Microbial metabolism of steviol and steviol-16alpha,17-epoxide.

Yang LM, Hsu FL, Chang SF, Cheng JT, Hsu JY, Hsu CY, Liu PC, Lin SJ.

Abstract

Steviol (2) possesses a blood glucose-lowering property. In order to produce potentially more- or less-active, toxic, or inactive metabolites compared to steviol (2), its microbial metabolism was investigated. Incubation of 2 with the microorganisms Bacillus megaterium ATCC 14581, Mucor recurvatus MR 36, and Aspergillus niger BCRC 32720 yielded one new metabolite, ent-7alpha,11beta,13-trihydroxykaur-16-en-19-oic acid (7), together with four known related biotransformation products, ent-7alpha,13-dihydroxykaur-16-en-19-oic acid (3), ent-13-hydroxykaur-16-en-19-alpha-d-glucopyranosyl ester (4), ent-13,16beta,17-trihydroxykauran-19-oic acid (5), and ent-13-hydroxy-7-ketokaur-16-en-19-oic acid (6). The preliminary testing of antihyperglycemic effects showed that 5 was more potent than the parent compound (2). Thus, the microbial metabolism of steviol-16alpha,17-epoxide (8) with M. recurvatus MR 36 was continued to produce higher amounts of 5 for future study of its action mechanism. Preparative-scale fermentation of 8 yielded 5, ent-11alpha,13,16alpha,17-tetrahydroxykauran-19-oic acid (10), ent-1beta,17-dihydroxy-16-ketobeyeran-19-oic acid (11), and ent-7alpha,17-dihydroxy-16-ketobeyeran-19-oic acid (13), together with three new metabolites: ent-13,16beta-dihydroxykauran-17-acetoxy-19-oic acid (9), ent-11beta,13-dihydroxy-16beta,17-epoxykauran-19-oic acid (12), and ent-11beta,13,16beta,17-tetrahydroxykauran-19-oic acid (14). The structures of the compounds were fully elucidated using 1D and 2D NMR spectroscopic techniques, as well as HRFABMS. In addition, a GRE (glucocorticoid responsive element)-mediated luciferase reporter assay was used to initially screen the compounds 3-5, and 7 as glucocorticoid agonists. Compounds 4, 5 and 7 showed significant effects.