



Cite this: *RSC Adv.*, 2025, 15, 44213

Received 13th August 2025  
Accepted 7th November 2025

DOI: 10.1039/d5ra05956a

rsc.li/rsc-advances

# An improved and convenient new synthesis of the pheromone components of the tomato leafminer *Tuta absoluta*

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A C6 + C4 + C4 regiodivergent synthesis of (3*E*,8*Z*,11*Z*)-3,8,11-tetradecatrienyl acetate (1) and (3*E*,8*Z*)-3,8-tetradecadienyl acetate (2), the major and minor sex pheromone components of the tomato leafminer *Tuta absoluta*, has been developed. The route employs alkylation of THP-protected 4-bromo-1-butanol followed by Wittig reactions, enabling preparation of each pheromone in seven steps (longest linear sequence).

Tomato (*Lycopersicon esculentum*) is an economically important crop cultivated worldwide, yet it is highly susceptible to insect damage. Among the most destructive pests in Brazil and other South American countries is *Tuta absoluta* (Lepidoptera: Gelechiidae). This insect infests tomato plants at all growth stages, from seedlings to mature plants, and can cause yield losses of up to 100%.<sup>1</sup> Chemical control has been the primary management strategy, but its effectiveness is limited due to the pest's concealed feeding habits and rapid development of insecticide resistance.<sup>2</sup> Environmentally sustainable alternatives are therefore urgently needed.

No environmentally acceptable control methods are currently available for this pest. Blanket applications of conventional insecticides, the most common approach, are largely ineffective because larvae feed within leaves, stems, and fruit, where they are protected from contact sprays.<sup>3</sup> Continuous pesticide use further promotes the development of resistant populations.<sup>4</sup> Moreover, pesticide residues can accumulate in the food web, posing risks to non-target organisms, including humans. An alternative control strategy informed by the chemical ecology of *T. absoluta* is therefore highly desirable.

Integrated pest management (IPM) strategies are increasingly applied to control *T. absoluta*.<sup>5</sup> Pheromone-based control is particularly promising, as female moths release potent sex pheromones that attract conspecific males. In 1995, Attygalle identified the major pheromone component as (3*E*,8*Z*,11*Z*)-3,8,11-tetradecatrienyl acetate (1) and reported its first synthesis.<sup>6</sup> The minor component was later identified as (3*E*,8*Z*)-3,8-tetradecadienyl acetate (2) (Fig. 1).<sup>7</sup> Field trials confirmed that the pheromone blend strongly attracts males,

and mating disruption using the major component alone is as effective as chemical control.<sup>8</sup>

Previous synthetic strategies have primarily varied in the site of key bond formation. In the C5 + C5 + C4 approach (Scheme 1a),<sup>6,9</sup> the C4–C5 bond was constructed *via* alkylation of THP-protected 3-buten-1-ol under *n*-BuLi conditions. In the C4 + C1 + C9 strategy,<sup>10</sup> a Li<sub>2</sub>CuCl<sub>4</sub>-catalyzed coupling between a Grignard reagent and an allylic substrate forms the C5–C6 bond. More recently, a C6 + C2 + C6 route based on the Wittig reaction has been reported (Scheme 1c).<sup>11</sup> This approach begins from hexane-1,6-diol, proceeding *via* a Knoevenagel condensation to form the C2–C3 bond, followed by a Wittig reaction to establish the C8–C9 bond.

In the C8 + C1 + C5 strategy, exo-2-hydroxyethyl-substituted cyclopropanol was employed as the starting material to construct an aldehyde bearing an eight-carbon backbone. Through a Corey–Fuchs transformation followed by a sequence of copper(i)-mediated coupling reactions between two alkynes, the C8–C9 (sp–sp) and C9–C10 (sp–sp<sup>3</sup>) linkages were successfully established (Scheme 1d).<sup>12</sup> In the C6 + C4 + C4 strategy, the C8–C9 (sp–sp) bond was formed *via* a Wittig reaction, while the C4–C5 bond was constructed by alkylation of THP-protected 3-buten-1-ol with an eight-carbon intermediate (Scheme 1e).<sup>13</sup> In the C6 + C5 + C3 strategy, a combination of Wittig reaction and cross-metathesis (CM) effectively shortened the synthetic sequence for two pheromones, although purification was

