for Tabasesquiterpene A.

TfOH Scheme 3.

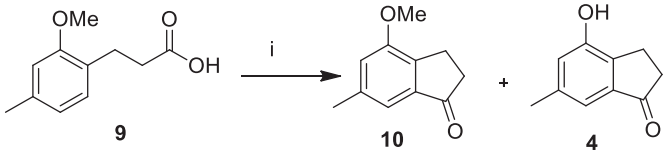
Delighted with a large quantity of **4** in hand, we next evaluated its modification to the desired intermediate indane **3**. Methylation of **4** with NaH and MeI in THF provided the *gem*-dimethylated indanone **11** in 92% yield [21]. Reduction of indanone **11** with ZnI_2 and $NaCNBH_3$ in DCE gave the indane derivative **12** in 96% yield [22], which upon demethylation with BBr_3 in DCM furnished indane **3** in 93% yield [23]. Once the indane core was generated, we thought that *o*-formylation followed by Knoevenagel condensation will regioselcetively incorporate the three carbon side chain Scheme 4.

In turn, compound **3** was readily converted to aldehyde **13** in 81% yield. However, subsequent Knoevenagel condensation of **13** to coumarin **14** not proceeded well and most of the aldehyde remains unreacted. Alternatively, protecting the phenolic group followed by condensation of **15** with malonic acid developed **16** in good yield. Next, reduction of **16** followed by demethylation of **17** with BBr_3 generated the precursor **2** in 95% yield Scheme 5. Finally, the DIBAL-H mediated reduction successfully furnished the target **1** in 95% yield [24]. This twelve-step sequence from known aldehyde **5** helped to achieve the proposed tabasesquiterpene A **1** in an overall 40% yield. At the end, we carefully compared the experimental data of the synthetic molecule **1** (^1H and ^{13}C NMR recorded in C_5D_5N as well as $CDCl_3$) with those reported for the natural molecule **1** in

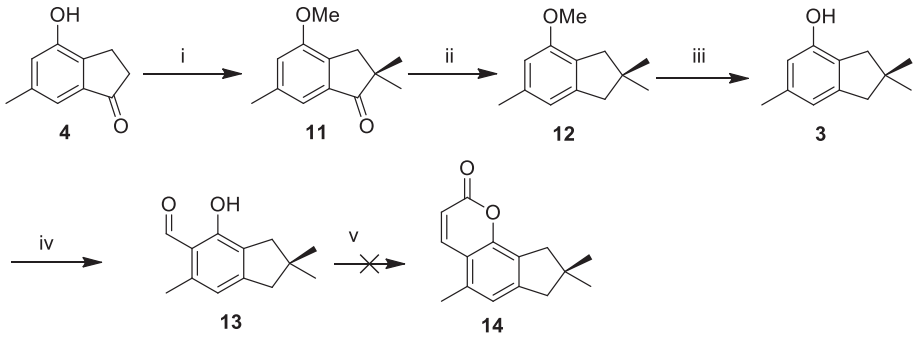


Scheme 2. Synthesis of indanone derivative **10**. Reagents and conditions: i. Et_3N, $MgCl_2$, $(HCHO)_n$, dry CH_3CN, 70 °C, 8 h, 72%; ii. K_2CO_3, MeI, dry DMF, rt, 6 h, 92%; iii. Malonic acid, pyridine, piperidine (cat.), reflux, 8 h, 93%; iv. Ni–Al alloy, 10% aq. NaOH, 12 h, rt, 96%; v. PPA, 110 °C, 12 h, 12%.

