Stereocontrolled Synthesis of Withaferin A and Withanolide D

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Synthesis of withaferin A(1a) and withanolide D(2), among the naturally occurring withanolides, have been paid the most attractive attention because of their unique structures and interesting biological activities, e.g. antitumor and antibacterial. Stereocontrolled synthesis of 1a and 2, together with some other natural withanolides, 27-deoxywithaferin A(1b), jaborosalactone A(3),B(4),D(5) and physalolactone B(6), will be reported. In the case of 1, 3, 4 and 5, the key intermediate (22S)-22,23-epoxide(8), which was prepared from a readily available 22,23-bisnorcholenic acid(7), was converted to the 25-phenylthio lactone 9, followed by introduction of the desired substituent at C-25 to give the lactone 10. On the other hand, the construction of the 20-hydroxylated side chain moiety of 2 and 6 was accomplished by direct γ-coupling reaction of the suitable enolate with (20R)-20-MOM-22-aldehyde (16), leading to natural configuration at C-22. A/B Ring functionality in 1 and 2 was stereoselectively introduced by a facile allyl sulfoxide-sulfenate rearrangement. The structures of these synthetic withanolides were confirmed by direct comparison with natural samples.