Stereoselective Synthesis of \((-\)
-Pironetin by an Iterative Prins Cyclisation and Reductive Cleavage Strategy

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Abstract: A stereoselective synthesis of pironetin, a natural product which is highly immunosuppressive and shows remarkable plant growth regulatory and antimicrobial activities, is described. The approach entails successfully the high stereoselection of Prins cyclisation. The route relies, in addition, on the reductive opening of cyclic ethers, olefin metathesis, and lithium acetylide displacement of tosylate.

Key words: natural products, Prins cyclisation, stereoselective synthesis, reductive cleavage, olefin metathesis

Pironetin (1) is an unsaturated 8-lactone derivative, which was isolated independently by two research groups from Streptomyces sp. NK10558 and from the fermentation broth of Streptomyces prantonicus PA-48153, respectively.1 Apart from plant growth regulatory and immunosuppressive activities, the biological effects of 1 and its derivatives on cell cycle progression and antitumor activities were reported.2 More importantly, the mode of action of 1 is different from those established for the immunosuppressant cyclosporine A (CsA) and FK506 that inhibit T cell activation.3 Pironetin showed suppressive effects on the responses of T and B lymphocytes to mitogens. Inspired by the biological properties and attracted by its consecutive 1,3-anti-diol system flanked by 2- or 4-alkyl groups for which we have recently established a method via Prins cyclisation,4,5 we investigated a synthesis of pironetin. Before the synthetic venture, a careful examination was made on the retrosynthetic analysis (Scheme 1). We first simplified the molecule to the intermediate 2 which has all the required stereochemistry and a homoolylic 1,3-diol system. We envisaged that this intermediate could be easily drawn from pyran 3, by a reductive opening, which in turn was expected through Prins cyclisation of acrolein and the intermediate 4. Intermediate 4, again a homoolylic 1,3-diol system, was envisaged to be available from pyranyl methanol 5 by a reductive opening. Finally, pyranyl methanol 5 could be obtained from Prins cyclisation of known homoolylic alcohol 6 and aldehyde 7.

Our synthesis of pironetin is outlined in Scheme 2. Prins cyclisation between known homooolylic alcohol 66 and aldehyde 77 in the presence of TFA8 resulted in the trifluoroacetic derivative of 5 which on direct treatment with K2CO3 in MeOH gave tetrahydropyran diol 5, the only isolable compound in 55% yield. The stereochemical aspects of such Prins cyclisations and structurally very close compounds of 5 have been discussed in detail previously.45 Transformation of the primary hydroxyl group to a tosylate using TsCl and triethylamine and protection of the secondary hydroxyl group as its THF ether using TBSCI and imidazole resulted in fully protected intermediate 8. Substitution of the tosylate using NaI in acetone followed by reductive opening5 of iodomethylpyran 9 produced alcohol 10. Alcohol 10 was converted to its methyl ether and the key homologation with homooolylic piv-

Scheme 1

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