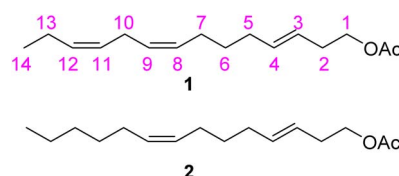
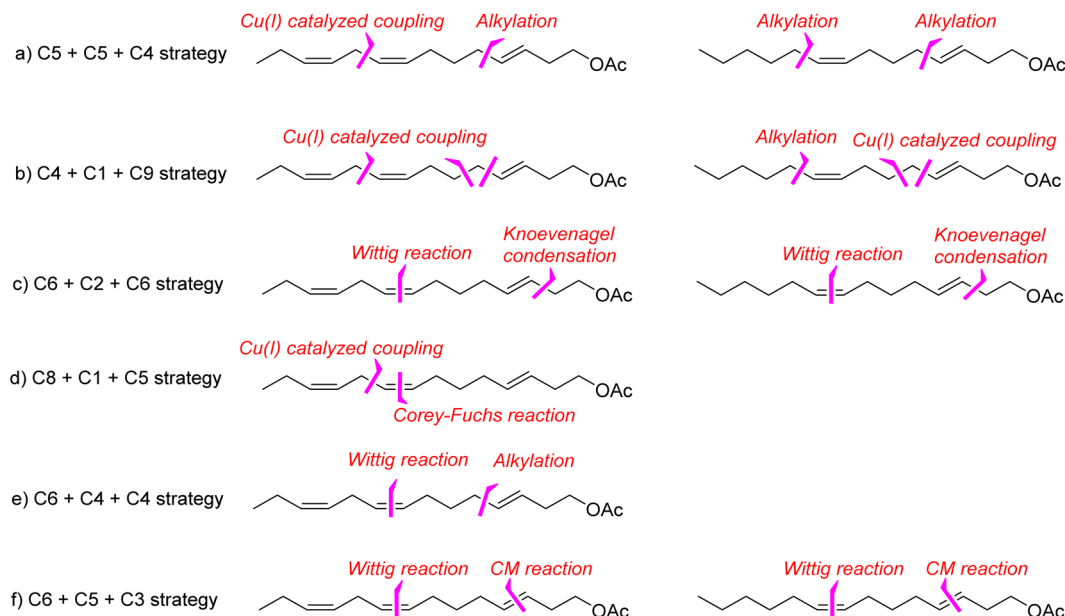


Fig. 1 Structure of (3*E*,8*Z*,11*Z*)-3,8,11-tetradecatrienyl acetate (1) and (3*E*,8*Z*)-3,8-tetradecadienyl acetate (2).

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Scheme 1 A brief outline of the previous syntheses of **1** and **2**.

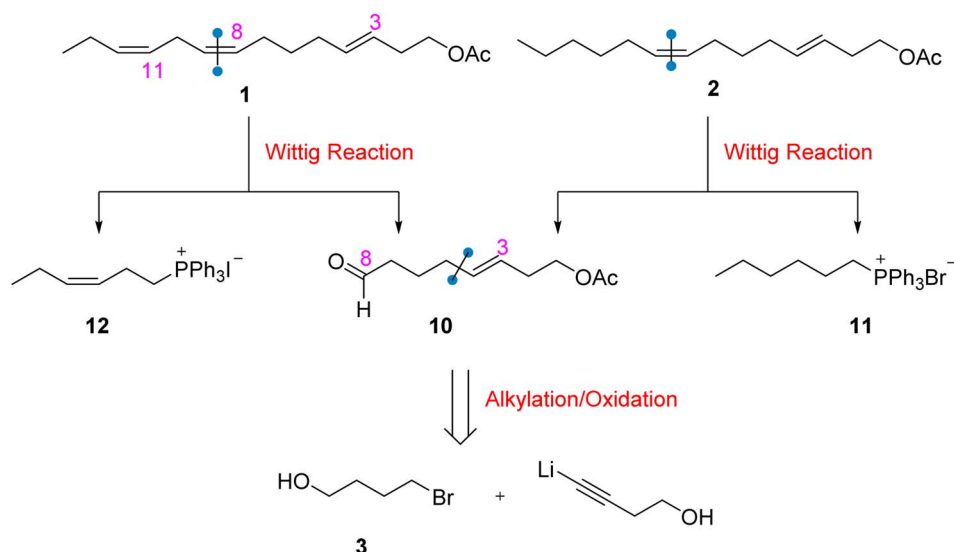
complicated by the formation of stereoisomeric byproducts (Scheme 1f).<sup>14</sup>

Reported syntheses of these two pheromones typically require more than ten steps. Given the severe threat posed by the pest, the strong biological activity of its pheromones, and the limited availability of these compounds, there is a clear need for a more efficient and economical synthesis from readily available materials. Here, we report a concise and efficient synthesis of pheromones **1** and **2** of *Tuta absoluta*. The strategy employs a convergent sequence, with formation of the C8–C9 bond as the key step *via* a Wittig reaction.

