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## A Novel Synthesis of (±) 2-epi-Validamine

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Dedicated to Professor Charles W. Rees with gratitude on the occasion of his seventy first birthday

Abstract: ( $\pm$ ) 2-epi-Validamine is synthesised in five steps by the chemical manipulation of bicyclic lactone cycloadduct of ethyl coumalate and vinylene carbonate. © 1998 Elsevier Science Ltd. All rights reserved.

2-epi-Validamine (1) was first isolated from the fermentation broth of *Streptomyces hygroscopicus* (subsp. *limoneus*).<sup>1</sup> As other known carbasugars, it exhibits a plethora of biological activities which are mainly associated with the inhibition of  $\alpha$ -glycosidase enzymes. As a constituent of validamycin A, 2-epi-validamine is currently used commercially against sheath blight of rice plants and in the prevention of damping off of cucumber seedlings.<sup>2</sup>

Previous syntheses of 2-*epi*-validamine, which have utilised either 7-oxanorbornenic  $acid^{3,4,5}$  or Quinic  $acid^6$  as starting materials, involve over ten steps. In this communication, we describe a novel, concise and very efficient synthesis of 2-*epi*-validamine.

Our retrosynthetic analysis for 2-*epi*-validamine (1) is shown below (Scheme 1). The key step in our methodology is the Diels-Alder cycloaddition of appropriately substituted 2-pyrones with their electronically matched dienophiles to stereoselectively afford bicyclic lactones such as (2).<sup>7</sup> Chemical manipulation of these cycloadducts afford densely substituted six membered rings which are synthetically very valuable. Although pyrone cycloaddition has been previously used for the construction of complex molecular architecture,<sup>7,8</sup> this is the first example of the use of this methodology in the synthesis of carbasugars.



Scheme 1

Ethyl coumalate (3) undergoes efficient cycloaddition to vinylene carbonate to afford 6:1 ratio of *endolexo* cycloadducts which can be easily separated by chromatography. Hydrogenation of the predominant *endo* cycloadduct, (4), affords bicyclic lactone (5) as a single diastereomer (Scheme 2).





## Scheme 2

Lactone (5) undergoes ammonolysis under very mild conditions to afford amide (6) without epimerisation (relative configuration confirmed by X-ray crystallography). Oxidation of the amide function followed by Hofmann rearrangement gives amine (7).<sup>9</sup> The rearrangement proceeds, as expected, with complete retention of relative configurations. Full reduction of amine (7) affords 2-*epi*-validamine (1) which is characterised as its pentaacetate, (8).<sup>4-6</sup>

In summary, we have utilised a novel methodology to develope a concise (5 steps) and very efficient (60% overall yield) synthesis of 2-*epi*-validamine. The extension of this methodology to the synthesis of a number of other carbasugars is currently under investigation and will be reported in due course.

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