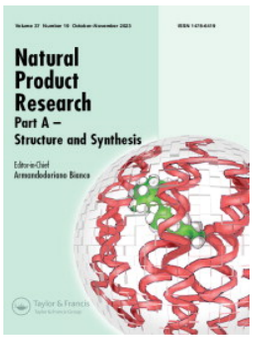

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Iodine-mediated one-step synthesis of ipomone from gibberellic acid

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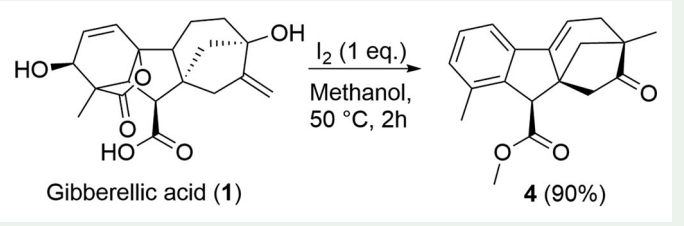
ABSTRACT

A fast and efficient method for synthesising ipomone (**4**), a bicyclo[3.2.1]octanone containing aromatised derivative, from gibberellic acid (**1**) has been developed using molecular iodine as a mild and effective mediator under heating conditions in a single step. Evidence was obtained that the reaction simultaneously proceeds through aromatisation and pinacol-pinacolone type 1,2-alkyl shift. Use of excess iodine afforded iodomethyl derivative (**5**) that could serve as starting material for the synthesis of additional analogs.



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gibberellic acid; ipomone; iodination; 1,2-alkyl shift; natural product

1. Introduction

Diterpenoids are a diverse class of plant and fungal products containing twenty carbon atoms. Gibberellic acid and allogibberic acids are typical examples of gibbane-type diterpenes. They have been found in a variety of plants like *Malus domestica*, *Pisum sativum*, *Ipomoea* spp., *Prunus* spp., as well as microorganisms like *Gibberella fujikuroi* (fungus), *Acetobacter diazotropicus* (bacteria). (MacMillan 2001; Mander 2003). The gibberellin derivatives have shown promising biological activities, primarily anticancer (Annand et al. 2015; Wu et al. 2018; Zhu et al. 2020). GA-13315 (Figure 1), a derivative inspired from gibberellin, exhibited high antitumor and antiangiogenic activity *in vitro* and *in vivo* and displayed selectivity against multi-drug resistant MCF- 7/ADR cells (Cheng et al. 2020). Thus, the gibberellic acid scaffold offers new chemical space to medicinal chemists for anticancer drug discovery. In our recent work,

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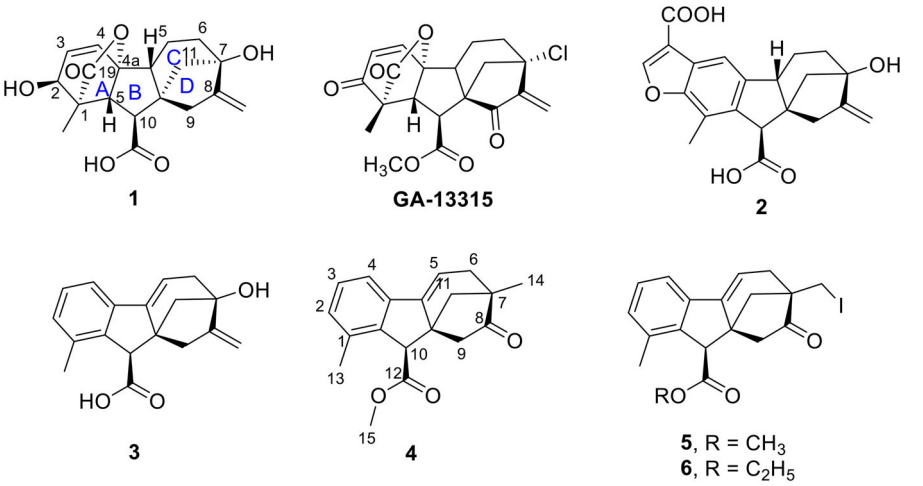


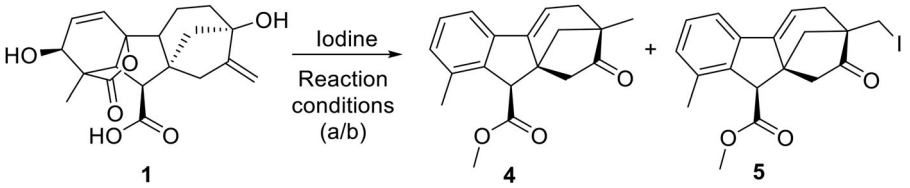
Figure 1. Chemical structures of gibberellic acid (1), and related compounds.

