Tetrahedron Letters, Vol. 33, No. 3, pp. 309-312, 1992
Printed in Great Britain

0040-4039/92 $3.00 + .00
Pergamon Press plc

Total Synthesis and Stereochemical Assignment of (±)-Epiderstatin

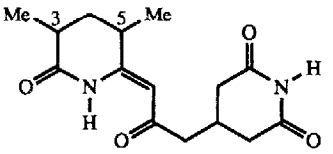
Robert L. Dow*, Marcella A. Hain and John A. Lowe III

Central Research Division, Pfizer Inc.
Groton, Connecticut 06340

Abstract: An efficient total synthesis of the glutarimide-based natural product, (±)-epiderstatin **1**, in 38% overall yield from acid chloride **4**, is described. This study has also allowed for assignment of the C_3/C_5-relative stereochemistry as trans.

Growth factor receptors possessing intrinsic tyrosine kinase activity have been suggested to function as signal transducers in both normal cellular and oncogenic processes.[1] Inhibitors of these receptors could serve as useful tools in defining these relationships as well as potential therapeutants for the treatment of diseases dependent on tyrosine kinases, i.e. cancer or immune-based disorders. Recently, Isono and coworkers isolated a potent (IC50 ~ 5 nM) inhibitor of the mitogenic activity induced by epidermal growth factor as part of a screening program directed towards the identification of epidermal growth factor receptor inhibitors.[2] This inhibitor, termed epiderstatin, is isolated as a minor component (9 mg/72 liters of broth) from a subspecies of *Streptomyces pulveraceus*. Epiderstatin has recently been shown to possess immunosuppressive effects, though no selectivity between T and B lymphocytes was observed.[3]

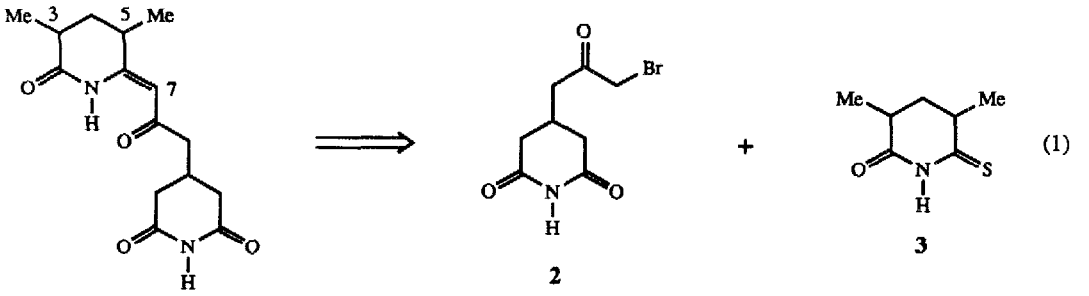
Using a combination of NMR, IR and UV spectroscopic techniques, Isono et al. proposed the structure of epiderstatin as **1**, a new member of the glutarimide family of antibiotics.[4] These spectroscopic studies, however, did not allow for the assignment of relative/absolute stereochemistries at C_3 and C_5. We undertook a total synthesis of (±)-epiderstatin to resolve the issue of relative stereochemistry at C_3/C_5 and to make sufficient quantities of this natural product available for further biological evaluation.



1

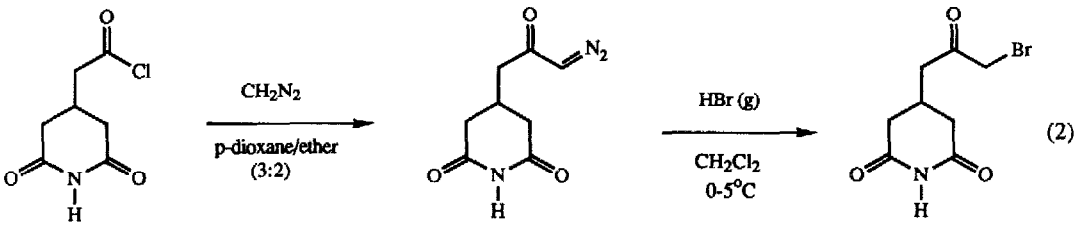
Retrosynthetic analysis of epiderstatin (eq. 1) suggested that disconnection of C_6-C_7 bond would allow for both a convergent synthesis as well as incorporation of the conjugated olefin in a stereochemically defined manner (*vide infra*). This disconnection provides the glutarimide-based intermediates, **2** and **3**. Eschenmoser

has detailed the chemical and stereochemical course of condensations between α-haloketones and cyclic thioamides and in all cases the stereochemical outcome is analogous to that present in epiderstatin.[5] For epiderstatin, α-haloketone **2** would be condensed with monothioglurarimide **3**, containing a defined C3-C5 stereochemical relationship.



