The inhibition of 11beta-hydroxysteroid dehydrogenase 1 (11beta-HSD1), which catalyzes the conversion of inactive 11-ketoglucocorticoids to active 11beta-hydroxyglucocorticoids, emerged as promising strategy to treat symptoms of the metabolic syndrome, including obesity and type 2 diabetes. In this study the leaves of the anti-diabetic medicinal plant loquat (Eriobotrya japonica) were phytochemically investigated following hints from a pharmacophore-based virtual screening and a bioactivity-guided approach. Determination of the 11beta-HSD1 and 11beta-HSD2 inhibitory activities in cell lysates revealed triterpenes from the ursane type as selective, low micro-molar inhibitors of 11beta-HSD1, that is, corosolic acid (1), 3-epicorosolic acid methyl ester (4), 2-alpha hydroxy-3-oxo urs-12-en-28-oic acid (6), tormentic acid methyl ester (8), and ursolic acid (9). Importantly, a mixture of loquat constituents with moderate activities displayed a pronounced additive effect. By means of molecular modeling studies and the identification of the 11beta-HSD1-inhibiting 11-keto-ursolic acid (17) and 3-acetyl-11-keto-ursolic acid (18) a structure-activity relationship was deduced for this group of pentacyclic triterpenes. The mechanism of action elucidated in the present work together with the previously determined pharmacological activities provides these natural products with an astonishing multi-targeted anti-diabetic profile.