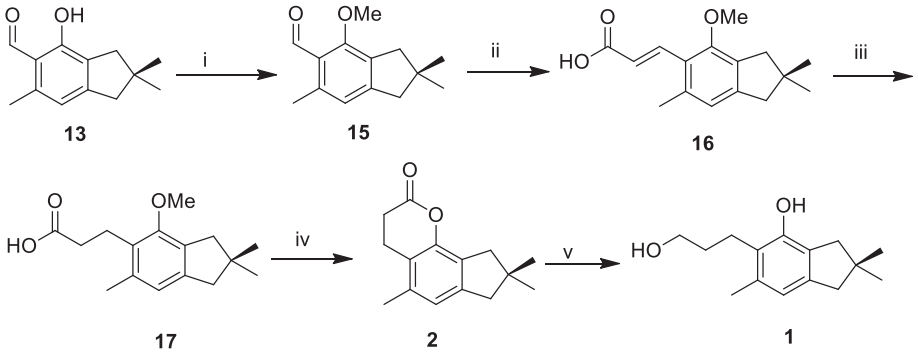
Reduction of the olefinic bond in **8** with Ni–Al alloy gave hydrocinnamic acid **9** in 96% yield [13], which was readily converted to indanone **10**. However, the polyphosphoric acid (PPA) mediated cyclization [14] gave drastically low yields (12%) than expected. Changing the reaction parameter did not improve the yield of **10**, which is probably due to an unfavourable electronic effect on the aromatic ring in **9.** At this stage, proceeding with a small quantity of indanone will affect the further conversion and overall yield, which will be unattractive. Since this indanone derivative has already been used in many natural product syntheses [9s, 15], we intended to prepare it in high yield using other possible alternative reagents. At the outset, the Friedel-Crafts acylation of **9** with various protic acid as well as Lewis acids was extensively studied. Efforts to obtain **10** with methanesulfonic acid [16], Eaton's reagent [17], a mixture of trifluoroacetic acid and its anhydride at 110 °C were not fruitful. Similarly, reaction of **9** with $Sc(OTf)_3$ [18], or $AlCl_3$ did not yield the desired indanone [19]. In all these attempts, we either recovered the starting material or the complex mixture obtained. Ultimately, the cyclised product was realised by the reaction of **9** with TfOH [20]. Attempt with 2 equivalents of TfOH at 110 °C for 6 h under neat condition compound **9** gave 52% of **10** and 37% of **4** which are compatible to further transformation. However, we obtained **4** in high yield (89%) with 4 equivalents of C_5D_5N (Supporting information of this reported article helps to realize that the ^1H and ^{13}C NMR spectrum of natural tabasesquiterpene A were recorded in solvent C_5D_5N, not in CD_3OD or CD_3Cl) [6]. Although the spectroscopic data of synthetic compound **1** strongly support the proposed structure, we found a significant difference in the position of the chemical shift with the natural compound **1** (See table in SI for more details). In particular, the CH_2 on the three-carbon side chain H-10, H-11, and H-12 appeared at 2.64 (t, J = 7.8, 2H), 1.83 (m, 2H), and 3.54 (t, J = 6.5, 2H) respectively, for naturally isolated **1** while for the same observed at 3.13 (t, J = 7.8 Hz, 2H), 2.14 (m, 2H), 3.95 (t, J = 6.3 Hz, 2H) in C_5D_5N and 2.79 (t, J = 7 Hz, 2H), 1.83 (m, 2H), 3.64 (t, J = 6 Hz, 2H) in $CDCl_3$ for synthetic **1**. However, we observed a large deviation mainly for C-1



Scheme 3. Synthesis of indanone **4**. Reagent and condition: i. 2 eq. TfOH, 110 °C, 8 h, **9** 52%, **4** 37% and 4 eq. TfOH, 110 °C, 8 h, **4** 89%.



Scheme 4. Synthesis of intermediate **14**. Reagents and conditions: i. NaH, MeI, dry THF, rt, 8 h, 92%; ii. ZnI_2, $NaCNBH_3$, dry DCE, reflux, 8 h, 96%; iii. BBr_3, dry DCM, 0 °C-rt, 3 h, 93%; iv. Et_3N, $MgCl_2$, $(HCHO)_n$, CH_3CN, 70 °C, 8 h, 81%; v. ii. malonic acid, pyridine, piperidine, reflux, 8 h.