bicyclo[3.2.1]octanone containing unique gibbane diterpenoid ipomone (**4**) was isolated from the methanolic extract of seeds of *Ipomoea nil* under acidic conditions. It was found to have moderate apoptosis-inducing activity (Goel et al. 2021). Ipomone (**4**) was obtained under acidic conditions, and when the extraction of *I. nil* seeds was done either in neutral or alkaline conditions, ipomone was not visible in TLC. It was hypothesised as a process generated product obtained from acid-catalysed pinacol-pinacolone type 1,2 alkyl rearrangement. Inspired by the fact that many gibberellins have already been reported from *I. nil* seeds, we initiated the synthetic strategy involving acid treatment of gibberellic acid (**1**, GA).

Since gibberellic acid (**1**, GA) is cheap and readily available, it could serve as a promising precursor for the synthesis of gibbane-type diterpenoids. Annand et al. (2015) synthesised a potential anti-inflammatory NF-κB inhibitor, pharbinilic acid (**2**) in 7 steps from GA. However, GA being a highly functionalised molecule with the strained ring, its reactivity poses inevitable challenges (Corey et al. 1978; Danheiser 1984). The very example of its reactivity could be seen in the synthesis of pharbinilic acid (**2**), as bicyclo[3.2.1]octanone was obtained as an undesirable product due to the dormant reactivity of the tertiary allylic hydroxyl group. The undesirable side product bicyclo[3.2.1]octanone was formed under the electrophilic environment due to 1,2 alkyl shift (Annand et al. 2015). In the present work, we have reported a fast and efficient one-step synthesis of natural product ipomone from the cheap and easily available GA under thermal conditions.

2. Results and discussion

Since ipomone was isolated from hydro-alcoholic extract under acidic conditions, we initiated the investigation by treating GA with different inorganic acids *viz.* HCl, HBr, HI, H_2SO_4, and HNO_3 in methanol and methanol-water (1:1) for 4 h at room temperature, GA methyl ester was obtained as a major product (∼90%) (entry 1-10, Table S1).



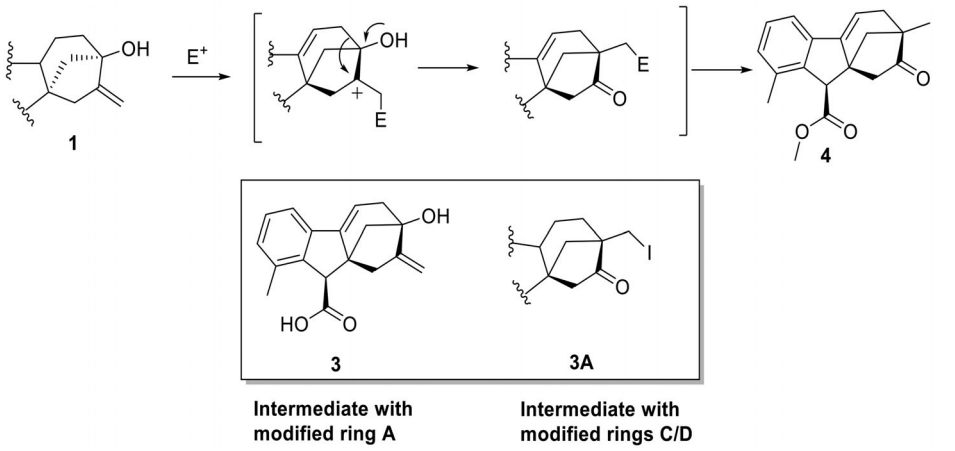
Scheme 1. Chemical reaction of gibberellic acid (**1**) with iodine to synthesise ipomone (**4**). Reaction conditions: a) I_2 (1 equiv.), methanol (2 mL), 50 °C, 2 h, yield (**4**: 90%, **5**: 0%). b) I_2 (2 equiv.), methanol (2 mL), 50 °C, 4 h, yield (**4**: 5%, **5**: 90%).

Ipomone was visible on TLC as minor product (<10%) in case of HCl, HBr, and HI (entry 1-3, Table S1).

