Enantioselective synthesis of *Anomala osakana* pheromone and *Janus integer* pheromone: a flexible approach to chiral γ-butyrolactones†

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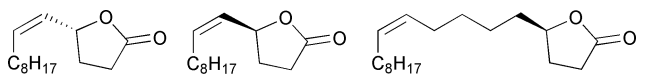
The enantioselective synthesis of *Anomala osakana* pheromone and *Janus integer* pheromone has been achieved without using any protecting groups. The synthesis involved using an asymmetric alkynylation to obtain γ-hydroxy-α,β-acetylenic esters with high ee (84%) and yields (~80%), followed by selective hydrogenation and lactonization in high overall yields (87% and 89%).

Chiral γ-butyrolactone frameworks are present in a large number of natural products[1], such as flavour components[2], sex pheromones of different insects[3] and plant-growth regulators.[4] These backbones are also important synthetic intermediates for many bioactive compounds.[5] In general, only one enantiomer of these chiral compounds displays strong bioactivity.[6] However, there are few enantioselective synthetic approaches to the chiral γ-butyrolactones.[7]



(4*R*, 5*Z*)-**1** Japonilure (4*S*, 5*Z*)-**1** *Anomala osakana* Pheromone (4*R*, 9*Z*)-**2** *Janus integer* pheromone

(4*R*,5*Z*)-**1** (Japonilure) is the sex pheromone of females of the Japanese Beetle, *Popillia japonica*[8], and its isomer (4*S*,5*Z*)-**1** is the pheromone of the Osaka Beetle, *Anomala osakana*.[10e] (4*R*,9*Z*)-**2** (*Janus integer* pheromone) is the sex pheromone of the female currant stem girdler, *Janus integer*.[9] The (*Z*)-double bond and a chiral γ-butyrolactone are present in all three of these pheromones, as well as in many other bioactive compounds.[10] Although asymmetric synthesis of (4*R*,5*Z*)-**1** and (4*R*,9*Z*)-**2** has been reported[11,12], chiral auxiliaries[11c] or chiral epoxides[7e,12a,12c] were generally explored for construction of the chiral center of the chiral γ-butyrolactone fragment.

Recently, we have developed a series of convenient protocols for the asymmetric alkynylation of aldehydes.[13] A variety of chiral propargylic alcohols can be synthesized under mild conditions. Highly functionalized chiral γ-hydroxy-α,β-acetylenic esters, which can be transformed into multi-substituted chiral γ-butyrolactones (Fig. 1), have also been provided by the addition of methyl propiolate (MPA) to various aldehydes with high enantioselectivity and good yield.[13e-f] As part of our ongoing studies on the application of asymmetric alkynylation to synthetic

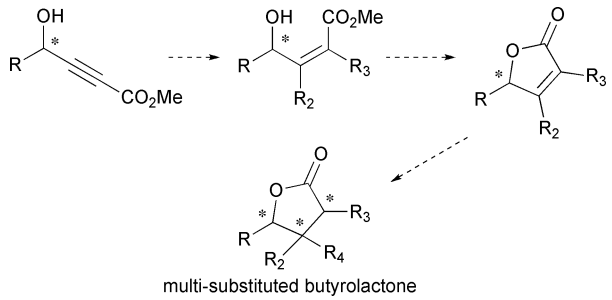


Fig. 1 Conversion of γ-hydroxy-α,β-acetylenic esters to multi-substituted chiral butyrolactone.

chemistry, we intend to develop a concise and versatile approach to chiral γ-butyrolactones employing γ-hydroxy-α,β-acetylenic esters as key intermediates.

Although exploring asymmetric alkynylation for construction of the chiral center in the synthesis of japonilure and its isomer (**1**) has been reported by Santos and Francke (Fig. 2)[11a], this strategy is limited, mainly for the following reasons: (1) routine functional group protection and deprotection would be required while using carbon substituted fragment **C** to synthesize multi-substituted γ-butyrolactones; (2) a long refluxing time‡ is required for preparing the alkynylzinc by combining alkyne **B** with diethylzinc. Also, unexpected side-reactions might easily occur as few functional groups can tolerate these harsh conditions, especially in the presence of diethylzinc. Furthermore, a terminal carbon–carbon triple bond has to troublesomely be constructed in fragment **B**. Herein, we report our convenient synthesis of (4*S*,5*Z*)-**1** and (4*R*,9*Z*)-**2**.

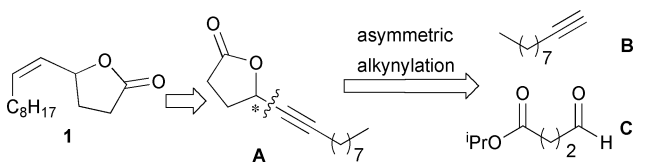


Fig. 2 Asymmetric alkynylation in the synthesis of japonilure.