Scheme 5. Synthesis of target **1**. i. K_2CO_3, MeI, dry DMF, rt, 96%; ii. malonic acid, pyridine, piperidine, reflux, 8 h, 89%; iii. Ni−Al alloy, 10% NaOH solution, 8 h, 98%; iv. BBr_3, dry DCM, 0 °C-rt, 8 h, 95%; v. DIBAL-H, THF, rt, 95%.

and C-3 in the ^{13}C NMR spectrum. Initially, we believed that the position of the three carbon side chain greatly alters the ^{1}H chemical shift. To support this hypothesis, we examined the spectroscopic data of various 2-(3-hydroxypropyl) phenol derivatives [25]. The results suggests that the −OH in the hydroxypropyl side chain at *ortho*-position of phenol exerts a strong intramolecular hydrogen bonding with the phenolic −OH, resulting in a deviation in the chemical shift of the terminal as well as the benzylic CH_2. Finally, HMBC correlation (Fig. 35, Supporting information) of H-11 to C-10 (δ 21.1), C-12 (δ 60.9), C-5 (δ 122.6) and H-10 to C-5 (δ 122.6), C-4 (δ 151.2), C-6 (δ 135.8) strongly indicated that three carbon side chain connected through the C-5. The correlation of H-15 to C-6 (δ 135.8), C-5 (δ 122.6) and C-7 (δ 118.9) indicated that C-15 (δ 19.6) is connected with C-6. Furthermore, strong correlation among H-1 to C-8 (δ 142.8), C-7 (δ 118.9), C-9 (δ 126.8) and H-3 to C-9 (δ 126.8), C-4 (δ 151.2), and C-7 (δ 118.9) suggested that the cyclopentane ring is fused with C-9 and C-8. All these comparisons, HMBC correlation and C-7 peak at 118.9 in DEPT spectra (Fig. 34, supporting information) strongly support that the synthetic molecule and the proposed structure of tabasesquiterpene A are identical.

3. Conclusion

The first total synthesis of the proposed structure of **1** have been successfully achieved from the commercially available starting material *m*-cresol in fourteen steps with 26.5% overall yield. Two non-consecutive Knoevenagel condensations are serviceable for the generation of three carbon chains in the initial and final stages. Triflic acid mediated Friedel-Crafts acylation enabled us to achieve the key intermediate indanone in good quantity, which is very difficult to produce with other known methods. Also, $MgCl_2$ and $(HCHO)_n$ supported regioselective formylation, BBr_3 supported lactone formation and DIBAL-H reduction were the other key transformations. While our spectroscopic data strongly supported the proposed structure of **1**, they did not fully agree with the natural **1**.

4. Experimental section

4.1. General experimental procedures

Reagents were obtained from commercial sources and used without further purifications. All reactions were performed in oven dried glassware under anhydrous condition and used freshly distilled solvents, whereas Ni−Al alloy mediated reduction performed in water. All reactions were monitored by thin layer chromatography, which was performed on 0.25 mm silica gel-coated aluminum sheets (F-254, Merck) and visualized using UV light and spraying with a $KMnO_4$ solution. Column chromatography was performed using silica gel (100−200 mesh) with hexane and ethyl acetate as eluent. ^{1}H NMR spectra, ^{13}C NMR, HMBC and DEPT spectra recorded in $CDCl_3$, C_5D_5N on a 300, 400 and 500 MHz Bruker-AVANCE spectrometers with TMS as internal standard. High-resolution electrospray ionization mass spectra (HRMS-ESI) were obtained with an Agilent 6520 Q-TOF instrument using chloroform solutions.

4.1.1. 2-Hydroxy-4-methylbenzaldehyde (7)

A mixture of *m*-cresol **6** (20 g, 185.1 mmol) and $MgCl_2$ (54.3 g, 572 mmol) was taken in a 500 mL round bottom flask. Triethylamine (72.7 mL, 518.5 mmol) followed by dry CH_3CN (150 mL) was added to the mixture and stirred for 5 min. Paraformaldehyde (20 g) was added to the mixture and heated at 70 °C for 12 h. After completion, the reaction mixture was acidified with dil. HCl

solution and extracted with ethyl acetate. The combined mixture was dried over anhydrous Na_2SO_4. The solvent was removed under vacuum at 40 °C to get the crude aldehyde (this aldehyde is slightly volatile). The crude residue was purified by column chromatography using hexane as eluent and concentrated to afford **7** (18 g, 72%) as a colourless crystalline solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.06 (s, 1H), 9.84 (s, 1H), 7.44 (d, J = 10 Hz, 1H), 6.84 (d, J = 10 Hz, 1H), 6.81 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.9, 161.8, 148.9, 133.6, 121.2, 118.7, 117.7, 22.2.