1 **2** **3** (1)

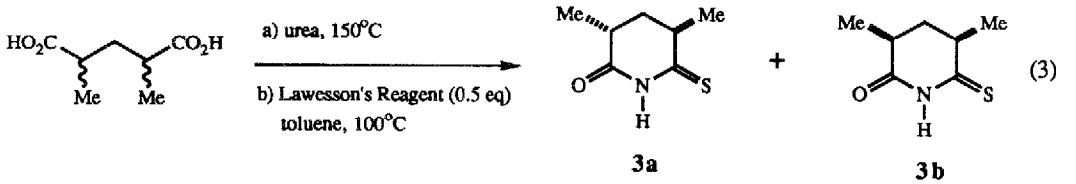
Preparation of α-bromoketone **2** was accomplished by a two-step procedure involving homologation of known acid chloride **4**[6] with diazomethane and decomposition of the resultant diazoketone with hydrogen bromide (eq. 2). Due to the insolubility of **4** in diethyl ether, the solvent commonly employed for these two-step/one-pot transformations, the first reaction is performed in a p-dioxane/diethyl ether solvent mixture. Thus, treatment of **4** with an excess of diazomethane (5 equiv.), followed by a quench (CH_3CO_2H) of the excess diazomethane and concentration of the reaction mixture *in vacuo* afforded diazoketone **5** as a stable solid. It is necessary to isolate this intermediate because p-dioxane is incompatible with the hydrogen bromide used in the next step. Reaction times for this transformation were kept to a minimum (<20 min) to suppress any competing N-methylation; the corresponding glutarimide functionality in epiderstatin has been shown to be N-methylated when exposed to diazomethane.[4] Treatment of an ice-cooled, dichloromethane solution of **5** with an excess of a solution of hydrogen bromide in dichloromethane provided **2** in 69% overall yield from **4**.



4 **5** **2** (2)

The syntheses of monothioglutarimides **3a/3b** (eq. 3) was initiated by melting a mixture of the d,l-/meso-2,4-dimethylglutaric acids with urea to provide the corresponding cis- and trans-dimethylglutarimides.[7] Reaction of this mixture of glutarimides under the conditions of Lawesson affords a 38% yield of **3a/3b**, from which the more crystalline cis isomer **3b** (mp 96-98°C) can be isolated in stereochemically pure form by

repeated crystallization from acetone/cyclohexane.[8] ^{1}H NMR assignment of these isomers was confirmed by a single crystal X-ray analysis of **3b**. Attempts to prepare **3a** and **3b** in stereochemically pure form, starting from the individual glutarimides, failed due to the partial equilibration of the monothioglutarimides which occurs under the thiolation conditions.



3a **3b** (3)

With the key synthetic intermediates **2** and **3** in hand, our attention was directed towards coupling these subunits to generate epiderstatin. For the condensation of thioamides with α-haloketones, the two reagents readily react at ambient temperatures to provide the S-alkylated intermediates, which are subsequently rearranged to the vinylogous amides by treatment with base and a thiophile.[5] In the case of monothioglutarimide **3**, attempted reaction with **2** failed to provide the corresponding S-alkylated intermediate (**7** in Scheme) even after prolonged heating. In all of these cases, both of the starting materials were recovered unchanged. However, condensation of the sodium anion of **3b** or mixtures of **3a/3b** with α-bromoketone **2** directly afforded (±)-epiderstatin and material epimeric at C_3, without the need for the addition of a thiophile to decompose the presumed intermediary epi-sulfide. The results of a small optimization study revealed that two equivalents of the sodium anion of **3**, relative to **2**, provide 40-45% yields of **1a/1b**.

The isomeric products, **1a** and **1b**, can be separated on a preparative scale by reverse phase HPLC.[9] Spectroscopic (^{1}H/^{13}C NMR, IR and UV) data obtained for synthetic (±)-**1a** matched that published for epiderstatin.[2,4] As a further confirmation of the trans-relative stereochemical assignment of epiderstatin, the C_4 hydrogens were found to be diagnostic of the relative orientation of the C_3 and C_5 methyl substituents of both **1** and **3**. That is, the C_4 methylene protons are highly diastereotopic (Δ = 0.4 ppm) in the case of the cis relative orientation, whereas in the trans isomer these protons appear as an unresolved multiplet.