It is reported that electrophilic attack on the terminal alkene and the latent reactivity of tertiary hydroxyl group leads to several rearrangement reactions in GA (Hanson 2018); hence, the electrophiles were chosen to react with GA. Br_2 and I_2 was taken as an electrophile for the further investigations. When GA was subjected to react with bromine at room temperature for 4 h in methanol, multiple products were visualised on TLC along with the desired product **4** (entry 11, Table S1). Similarly, Reaction with iodine produced compound **4** in a yield of ~40% (entry 12, Table S1). Increasing the reaction temperature to 50 °C with 1 eq. of iodine in methanol resulted in a good yield of compound **4** (90%) within 2 h (entry 13, Table S1, Scheme 1). The compound was purified with silica gel column chromatography and subjected to structural characterisation. The spectroscopic properties of the isolated compound were same as ipomone (Goel et al. 2021).

However, when 2 eq. of iodine was used, the yield of compound **4** decreased to 60%, and a new product (**5**) appeared in a significant amount (yield 35%) within 2 hours (entry 14). Prolonging the reaction time to 4 h at 50 °C resulted in the synthesis of compound **5** with the increased yield of 90% (entry 15, Table S1, Scheme 1). Compound **5** was purified by silica gel column chromatography and characterised by 2 D NMR and HRMS (Supplementary Material). The ^{1}H-NMR and ^{13}C-NMR were almost similar to that of ipomone, except for an aliphatic CH_3 corresponding to δ_H 1.22 ppm and δ_C 20.7 ppm. An extra peak of CH_2 was also observed in the ^{13}C NMR spectrum (confirmed by DEPT-135) at δ_C 10.4 ppm and corresponding peaks in ^{1}H NMR at 3.50 and 3.34 ppm. The CH_2 peak at δ_C 10.4 ppm was highly shielded because of the substitution of electrophile-iodine (CH_2I). All the correlations, as shown in supplementary material, are in agreement and it was confirmed as methyl (7*S*,9a*S*,10*R*)-7-(iodomethyl)-1-methyl-8-oxo-6,8,9,10-tetrahydro-7H-7,9a-methanobenzo[a]azulene-10-carboxylate (**5**). The iodinated derivative **5** was obtained only when excess of iodine was used in the reaction.

To establish the plausible mechanism of the reaction, we collected and analysed an aliquot during the reaction. Immediately the reaction mixture was subjected to preparative TLC to isolate two intermediates **3** and **3 A** (Scheme 2). When intermediate **3 A** was analysed by NMR, it was found that the ^{13}C NMR peak at 215.8 ppm appeared due to the formation of a carbonyl group. At the same time, peaks for exocyclic double bond (in ring D) at 157.0 ppm and 106.6 ppm disappeared. A peak also appeared at 10.3 ppm that is due to CH_2I group (confirmed by DEPT-135). However, in this



Scheme 2. A plausible mechanism involved in the synthesis of ipomone (4). (E^+ for electrophile).

intermediate, NMR peaks were not observed in the aromatic region (Supplementary Material). This data concludes the formation of iodomethyl group as well as bicyclo[3.2.1]octanone, even before the aromatisation of ring A. Owing to the unstability of this intermediate, it couldn't be characterised completely. While in another intermediate **3**, we observed that the aromatic system was formed in ring A, but 1,2-alkyl rearrangement was not observed in rings C/D (Supplementary Material). This investigation supports that both aromatisation of ring A and 1,2-alkyl shift/rearrangement took place simultaneously.

Four major modifications happened in the entire process *viz*. deacarboxylation, aromatisation of ring A, esterification, and 1,2-alkyl rearrangement in rings C/D. Molecular iodine is a versatile catalyst for the oxidative aromatisation of unsaturated carbonyl compounds and several protocols have been reported for the same (Mphahlele 2009). The reaction was conducted in a protic solvent (methanol); therefore, it is possible that the protic solvent induced HI generation. The acidic conditions facilitated the elimination of lactone, decarboxylation, and dehydration, and is followed by iodine promoted aromatisation to produce fully aromatised ring A. Plausible mechanism of aromatisation includes the hydrolysis of C1-C4a lactone bridge (intermediate **a**), followed by decarboxylation and dehydration to generate a cyclohexadiene ring system (intermediate **c**). The cyclohexadiene then forms a 1,4-iodine adduct (intermediate **d**) that undergo elimination of HI to form aromatic ring A (Scheme S1) (Mphahlele et al. 1996). Iodine being an electrophile, has also been used for the aromatisation of terpenoids due to its rapid reactivity with unsaturated systems (Domingo et al. 2016; Singh et al. 2019). 1,2-alkyl rearrangement in rings C/D may have been proceeded *via* acid-catalysed pinacol – pinacolone type 1,2 alkyl shift, as reported previously (Goel et al. 2021). Further the unsaturation in ring C (C4b-C5 double bond) might be due to iodine-mediated addition and elimination reactions. Iodine also mediated the esterification; hence, the methyl ester was obtained from iodine-methanol. In the present work, the aromatisation and 1,2-alkyl rearrangement occurred simultaneously to produce bicyclo[3.2.1]octanone containing ipomone in one step.