*4.1.2. 2-Methoxy-4-methylbenzaldehyde (**5**)*

An anhydrous K_2CO_3 (32.5 g, 235.2 mmol) was added to the solution of **7** (16 g, 117.6 mmol) in 100 mL dry DMF and the heterogeneous mixture was stirred for 10 min. Iodomethane (15.18 mL, 235.2 mmol) was added dropwise to the mixture and stirred at room temperature for 6 h. After completion, cold distilled water was added and extracted with ethyl acetate. Organic layer was washed with brine, dried on anhydrous Na_2SO_4 and concentrated. The resulted residue was purified by column chromatography using hexane as an eluent to provide **5** (16.2 g, 92%) as off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.4 (s, 1H), 7.72 (d, J = 8 Hz, 1H), 6.83 (d, J = 7.5 Hz, 1H), 6.79 (s, 1H), 3.91 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.4, 161.9, 147.5, 128.5, 122.6, 121.6, 112.2, 55.5, 22.3.

*4.1.3. 3-(2-Methoxy-4-methylphenyl)propenoic acid (**8**)[12b]*

A mixture of pyridine 200 mL and piperidine 2 mL was taken in a 500 mL round bottom flask which contains aldehyde **5** (18 g, 120 mmol) and malonic acid (26.70 g, 256 mmol). The mixture was refluxed for 8 h, and then poured to ice cold water containing excess of con. HCl. The precipitate was filtered, washed with excess cold water, dried and recrystallized using methanol to get **8** (22 g, 93%) as a white solid. Mp. 193–195 °C.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 16.2 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 6.79 (d, J = 8.1 Hz, 1H), 6.74 (s, 1H), 6.51 (d, J = 16.2 Hz, 1H), 3.88 (s, 3H), 2.38 (s, 3H);

^{1}H NMR (300 MHz, DMSO-d_6) δ 7.79 (d, J = 16.2 Hz, 1H), 7.54 (d, J = 7.8 Hz, 1H), 6.91 (s, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.44 (d, J = 16.2 Hz, 1H), 3.85 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.0, 157.7, 142.1, 138.8, 128.3, 121.5, 119.8, 118.0, 112.3, 55.5, 21.4.

*4.1.4. 3-(2-Methoxy-4-methylphenyl)propanoic acid (**9**)*

Cinnamic acid **8** (16 g, 81.6 mmol) was taken in 1000 mL beaker, and 10% NaOH (48 g in 480 mL distilled water) solution was added. Ni–Al alloy (22 g) was added portion wise to the reaction mixture over 30 min period and stirred for 8 h. The completion of the reaction was monitored by TLC, and the mixture was filtered using the Celite bedded sintered funnel. The filtrate was acidified by pouring to ice cold water with excess of concentrated HCl, and extracted with ethyl acetate. The solvent was dried over anhydrous Na_2SO_4, and concentrated under vacuum and purified by column chromatography using mixture of hexane and ethyl acetate (8:2) as an eluent to obtain **9** (15.5 g, 96%) as colourless crystalline solid. Mp. 80–82 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, J = 7.2 Hz, 1H), 6.69 (d, J = 7.6 Hz, 1H), 6.66 (s, 1H), 3.80 (s, 3H), 2.90 (t, J = 8 Hz, 2H), 2.64 (t, J = 8 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.0, 157.6, 137.8, 129.9, 125.9, 125.7, 121.2, 111.5, 55.3, 34.3, 25.8, 21.7. HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_{11}H_{15}O_3^+$ 195.1021; found, 195.1026.