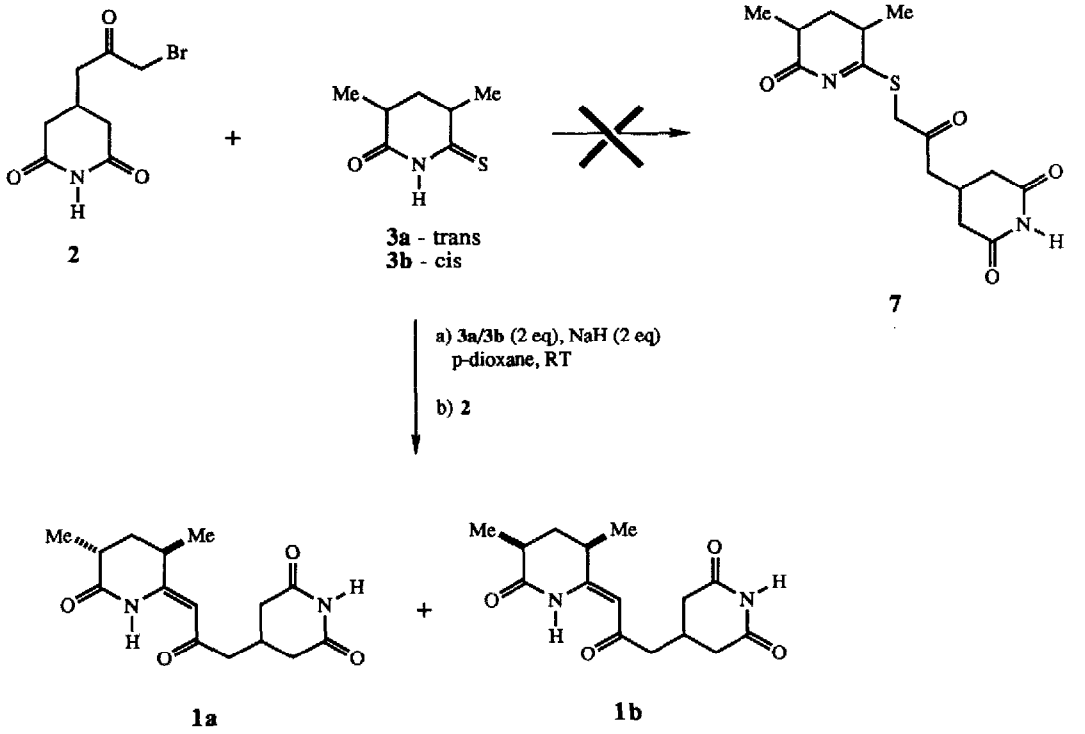
During the course of the condensation reactions in which pure **3b** is utilized, an erosion in the stereochemical integrity is observed, resulting in the production of approximately 25% of (±)-epiderstatin **1a**. For a more efficient preparation of epiderstatin, the ~1:1 mixture of **3a/3b**, obtained directly from the thiolation procedure, is condensed with **2** to afford a 3:1 mixture of (±)-epiderstatin and diastereomer **1b**.

In summary, a concise total synthesis of (±)-epiderstatin has been accomplished, confirming the structure of this unique "diglutarimide-based" natural product. This total synthetic effort has proven the C_3/C_5 relative stereochemical orientation present in epiderstatin to be trans and makes sufficient quantitites of epiderstatin and its corresponding C_3-epimer available for expanded biological evaluation.

Acknowledgements

We gratefully acknowledge the Scientific Proposal Advisory Committee at Pfizer for support of M.A.H. We would also like to thank R. Gallaschun for assisting us with HPLC separations and Dr. J. Bordner for the X-ray analysis of **3b**.

Scheme . Synthesis of (±)-Epiderstatin



References and Notes

1. Ullrich, A.; Schlessinger, J. *Cell* **1990**, *61*, 203.
2. Osada, H.; Sonoda, T.; Kusakabe, H.; Isono, K. *J. Antibiotics* **1989**, *42*, 1599.
3. Sonoda, T.; Osada, H.; Magae, J.; Isono, K. *Agric. Biol. Chem.* **1990**, *54*, 1259.
4. Sonoda, T.; Osada, H.; Uramoto, M.; Uzawa, J.; Isono, K. *J. Antibiotics* **1989**, *42*, 1607.
5. Roth, M.; Dubs, P.; Gotschi, E.; Eschenmoser, A. *Helv.* **1971**, *54*, 710.
6. Egawa, Y.; Suzuki, M.; Okuda, T. *Chem. Pharm. Bull.* **1963**, *11*, 589.
7. Crouse, G. D.; Terando, N. H. *J. Labelled Cpds. Radiopharm.* **1989**, *27*, 465.
8. Shabana, R.; Scheibye, S.; Clausen, K.; Olesen, S.O.; Lawesson, E.O. *Nouv. J. Chim.* **1980**, *41*, 47.
9. Rainin C-18 Dynamax-8 μm silica, 2.1 x 30 cm. Mobile phase = 40% methanol/water.

(Received in USA 30 September 1991)