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Synthesis of some monosaccharide-related ester derivatives as insecticidal and acaricidal agents

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ABSTRACT

To develop natural-product-based pesticidal agents, a series of monosaccharide-related ester derivatives (**17a–q** and **18a–f**), glucose (xylose)-piperic acid/piperic acid-like conjugates, were synthesized. Three-dimensional structures of compounds **17b**, **17g**, **17h**, and **17n** were unambiguously determined by single-crystal X-ray diffraction. Especially compounds **18e** and **18f** exhibited the most potent insecticidal and acaricidal activities against *Mythimna separata* and *Tetranychus cinnabarinus*. Their structure-activity relationships were also discussed.

Introduction

Oriental armyworm (*Mythimna separata* Walker) and spider mite (*Tetranychus cinnabarinus* Boisduval) are two crop-threatening insect pests, and their outbreaks are generally hard to control.[1–3] Meanwhile, due to extensive and unreasonable application of synthetic agrochemicals, development of resistance in pest populations and negative impacts on human health and environment has occurred.[4,5] Consequently, development of the potential alternatives to efficiently control insect pests is highly desirable.[6–8]

Piperine (Fig. 1), a simple alkaloid isolated as from *Piper nigrum* Linn., exhibited a variety of biological properties including anti-inflammatory activity, antimicrobial activity, antitumor activity, and insecticidal activity.[9] Previously, by using piperine as a lead compound, we prepared a series of piperine-based hydrazone derivatives (**I**, Fig. 1),[10] and piperine-based phenylsulfonylhydrazone derivatives (**II**, Fig. 1)[11] as insecticidal agents; especially piperine-based 4-ethylphenylsulfonylhydrazone and piperine-based 4-bromophenylsulfonylhydrazone exhibited more potent narcotic activity against *M. separata* than wilfortrine and wilforgine, two macrocyclic alkaloids isolated from *Tripterygium hypoglaucum* Hutch.[11] On the other hand, Xu et al. pioneeringly reported some glucose-fipronil conjugates (**III** and **IV**, Fig. 1) showing excellent phloem mobility.[12–16] Huang et al. found that some fluorine-containing saccharide esters (**V** and **VI**, Fig. 1) showed potent antiviral activities against tobacco mosaic virus.[17] In continuation of our program aimed at the development of natural-product-based pesticidal agents,[18–20] therefore, in this Letters some glucose (xylose)-piperic acid conjugates (**VII**, Fig. 1) were prepared by combination of glucosides with the piperic acid together. Meanwhile, to study the structure-activity relationships of these type compounds, other glucose (xylose)-piperic acid-like conjugates (**VIII** and **IX**, Fig. 1) were also synthesized. Their insecticidal and acaricidal activities were evaluated against *Mythimna separata* and *Tetranychus cinnabarinus*.

As shown in Scheme 1, 1,2,3,4-tetra-*O*-acetylxylose (**2a**) and 1,2,3,4,6-penta-*O*-acetylglucose (**2b**) were firstly prepared by reaction of iodine with xylose (**1a**) and glucose (**1b**), respectively.[21] Then two intermediates, 2,3,4-tri-*O*-acetyl-*β*-D-xylopyranosyl-bromine (**3a**) and 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl-bromine (**3b**), were smoothly obtained by reaction of bromine with **2a** and **2b**, respectively.[22]

As described in Scheme 2, malonic acid reacted with benzaldehydes (**4a–c**) to give cinnamic acids (**5a–c**);[23] methyl cinnamates (**6a–c**) were prepared by reaction of **5a–c** with methanol in the presence of conc. sulfuric acid.[10] Then reduction of **6a–c** with $LiAlH_4$ and $AlCl_3$ afforded γ-phenylallyl alcohols (**7a–c**), which were oxidized by MnO_2 to produce phenylacrolein (**8a–c**).[10]

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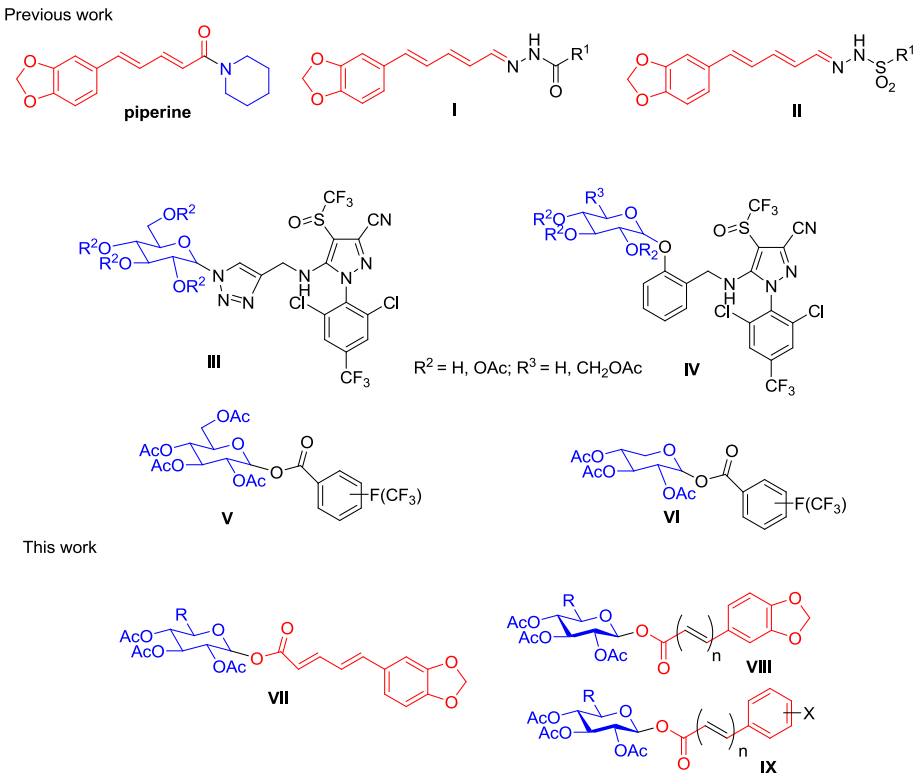
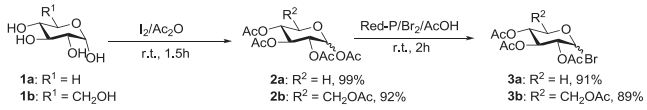