*4.1.5. 4-Methoxy-6-methyl-2,3-dihydro-1H-inden-1-one (**10**)*

Compound **9** (1 g, 5.2 mmol) was added to a freshly prepared PPA [P_2O_5 (3.69 g, 26.2 mmol) and H_3PO_4 88% (3.7 mL) heated at 95 °C for 1 h] and the mixture was heated at 110 °C under anhydrous condition for 12 h. The reaction was monitored by TLC. The mixture was poured on crushed ice and extracted with ethyl acetate. Organic layer was washed twice with excess of sat. $NaHCO_3$ solution followed by distilled water and dried over anhydrous Na_2SO_4. The concentrated residue was purified by column chromatography using a mixture of hexane and ethyl acetate (9.5:0.5) to obtain **10** (12%) as light brown liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (s, 1H), 6.85 (s, 1H), 3.89 (s, 3H), 2.98 (t, J = 5.7 Hz, 2H), 2.66 (t, J = 5.7 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 156.9, 141.7, 139.3, 138.8, 116.3, 115.4, 55.6, 36.6, 22.4, 21.7.

*4.1.6. 4-Hydroxy-6-methyl-2,3-dihydro-1H-inden-1-one (**4**)*

Mixture of compound **9** (1 g, 5 mmol), TfOH (1.8 mL, 20.6 mmol) was cooled at 0 °C for 10 min, and then heated at 110 °C for 8 h under anhydrous conditions. The reaction was monitored by TLC and the mixture was poured on the crushed ice and extracted with ethyl acetate. Organic layer was washed twice with sat. $NaHCO_3$ solution followed by dried over anhydrous Na_2SO_4 and concentrated. The precipitate was purified by column chromatography using hexane and ethyl acetate (9:1) as eluent to obtain **4** (0.72 g, 89%) as white solid, mp. 160–162 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (s, 1H), 6.88 (s, 1H), 5.67 (broad s, 1H), 3.03 (t, J = 6 Hz, 2H), 2.72 (t, J = 5.7 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 153.3, 139.6, 139.1, 139.1, 121.6, 116.4, 36.7, 22.1, 21.3. HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_{10}H_{11}O_2^+$ 163.0759; found, 163.0764.

*4.1.7. 4-Methoxy-2,2,6-trimethyl-2,3-dihydro-1H-inden-1-one (**11**)*

Compound **4** (2 g, 12.3 mmol) in dry THF (10 mL) was added dropwise to a stirred heterogeneous solution of NaH (1.18 g, 49 mmol) in dry THF. After 10 min, MeI (1.6 mL, 24.6 mmol) was added dropwise and stirred further for 6 h. After completion, the reaction was quenched with crushed ice and extracted with ethyl acetate. Organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography using hexane as eluent to obtain **11** (2.3 g, 92%) as light brown liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1H), 6.86 (s, 1H), 3.88 (s, 3H), 2.85 (s, 2H), 2.41 (s, 3H), 1.22 (s 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.8, 156.9, 139.4, 138.6, 137.0, 116.6, 116.1, 55.5, 45.7, 39.4, 25.5, 21.7; HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_{13}H_{17}O_2^+$ 205.1229; found, 205.1229.

*4.1.8. 4-Methoxy-2,2,6-trimethyl-2,3-dihydro-1H-indene (**12**)*

Mixture of compound **11** (2 g, 9.80 mmol), ZnI_2 (4.69 g, 14.7 mmol) and $NaCNBH_3$ (4.62 g, 73.5 mmol) in dry DCE (30 mL) was refluxed for 8 h. The reaction was monitored by TLC. Then mixture of saturated NH_4Cl and concentrated HCl was added to the heterogeneous reaction mixture at 0 °C, and extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced vacuum. The resulted residue was purified by column chromatography using hexane as eluent to obtain **12** (1.8 g, 96%) as colourless thin liquid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.62 (s, 1H), 6.48 (s, 1H), 3.79 (s, 3H), 2.68 (s, 2H), 2.64 (s, 2H), 2.32 (s, 3H), 1.14 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 145.6, 137.6, 127.9, 118.1, 109.1, 55.3, 48.2, 44.2, 40.1, 29.4, 21.9. HRMS (ESI+) m/z $[M + H]^+$ calcd for $C_{13}H_{19}O^+$ 191.1436; found, 191.1432.