Retrosynthetic analysis of (4*S*,5*Z*)-**1** and (4*R*,9*Z*)-**2** is shown in Fig. 3. The key intermediate (**8**) can be easily prepared *via* the asymmetric addition of methyl propiolate to decynylaldehyde **5**. Semi-hydrogenating the triple bonds of the chiral γ-hydroxy-α,β-acetylenic ester **8** by Lindlar catalyst can gave intermediate **9**, which contains an isolated double bond and a conjugated one. Then (4*S*,5*Z*)-**1** or (4*R*,9*Z*)-**2** can be afforded simply by exploring stereoselective reduction of the conjugate C–C double bond followed by intramolecular lactonization.

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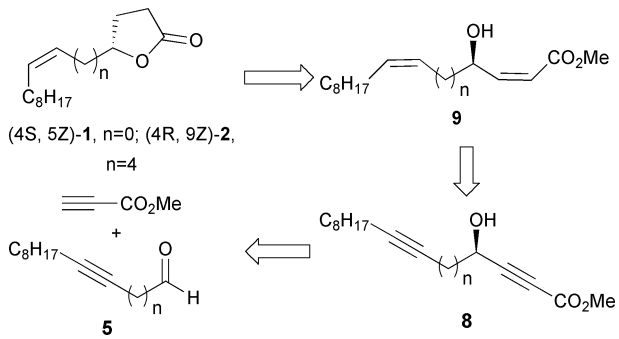
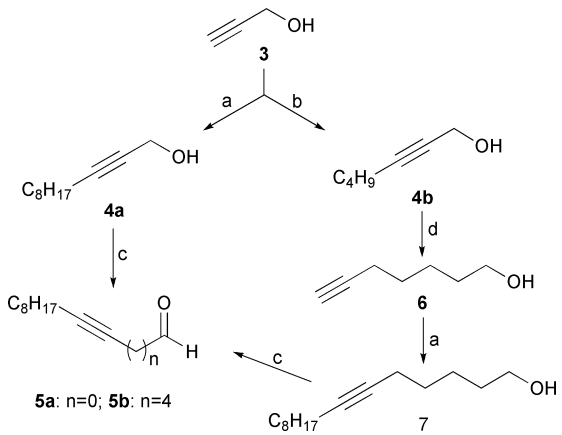


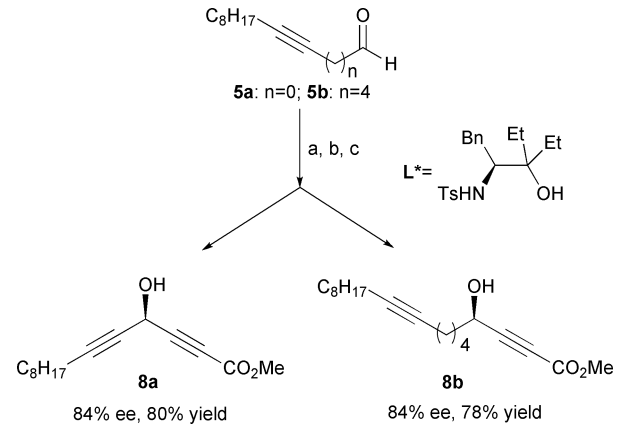
Fig. 3 Retrosynthetic analysis of (4*S*,5*Z*)-**1** and (4*R*,9*Z*)-**2**.

In the first stage of our synthesis, decynylaldehyde **5** was easily prepared using commercially available propargylic alcohol **3**, 1-bromobutane and 1-bromooctane as sample starting materials (Scheme 1). The prolonged reaction time for the coupling of **3** with 1-bromobutane or 1-bromooctane didn't make the yield improved.[14] However, a much higher yield (95%) for **7** was obtained based on 40% of the recovered **6**. Zipper isomerization of **4b** with KAPA reagent proceeded smoothly to afford **6** in 90% yield.[15] It is noteworthy that plenty of water is needed to quench the reaction since it is troublesome to extract **6** from 1,3-diaminopropane using a general organic solvent (DCM or Et_2O). Then decynylaldehyde **5** was afforded *via* Swern oxidation of **4a** and **7** in good yields (75% for **5a**, 73% for **5b**).[16]



