

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

Kamyar Afarinkia* and Farzana Mahmood

Department of Chemistry, King's College London, The Strand, London WC2R 2LS, UK.

Received 12 June 1998; accepted 27 July 1998

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

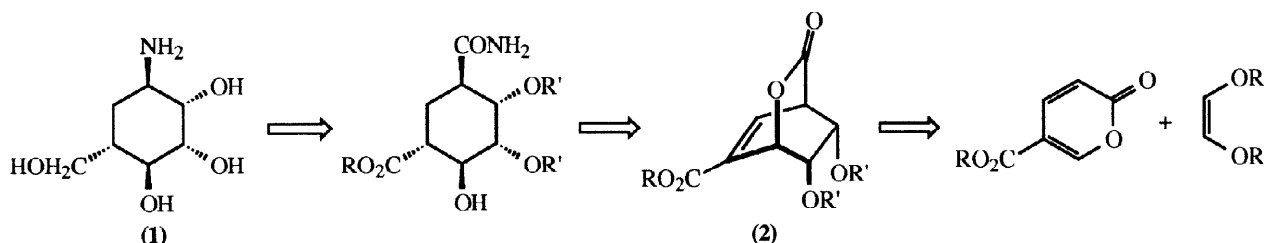
Abstract: (±) 2-*epi*-Validamine is synthesised in five steps by the chemical manipulation of bicyclic lactone cycloadduct of ethyl coumalate and vinylene carbonate.

© 1998 Elsevier Science Ltd. All rights reserved.

2-*epi*-Validamine (**1**) was first isolated from the fermentation broth of *Streptomyces hygroscopicus* (subsp. *limoneus*).¹ As other known carbasugars, it exhibits a plethora of biological activities which are mainly associated with the inhibition of α -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.²

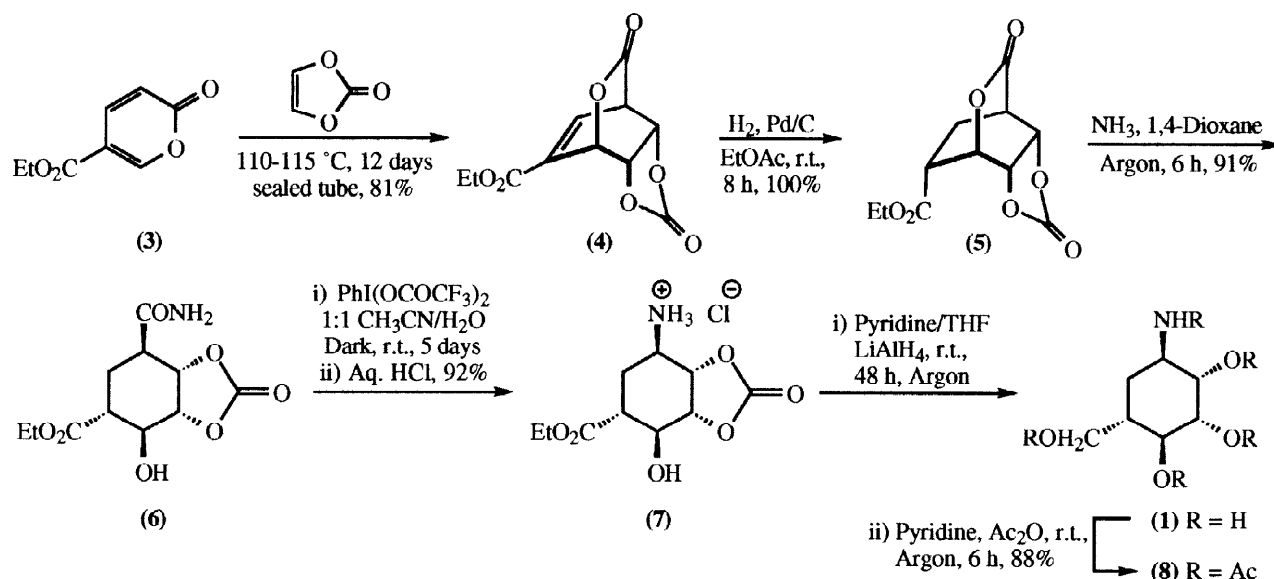
Previous syntheses of 2-*epi*-validamine, which have utilised either 7-oxanorbornenic acid^{3,4,5} or Quinic acid⁶ as starting materials, involve over ten steps. In this communication, we describe a novel, concise and very efficient synthesis of 2-*epi*-validamine.

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**).⁷ 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,^{7,8} 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 *endo*/*exo* 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).



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).⁹ 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).⁴⁻⁶

In summary, we have utilised a novel methodology to develop 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.

ACKNOWLEDGEMENT

We would like to thank Commonwealth Scholarship Commission for studentship to FM. We are indebted to the University of London Intercollegiate Research Services (ULIRS) at King's College and EPSRC's Chemical Database Service at Daresbury Laboratories for the use of their facilities. This work is made possible by a grant from University of London Central Research Fund (Stern Trust).

REFERENCES

- Iwasa, T.; Yamamoto, H.; Shibata, M. *J. Antibiot.*, **1970**, 23, 595. Kameda, Y.; Asano, N.; Yoshikawa, M.; Takeuchi, M.; Yamaguchi, T.; Matsui, K.; Horii, S.; Fukase, H. *J. Antibiot.*, **1984**, 37, 1301.
- Horii, S.; Iwasa, T.; Mizuta, E.; Kameda, Y. *J. Antibiot.*, **1971**, 24, 59. Asano, N.; Yamaguchi, T.; Kameda, Y.; Matsui, K. *J. Antibiot.*, **1987**, 40, 526. Suami, T.; Ogawa, S. *Adv. in Carbohydrate Res.*, **1990**, 48, 21.
- Ogawa, S.; Ara, M.; Kondoh, T.; Saitoh, M.; Masuda, R.; Tokokuni, T.; Sumi, T. *Bull. Chem. Soc. Jpn.*, **1980**, 53, 1121.
- Takahasi, T.; Kotsubo, H.; Iyobe, A.; Namiki, T.; Koizumi, T. *J. Chem. Soc. Perkin Trans. 1*, **1990**, 3065.
- Aceña, J. L.; Arjona, O.; Fernandez de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.*, **1994**, 59, 6419.
- Shing, T. K. M.; Tai, V. W.-F. *J. Org. Chem.*, **1995**, 60, 5332.
- For a review see: Afarinkia, K.; Vinader, M. V.; Nelson, T. D.; Posner, G. H. *Tetrahedron*, **1992**, 48, 9111.
- Markó, I. E.; Seres, P.; Evans, G. R.; Swarbrick, T. M. *Tetrahedron Letts*, **1993**, 34, 7305.
- Radhakrishna, M. R.; Parham, M. E.; Riggs, R. M.; Loudon, G. M. *J. Org. Chem.*, **1979**, 44, 1746. Loudon, G. M.; Radhakrishna, M. R.; Almond, M. R.; Blodgett, J. K.; Boutin, R. H. *J. Org. Chem.*, **1984**, 49, 4277.