Fig. 1. The chemical structures of piperine, its derivatives (**I** and **II**), monosaccharide-related derivatives (**III**–**VI**), and target compounds **VII**–**IX**.



Scheme 1. Synthesis of 2,3,4-tri-*O*-acetyl-*β*-D-xylopyranosylbromine (**3a**) and 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosylbromine (**3b**).

Finally, 5-phenyl-2,4-pentadienoic acids (**9a**–**c**) were obtained by reaction of **8a**–**c** with malonic acid.[23] 3,4-Methylenedioxybenzoic acid (**12**) and 3,4-methylenedioxycinnamic acid (**13**) were obtained from 3,4-methylenedioxybenzaldehyde (**11**),[24] which was prepared from 3,4-dihydroxybenzaldehyde (**10**).[25] The piperic acid (**15**) was obtained from piperine (**14**) by the basic hydrolysis.[26]

As shown in Scheme 3, target compounds **17a**–**q**, and **18a**–**f** were obtained by reaction of 2,3,4-tri-*O*-acetyl-*β*-D-xylopyranosylbromine (**3a**)/2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosylbromine (**3b**) with the corresponding carboxylic acids (**5a**–**c**, **9a**–**c**, **12**, **13**, **15**, and **16a**–**c**). Their structures were well characterized by ^{1}H NMR, optical rotation, HRMS and mp (see Supplementary data).

The represental three-dimensional structure of **17b** was shown in Fig. 2, and other X-ray crystal structures of compounds **17g**, **17h**, and **17n** were depicted in Figs. S1–S3 (see Supplementary data). The substituents on the C=C double bond of **17b**, **17h**, and **17n** all adopted *E* configuration. Crystallographic data (excluding structure factors) for the structures of **17b**, **17g**, **17h**, and **17n** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1552146, 1552149, 1552147, and 1552150, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

The insecticidal activity of compounds **17a**–**q**and **18a**–**f** against the pre-third-instar larvae of *Mythimna separata* was evaluated by leaf-dipping method at a concentration of 1 mg/mL.[27–29] Toosendanin, a commercial botanical insecticide isolated from *Melia azedarach*, was used as a positive control at 1 mg/mL. Leaves treated with acetone alone were used as a blank control group. The symptoms of *M. separata* treated with the above compounds only during larval and pupation stages were in the same way as in our previous reports.[27–29] For example, some larvae with the wrinkled bodies died at the larval stage (Fig. S4, see Supplementary data), and some larvae molted to malformed pupae or died during the pupation period (Fig. S5, see Supplementary data). Interestingly, in this experiment malformed moth did not appear during the adult emergence stage. Finally, the percentages of the final mortality rates (FMRs) at different growth stages of **17n**, **18b**, **18c**, **18e**, **18f** and toosendanin were described in Fig. 3. The percentages of FMRs at larval, pupation, and adult emergence stages of toosendanin were 53.3%, 16.1% and 28.6%, respectively. On the contrary, the percentages of FMRs of **17n**, **18b**, **18c**, **18e**, and **18f** were only at larval and pupation stages. Especially more than half of FMRs for compounds **17n**, **18b**, **18c**, **18e**, and **18f** were at the pupation stage. As shown in Table 1, among all derivatives, only 2,3,4-tri-*O*-acetyl-*β*-D-xylopyranosylcarbonyl derivative **18f** showed higher insecticidal activity than piperine and toosendanin; for instance, FMRs of **18f**,piperine and toosendanin were 51.7%, 44.8%, and 48.3%, respectively. Generally, the insecticidal activity of **18a**–**f** was more potent than that of **17a**–**q**, and it suggested that the 3,4-methylenedioxy of **18a**–**f** was necessary for the activity. The insecticidal activity of 2,3,4-tri-*O*-acetyl-*β*-D-xylopyranosylcarbonyl derivatives **18d**–**f** was more potent than that of 2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosylcarbonyl derivatives **18a**–**c**. Among derivatives **18a**–**f**, it demonstrated that introduction of one C=C double bond or two C=C double bonds on **18a** or **18d** was impor-