*4.1.9. 2,2,6-Trimethyl-2,3-dihydro-1H-inden-4-ol (**3**)*

Boron tribromide (1.53 mL, 16.1 mmol) was added dropwise to the stirred solution of **12** (1 g, 5.68 mmol) in 10 mL dry DCM at 0 °C. The mixture was stirred for 30 min at 0 °C and 4 h at room temperature. After completion, saturated NH_4Cl solution was added and extracted with ethyl acetate. The combined organic layer was

washed twice with sat. $Na_2S_2O_4$ solution followed distilled water, then dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography using hexane and ethyl acetate (9:1) as eluent to obtain **3** (0.9 g, 93%) as light yellow gum.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 1H), 6.44 (s, 1H), 2.68 (s, 2H), 2.61 (s, 2H), 2.26 (s, 3H), 1.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 146.1, 138.0, 125.6, 118.3, 113.6, 48.2, 43.3, 40.5, 29.3, 21.4. HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{12}H_{17}O^+$ 177.1279; found, 177.1272.

4.1.10. 4-Hydroxy-2,2,6-trimethyl-2,3-dihydro-1H-indene-5-carbaldehyde (**13**)

Using the abovementioned procedure (4.1.1), reaction of compound **3** (0.08 g, 0.5 mmol) with Et_3N (0.18 mL, 1.26 mmol), $MgCl_2$ (0.13 g, 1.4 mmol), and $(HCHO)_n$ in dry CH_3CN (10 mL) provided **13** (0.08 g, 81%) as a colourless liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.03 (s, 1H), 10.24 (s, 1H), 6.57 (s, 1H), 2.69 (s, 4H), 2.56 (s, 3H), 1.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1, 160.0, 155.6, 141.1, 129.0, 118.9, 117.4, 49.1, 43.3, 40.2, 29.1, 18.4. HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{13}H_{17}O_2^+$ 205.1229; found, 205.1227.

4.1.11. 4-Methoxy-2,2,6-trimethyl-2,3-dihydro-1H-indene-5-carbaldehyde (**15**)

Using abovementioned procedure (4.1.2), reaction of compound **13** (0.3 g, 1.47 mmol) with anhydrous K_2CO_3 (0.4 g, 2.94 mmol) in dry DMF and MeI at room temperature provided **15** (0.31 g, 96%) as light brown liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ10.53 (s, 1H), 6.80 (s, 1H), 3.87 (s, 3H), 2.80 (s, 2H), 2.70 (s, 2H), 2.55 (s, 3H), 1.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.5, 161.3, 153.1, 140.9, 132.3, 125.4, 123.9, 61.6, 48.3, 44.9, 40.8, 28.9, 21.7. HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{14}H_{19}O_2^+$ 219.1385; found, 219.1378.

4.1.12. 3-(4-Methoxy-2,2,6-trimethyl-2,3-dihydro-1H-inden-5-yl) propenoic acid (**16**)

Using abovementioned Knoevenagel condensation procedure (4.1.3), reaction of compound **15** (0.3 g, 1.38 mmol) with malonic acid in mixture of pyridine (10 mL) and piperidine (0.25 mL) provided **16** (0.37 g, 89%) as white solid. Mp. 158–161 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 16.2, 1H), 6.82 (s, 1H), 6.64 (d, J = 15.9 Hz, 1H), 3.76 (s, 3H), 2.78 (s, 2H), 2.68 (s, 2H), 2.41 (s, 3H), 1.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ173.4, 156.9, 148.6, 142.0, 138.6, 133.0, 123.9, 123.1, 120.6, 59.8, 48.1,45.2, 40.6, 28.9, 21.3. HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{16}H_{21}O_3^+$ 261.1491; found, 261.1483.