Retrosynthetic analysis indicates that pheromones **1** and **2** can be assembled from the eight-carbon fragment (*E*)-8-oxooct-3-enyl acetate (**10**) and the appropriate Wittig reagents (**12** or **11**,

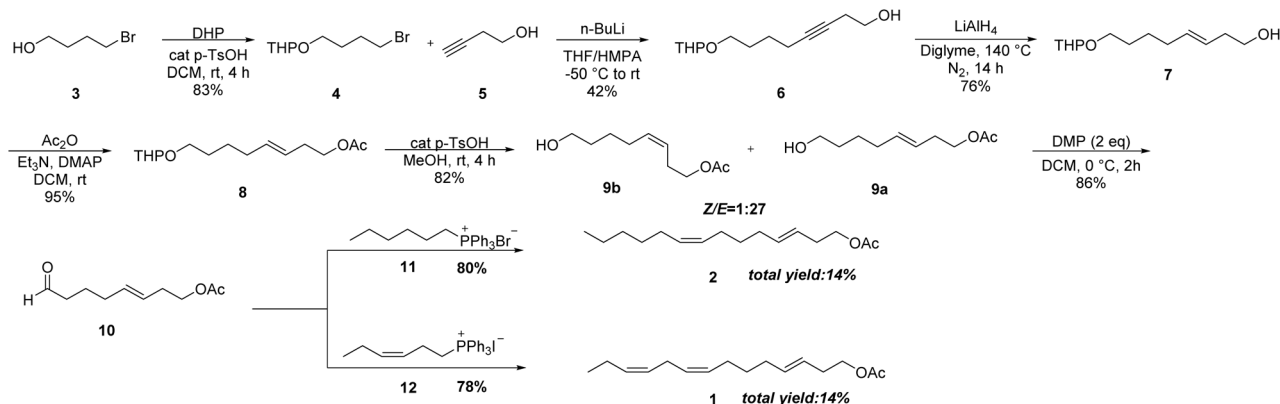
respectively). Synthesis of fragment **10** is achieved *via* alkylation of alcohol **3** followed by oxidation (Scheme 2).

Following the synthetic plan, pheromones **1** and **2** were prepared from commercially available 4-bromo-1-butanol (**3**). Alkylation of its THP-protected derivative (**4**) afforded compound **6**. Reduction of **6** with LiAlH<sub>4</sub> in diglyme at 140 °C for 14 h yielded the *E*-olefin **7** in 76% yield. Attempts to replace the THP protecting group with TBDPS were unsuccessful due to instability under the reduction conditions. Olefin **7** was then acetylated and deprotected to furnish alcohol **9a** in a *Z/E* ratio of 1 : 27. Oxidation of **9a** with DMP afforded aldehyde **10**, which underwent Wittig reaction with phosphate salt **11** to produce diene pheromone **2** (14% total yield), or with phosphate salt **12** to give triene pheromone **1** (14% total yield) (Scheme 3). The



Scheme 2 Retrosynthetic analysis of pheromone **1** and **2**.