Furthermore, the stipulated reason for compound **5** could be the formation of *in-situ* HI that reacts with ipomone (**4**) and produce **5** as a side product. The formation of alkyl iodide proves the Wagner–Meerwein rearrangement (sort of 1,2-alkyl rearrangement) which is initiated by the addition of iodine, and the configuration of ring C is identical to the product obtained by chlorination of gibberellic acid (Hanson 2018). This is in agreement with our hypothesis for the origin of ipomone, i.e., an acid-catalysed pinacol-pinacolone rearrangement (a type of 1,2-alkyl shift) in which during rearrangement of rings C and D, the bond C_6-C_7 migrates to C_8 to produce ring C chair conformation (Scheme 2).

To evaluate the role of methanol in esterification of carboxylic group, the same reaction was carried out in ethanol (in place of methanol), this resulted in the formation of ethyl ester (**6**) (entry 16, Table S1). This proved the participation of methanol/ethanol in the esterification of carboxylic acid functionality. When this reaction was scaled up with 4.0 gm of gibberellic acid, a yield of 65% was obtained.

3. Experimental

3.1. General experimental procedures

All chemicals were obtained from Sigma-Aldrich Company and used as received. Bulk solvents were used after distillation. Gibberellic acid was procured from SRL Pvt. Ltd. (Batch No.: 4259079; Mfg. date: 06/2020). Melting points were recorded on digital melting point apparatus (Buchi) and are uncorrected. ^{1}H, ^{13}C NMR spectra were recorded on Bruker-Avance III HD 500 MHz NMR spectrometer using tetramethylsilane (TMS) as the internal standard. All chromatographic purifications were performed on silica gel (#60–120 or #100–200 from E. Merck, Germany). The thin-layer chromatography (TLC) was performed on pre-coated silica gel 60 GF254 aluminum sheets (Merck), and the spots were visualised under short-waved (254 nm) ultraviolet light. ESI-MS spectra were recorded on Agilent 1100LC-QTOF machine. HRMS spectra were recorded on Sciex X500R QTOF system.

3.2. Procedure for the synthesis of ipomone (4)

In a round bottom flask containing 2 mL of methanol, gibberellic acid (346 mg, 1.0 mmol) and iodine (126 mg, 1.0 mmol) were added subsequently. The reaction mixture was stirred at 50 °C for 2 hours and its progress was monitored by TLC. After completion, the reaction mixture was cooled to room temperature, diluted with a saturated solution of sodium thiosulfate (50 mL) to remove the unreacted iodine and colored impurities. Then the mixture was partitioned with ethyl acetate and the organic layer was collected and dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Finally, the crude product was purified by silica gel column chromatography using hexane and ethyl acetate.

3.2.1. Ipomone (methyl (7 R,9aS,10R)-1,7-dimethyl-8-oxo-6,8,9,10-tetrahydro-7H-7,9a-methanobenzo-[a]azulene-10-carboxylate, 4)

Brown gummy solid; Yield: 90%; m.p. 155-157 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, $J = 7.6$ Hz, 1H), 7.22 (t, $J = 7.5$ Hz, 1H), 7.08 (d, $J = 7.4$ Hz, 1H), 5.93 (t,

$J = 3.0$ Hz, 1H), 4.02 (s, 1H), 3.70 (s, 3H), 2.55 – 2.46 (m, 1H), 2.43 (d, $J = 17.4$ Hz, 1H), 2.34 (m, 1H), 2.30 – 2.25 (m, 1H), 2.23 (s, 3H), 2.07 (d, $J = 10.9$ Hz, 1H), 1.99 (dd, $J = 10.8$, 2.9 Hz, 1H), 1.22 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 219.9, 172.2, 148.8, 139.8, 138.5, 135.1, 129.7, 128.7, 118.7, 114.0, 55.2, 54.8, 51.9, 49.7, 48.8, 42.1, 39.2, 20.7, 18.6; ESIMS *m/z* 297.30 $[M + H]^+$; HRMS *m/z* 297.1487 $[M + H]^+$ (calcd for $C_{19}H_{21}O_3^+$, 297.1485) (Goel et al. 2021).