4.1.13. 3-(4-Methoxy-2,2,6-trimethyl-2,3-dihydro-1H-inden-5-yl) propanoic acid (**17**)

Using abovementioned Ni–Al alloy reduction procedure (4.1.4), reaction of compound **16** (0.2 g, 0.76 mmol) with Ni–Al alloy (0.23 g) in aqueous NaOH (0.6 g in 6 mL distilled water) provided **17** (0.196 g, 98%) as colourless solid. Mp.77-79 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (s, 1H), 3.79 (s, 3H), 2.95 (t, J = 8.7, 2H), 2.76 (s, 2H), 2.65 (s, 2H), 2.54 (t, J = 8.7 Hz, 2H), 2.29 (s, 3H), 1.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ179.8, 155.3, 144.2, 135.8, 131.6, 128.4, 122.2, 60.1, 47.7, 45.7, 40.6, 34.5, 29.1, 22.3, 19.7. HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{16}H_{23}O_3^+$ 263.1647; found, 263.1648.

4.1.14. 5,8,8-Trimethyl-3,4,8,9-tetrahydrocyclopenta[h]chromen-2(7H)-one (**2**)

Boron tribromide (0.2 mL, 2.8 mmol) was added to the stirred solution of **17** in dry DCM at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and 6 h at room temperature. Saturated NH_4Cl solution was added and extracted with ethyl acetate. The combined organic layer was washed twice with saturated $Na_2S_2O_3$ solution, dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude mixture was purified by column chromatography using hexane as eluent to obtain the lactone **2** (0.25 g, 95%) as colourless liquid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (s, 1H), 2.92 (t, J = 7 Hz, 2H), 2.78 (t, J = 8 Hz, 2H), 2.76 (s, 2H), 2.72 (s, 2H), 2.28 (s, 3H), 1.17 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.0, 148.7, 144.5, 134.0, 128.4, 122.1, 118.3, 47.8, 43.7, 40.4, 29.1, 28.9, 20.8, 19.2. HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{15}H_{19}O_2^+$ 231.1385; found, 231.1381.

4.1.15. 5-(3-hydroxypropyl)-2,2,6-trimethyl-2,3-dihydro-1H-inden-4-ol (tabasesquiterpene A) (**1**)

DIBAL-H (1 M toluene solution) (1 mL, 1 mmol) was added to a stirred solution of lactone **2** (0.045 g, 0.2 mmol) in dry toluene under anhydrous condition. The mixture was stirred at room temperature for 1 h. The reaction was quenched with dil. HCl, extracted with diethyl ether. The dried organic layer was concentrated under reduced pressure and the residue was purified by column chromatography using hexane and ethyl acetate (7:3) as eluent to afford **1** (0.044 g, 95%) as pale yellow solid, mp. 60–62 °C. ^{1}H NMR (300 MHz, C_5D_5N) δ 6.69 (s, 1H), 3.95 (t, J = 6.3 Hz, 2H), 3.13 (t, J = 7.8 Hz, 2H), 2.90 (s, 2H), 2.68 (s, 2H), 2.38 (s, 3H), 2.14 (m, 2H), 1.09 (s, 6H); ^{13}C NMR (75 MHz, C_5D_5N) δ 153.0, 142.6, 127.6, 125.9, (one carbon peak at position 124 is overlapped with solvent peak), 118.9, 62.0, 48.5, 45.7, 40.3, 33.3, 29.4, 23.6, 20.2.^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (s, 1H), 3.64 (t, J = 6 Hz, 2H), 2.79 (t, J = 7 Hz, 2H), 2.67 (s, 2H), 2.65 (s, 2H), 2.27 (s, 3H), 1.83 (m, 2H), 1.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.2, 142.8, 135.8, 126.8, 122.6, 118.9, 60.9, 48.0, 44.0, 40.1, 30.5, 29.2, 21.1, 19.6; DEPT ($CDCl_3$, 125 MHz) δ 118.9 (C-H), 60.9, 48.0, 44.0, 30.5, 21.2 (for five CH_2), 29.2, 19.6 (for three CH_3) HRMS (ESI+) *m/z* $[M + H]^+$ calcd for $C_{15}H_{23}O_2^+$ 235.1698; found, 235.1700.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Raj Bahadur Singh reports financial support was provided by Science and Engineering Research Board, New Delhi, India.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.132282.

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