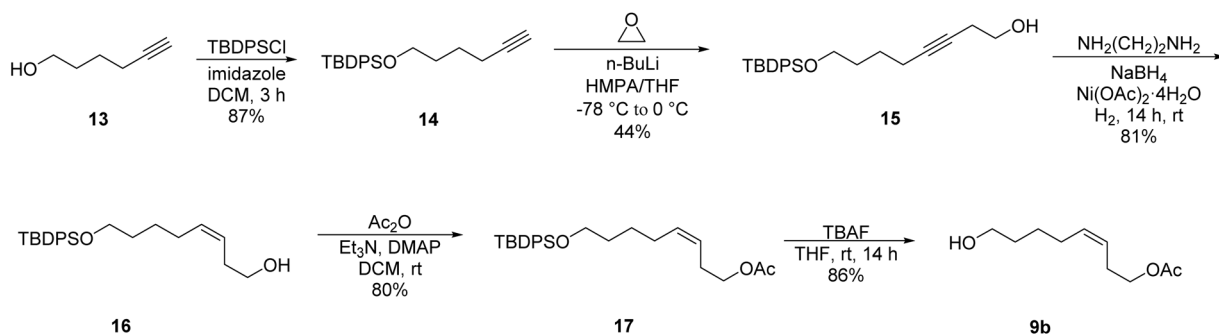
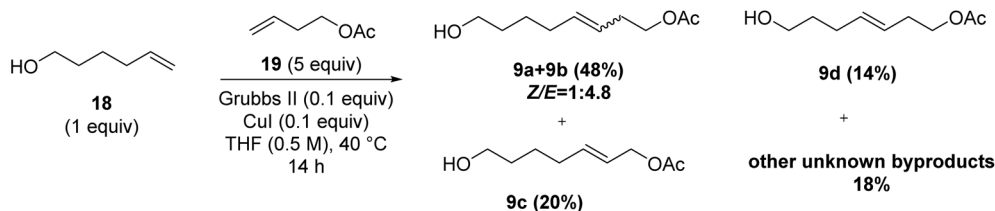
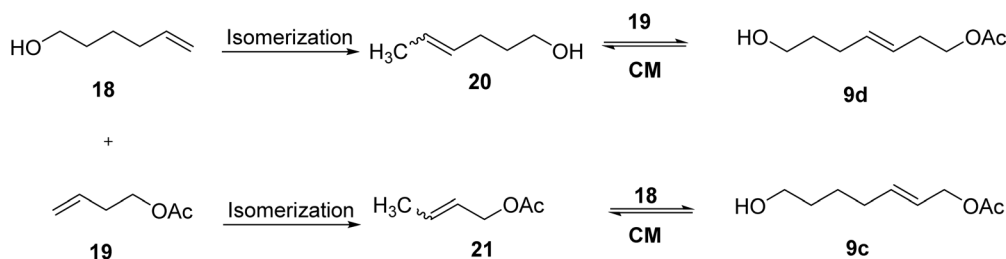


Scheme 3 Syntheses of pheromone 1 and 2.

NMR spectra of synthetic pheromones **1** and **2** matched the reported values, thus confirming the double-bond configuration.<sup>9</sup>

To quantify the stereoisomer **9b** present in **9a**, **9b** was independently synthesized. Starting from alkyne alcohol **13**, TBDPS

protection afforded intermediate **14**. Deprotonation with *n*-BuLi generated the terminal alkyne anion, which was quenched with excess ethylene oxide to yield alcohol **15** in 44% yield. Subsequent hydrogenation, acetylation, and deprotection furnished alcohol **9b** (Scheme 4).

Scheme 4 Synthesis of (Z)-8-hydroxyoct-3-en-1-yl acetate (**9b**).Scheme 5 Synthesis of (E)-8-hydroxyoct-3-en-1-yl acetate (**9a**) by olefin cross-metathesis.Scheme 6 Proposed pathway of the generation of **9c** and **9d**.

Cross-metathesis (CM) has recently been applied to the synthesis of various insect pheromones, including those of Lepidoptera, *Tenebrio molitor*, and *Aromia bungii*.<sup>15</sup> To simplify the synthesis of **9a**, we explored an olefin cross-metathesis route as a protecting-group-free strategy (Scheme 5). However, the reaction between **18** and **19** showed limited efficiency. The major products were (Z)-8-hydroxyoct-3-en-1-yl acetate (**9b**) and two homologues with one fewer carbon (**9c** and **9d**).<sup>16</sup> The formation of **9c** and **9d** is likely initiated by isomerization of **18** and **19** to **20** and **21**, respectively, followed by cross-metathesis to produce **9c** and **9d** (Scheme 6).<sup>17</sup>

## Conclusions

In summary, we have developed a regiodivergent synthesis of insect pheromones **1** and **2** using a C6 + C4 + C4 strategy. Alkylation of THP-protected 4-bromo-1-butanol with 3-butyne-1-ol constructed the C4–C5 bond, and a Wittig reaction formed the C8–C9 double bond. Each pheromone was obtained in seven steps (overall eight operations), representing the shortest syntheses to date of pheromone **1** (14% total yield) and pheromone **2** (14% total yield). An alternative protecting-group-free approach to **9a** via olefin cross-metathesis was also explored, though separation was complicated by byproducts **9b**, **9c**, and **9d**. Further optimization of this route is ongoing.

## Conflicts of interest

There are no conflicts to declare.

## Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information: experimental details, additional experimental results, characterization data, and copies of NMR spectra for all new products (in PDF format). See DOI: <https://doi.org/10.1039/d5ra05956a>.

## Acknowledgements

We are grateful for financial supports from NSFC (22071113) and the Committee of Science and Technology of Tianjin (24JCYBJC01960).

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