3.3. Procedure for the synthesis of compounds 5 and 6

Gibberellic acid (346 mg, 1.0 mmol) was dissolved in 2 mL of respective solvent (methanol for **5**, and ethanol for **6**). To this iodine (507.6 mg, 2 mmol) was added. The reaction flask was stirred at 50 °C for 4 hrs. The reaction was monitored over time via TLC. After reaction completion, reaction was quenched by the addition of 50 mL of ethyl acetate and washed with 3 × 50 mL of saturated sodium thiosulfate solution to remove the residual iodine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated via rotary evaporation. Finally, the crude product was purified by silica gel column chromatography using hexane and ethyl acetate.

3.3.1. Methyl (7S,9aS,10R)-7-(iodomethyl)-1-methyl-8-oxo-6,8,9,10-tetrahydro-7H-7,9a-methanobenzo[a]azulene-10-carboxylate (5)

White crystalline solid; Yield: 90%; m.p. 146-150 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, $J = 7.6$ Hz, 1H), 7.25 (t, $J = 7.5$ Hz, 1H), 7.12 (d, $J = 7.4$ Hz, 1H), 5.91 (t, $J = 3.5$ Hz, 1H), 4.07 (s, 1H), 3.75 (s, 3H), 3.51 (d, $J = 10.3$ Hz, 1H), 3.34 (d, $J = 10.4$ Hz, 1H), 2.65 (dd, $J = 18.1$, 3.0 Hz, 1H), 2.57 (dd, $J = 17.3$, 3.5 Hz, 1H), 2.46 (d, $J = 17.4$ Hz, 1H), 2.39 (d, $J = 10.9$ Hz, 1H), 2.30 (dd, $J = 18.3$, 4.1 Hz, 1H), 2.27 (s, 3H), 2.09 – 2.05 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.4, 172.0, 149.1, 139.9, 138.1, 135.2, 130.0, 128.8, 118.8, 113.1, 55.0, 54.9, 53.7, 52.1, 48.5, 40.9, 37.9, 18.6, 10.4; HRMS *m/z* 423.0434 $[M + H]^+$ (calcd for $C_{19}H_{20}IO_3^+$, 423.0452)

3.3.2. Ethyl (7S,9aS,10R)-7-(iodomethyl)-1-methyl-8-oxo-6,8,9,10-tetrahydro-7H-7,9a-methanobenzo[a]azulene-10-carboxylate (6)

White crystalline solid; Yield: 90%; m.p. 141-144 °C (uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, $J = 7.6$ Hz, 1H), 7.24 (t, $J = 7.5$ Hz, 1H), 7.11 (d, $J = 7.4$ Hz, 1H), 5.90 (t, $J = 3.5$ Hz, 1H), 4.28 – 4.24 (m, 1H), 4.24 – 4.20 (m, 1H), 4.04 (s, 1H), 3.51 (d, $J = 10.3$ Hz, 1H), 3.35 (s, 1H), 2.65 (dd, $J = 18.1$, 3.0 Hz, 1H), 2.57 (dd, $J = 17.3$, 3.4 Hz, 1H), 2.46 (d, $J = 17.4$ Hz, 1H), 2.40 (d, $J = 11.0$ Hz, 1H), 2.31 (d, $J = 3.9$ Hz, 1H), 2.27 (s, 3H), 2.11 (dd, $J = 11.0$, 3.4 Hz, 1H), 1.30 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.5, 171.4, 149.2, 140.1, 138.1, 135.2, 130.0, 128.7, 118.8, 113.0, 61.1, 55.1, 54.9, 53.6, 48.5, 41.1, 37.9, 18.6, 14.5, 10.5; HRMS *m/z* 437.0615 $[M + H]^+$ (calcd for $C_{20}H_{22}IO_3^+$, 437.0608).

4. Conclusions

In conclusion, we have developed a fast and efficient protocol for synthesising a biologically important natural product, ipomone (**4**), from gibberellic acid using a stoichiometric amount of iodine. The reaction proceeds through aromatisation and 1,2-

alkyl rearrangement simultaneously. Compounds **5** and **6** could be interesting starting materials to synthesise additional analogs for the future prospects.

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