Synthesis and Biological Activity of 2,3-Diol Stereoisomers of 28-Homobrassinolide and Brassinolide

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As possible candidates for natural products and metabolites, three 2,3-diol stereoiosomers of 28-homobrassinolide (28-HBL) and those of brassinolide (BL) were synthesized and their biological activities evaluated by a modified dwarf rice lamina inclination assay, indicating that the biological activity decreased in the order 2α,3α-, 2α,3β-, 2β,3α- and 2β,3β-diol isomers of both the 28-HBL and BL series, suggesting that epimerization of configuration at the 2,3-diol position is an inactivation step in metabolism.

We have reported the presence of three unknown stereoisomers of 28-homobrassinolide (28-HBL) **1a** in Japanese cedar.[2] Based on the fact that up to date all natural BRs with the 22,23-diol group have the (22*R*,23*R*)-configuration,[1] the natural occurrence of four 2,3-diol group stereoisomers of castasterone,[1] and also the results of metabolic studies of BRs[1,3] we have at first selected three 2,3-diol stereoisomers of 28-HBL **1a** as possible candidates for the natural products. In addition, a metabolic study of brassinolide (BL) **1b** has suggested that BL **1b** is metabolized into some conjugates, and aglycone parts of them are assumed to be BL isomers of unknown configuration.[4] Thus, to identify the natural products and the metabolites and also to obtain information on the biochemical significance of these epimerized BRs, we undertook the synthesis of 2-epi-28-HBL (**2a**), 3-epi-28-HBL (**3a**) and 2,3-diepi-28-HBL (**4a**), and also that of 2-epiBL (**2b**), 3-epiBL (**3b**) and 2,3-diepiBL (**4b**) (Fig. 1) and evaluated their biological activity.

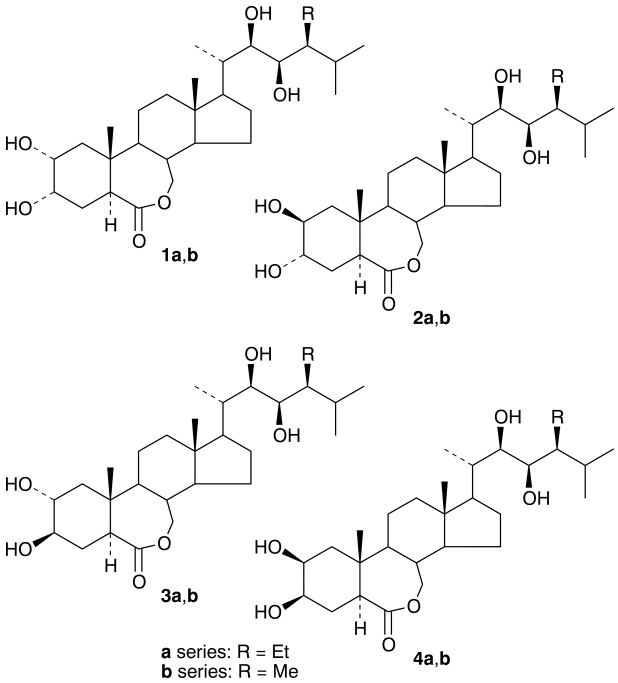

Fig. 1 Structures of 28-homobrassinolide, brassinolide and their 2,3-diol stereoisomers

The three 28-HBL isomers **2a**, **3a** and **4a** were synthesized by introduction of a 7-oxalactone group into the B-ring of stigmasterol and that of 2β,3α-, 2α,3β- and 2β,3β-diol groups. Key reactions for the 2- and 3-epimers were opening of an 2α,3α-epoxide with $HClO_4$ and reduction of the 3-oxo group. The 2,3-diepimer was elaborated from a by-product of OsO_4 dihydroxylation of the Δ^2-steroid. After contracting the A/B-ring part, the (22*R*, 23*R*)-diol group was introduced into the C-22(23) double bond of each isomer by asymmetric dihydroxylation.[7] The two BL stereoisomers, 2-epiBL (**2b**) and 3-epiBL (**3b**), were synthesized from BL **1b** by the modification of its 2α,3α-diol group, and another isomer, 2,3-diepiBL (**4b**) was also prepared from 2,3-diepicastasterone.

The biological activity of these synthetic stereoisomers was evaluated by our modified dwarf rice lamina inclination assay.[11] The relative activities in both the 28-HBL and BL series were as follows: 28-HBL, **1a** (100); 2-epi-28-HBL, **2a** (2); 3-epi-28-HBL, **3a** (11); and 2,3-diepi-28-HBL, **4a** (0.05); and BL, **1b** (100); 2-epiBL **2b** (2); 3-epiBL, **3b** (12); and 2,3-diepiBL, **4b** (0.03). The results indicated that the biological activity decreased in the order of 2α,3α-, 2α,3β-, 2β,3α- and 2β,2β-diol isomers of both series. Epimerization of the configuration at the 2- and/or 3-diol position is suggested to be an inactivation step in metabolism.

Identification of the natural products is now in progress and the results will be reported elsewhere.

Techniques used: ^{1}H NMR, EI-HR-MS and FAB-HR-MS

References: 12

Fig. 2: Biological activity of 28-HBL (**1a**), 2-epi-28-HBL (**2a**), 3-epi-28-HBL (**3a**) and 2,3-diepi-28-HBL (**4a**) in the dwarf rice lamina inclination bioassay

Fig. 3: Biological activity of BL (**1b**), 2-epiBL (**2b**), 3-epiBL (**3b**) and 2,3-diepiBL (**4b**) in the dwarf rice lamina inclination assay

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