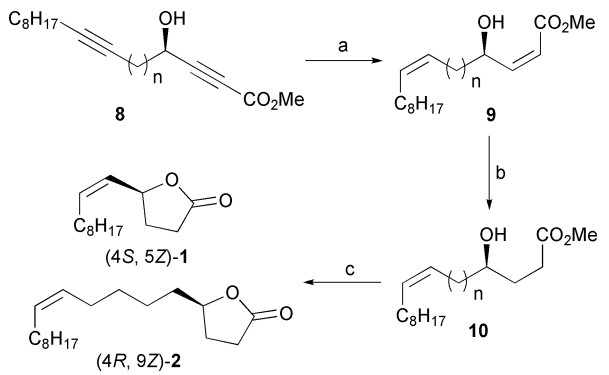
Scheme 1 *Reagents and conditions*: (a) *n*-BuLi (1.5 M in hexane), *n*-$C_8H_{17}Br$, THF, −78 °C to r.t., overnight (70% for **4a**; 95% for **7**); (b) *n*-BuLi (1.5 M in hexane), *n*-C_4H_9Br, THF, −78 °C to r.t., overnight (71%); (c) $(COCl)_2$, DMSO, TEA, DCM, −60 °C, 1 h (75% for **5a**, 73% for **5b**); (d) Li, *t*-BuOK, 1,3-diaminopropane, r.t., 3 h (90%).

With decynylaldehyde **5** in hand, the enantioselective synthesis of the key intermediate **8** (Scheme 2) was studied. A series of conditions were examined based on our initial studies[13e], including different loadings of **L***, $Ti(O^iPr)_4$, $ZnEt_2$ and DME as well as different temperatures. As we expected, (4*R*)-**8a** and (4*R*)-**8b** with the same configuration can be obtained under the same conditions using **L***–titanium as a catalyst. Since the conjugate aldehyde **5a** was less reactive than the aliphatic aldehyde **5b**, it took longer for the synthesis of **8a** than **8b**. Under the optimal conditions (see experimental section), (4*R*)-**8a** and (4*R*)-**8b** were obtained with the same ee (84%) and with high yields (80% and 78%).



Scheme 2 *Reagents and conditions*: (a) MPA (2 eqv.), **L*** (30 mol%), $ZnEt_2$ (2 eqv.), DME (1 eqv.), r.t., overnight; (b) $Ti(O^iPr)_4$ (30 mol%), r.t., 1 h; (c) **5a** or **5b**, 0 °C.

Semi-hydrogenation of **8** over Lindlar catalyst (5% of Pd on $BaSO_4$) in hexane formed **9** favorably in 2 h as detected by ^1H NMR spectrum (Scheme 3). Selectively hydrogenating the conjugate double bond of **9** with $NaBH_4$ was achieved by using CuCl as a co-catalyst.[17] This was followed by acid promoted intramolecular lactonization to afford (4*S*,5*Z*)-**1** and (4*R*,9*Z*)-**2**, respectively.[18] The overall yields for (4*S*,5*Z*)-**1** and (4*R*,9*Z*)-**2** were 87% and 89% from the key intermediate **8** in three steps with only one purification.



Scheme 3 *Reagents and conditions*: (a) Lindlar Pd/$BaSO_4$, quinoline, H_2, hexane, r.t., 2 h; (b) CuCl, $NaBH_4$, MeOH, 0 °C, 0.5 h; (c) PTSA, benzene, reflux, 2 h.

In conclusion, we have developed a flexible approach to chiral γ-butyrolactones from chiral γ-hydroxy-α,β-acetylenic esters in high overall yields using three steps and only one purification. The enantioselective synthesis of chiral γ-hydroxy-α,β-acetylenic esters can be successfully catalyzed by our catalytic system. Using this strategy, the enantioselective synthesis of *Anomala osakana* pheromone and *Janus integer* pheromone has been achieved without using any protecting groups. Application of this approach to multi-substituted chiral butyrolactones is under investigated.

Acknowledgements

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Notes and references

‡ It was necessary to reflux a mixture of succinic anhydride in isopropyl alcohol for 10 h for the preparation of isopropyl 4-oxobutanoate **C**, and 12 h was required to prepare the alkynylzinc at 100 °C in toluene.

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18 The absolute configurations of (4*S*,5*Z*)-**1** and (4*R*,9*Z*)-**2** are based on a comparison of the optical rotation with the literature values. (4*S*,5*Z*)-**1**: $[\alpha]^{20}_{D} = +49$ (c = 1.14, $CHCl_3$). Lit. (ref. 8a): $[\alpha]^{26}_{D} = +70.5$ (c = 5.5, $CHCl_3$). (4*R*,9*Z*)-**2**: $[\alpha]^{20}_{D} = +13$ (c = 1.19, $CHCl_3$). Lit. (ref. 12b): $[\alpha]^{26}_{D} = +24$ (c = 0.50, $CHCl_3$).