A Stereoselective Synthesis of (±)-Actinobolamine

Andrew B. Holmes,* Alexander Kee, Tamara Ladduwahetty and David F. Smith

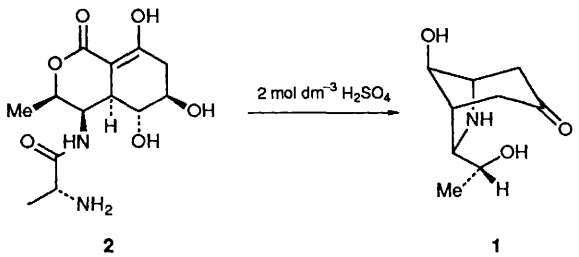
University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK

A three-step sequence involving an imino ester heterocycloaddition, stereoselective epoxidation of the adduct **4** and subsequent toluene-*p*-sulphonic acid-promoted rearrangement afforded the 6-azabicyclo[3.2.1]octane **7** in excellent overall yield; elaboration of this 6-azabicyclo[3.2.1]octane skeleton to (±)-actinobolamine is described.

Actinobolamine **1**† is the main degradation product of the antitumour compound actinobolin **2**. Its structure elucidation was first described by Munk *et al.*[1] during the search for the structure of actinobolin itself. The total synthesis of actinobolin and a close derivative, bactobolin has recently been reported by Weinreb,[2] and important earlier contributions in this area have also been made by a number of workers.[3–6]

We have previously reported the bromonium ion-induced rearrangement of the azabicyclo[2.2.2]octene **4** to an azabicyclo[3.2.1]octane skeleton present in actinobolamine and several other naturally occurring alkaloids.[7] We now report the first synthesis of (±)-actinobolamine utilising a novel toluene-*p*-sulphonic acid-induced rearrangement of the epoxide **5**.

The azabicyclo[2.2.2]octene **4**, obtained from cycloaddition[7] of the tosyl imine **3**‡ with cyclohexa-1,3-diene, was treated with *m*-chloroperoxybenzoic acid (*m*-CPBA) to afford the *anti*-epoxide **5** (Scheme 1). Slow addition of **5** in benzene/dichloromethane (1 : 1) to a suspension of toluene-*p*-sulphonic acid monohydrate ($TsOH \cdot H_2O$) in refluxing benzene resulted in the formation of the 6-azabicyclo[3.2.1]octane **7**, in consistently high yields (85–92%).

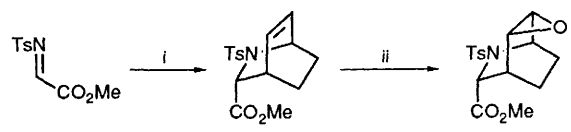


2 **1**

The proposed mechanism of this rearrangement involves participation of the sulphonamide nitrogen lone pair in the formation of an aziridinium ion intermediate **6**, followed by ring opening by attack of the tosylate ion at the bridgehead carbon atom to give the 6-azabicyclo[3.2.1]octane skeleton **7** (Scheme 2). The above mechanism is consistent with the findings of Heesing in his recent work on tricyclic aziridines,[9] and has parallels with the previously reported[7] bromonium ion rearrangement and the work of Nagata,[10] Paquette,[11] Hutchins,[12] and Krow.[13]

It was envisaged that oxygenation at C(3) could be achieved by elimination of the tosylate group followed by iodolactonisation to give intermediate **8**. In fact, all attempts to carry out this elimination in the presence of the ester side chain failed, and an alternative strategy was sought.

The 6-azabicyclooctene **9** was prepared by tetrahydropyran-2-yl (THP) protection of the hydroxy group, diisobutylalum-



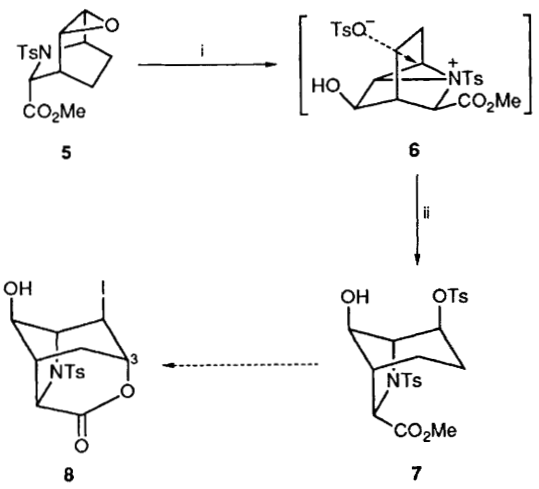
3 **4** **5**

Ts = MeC_6H_4-*p*-SO_2

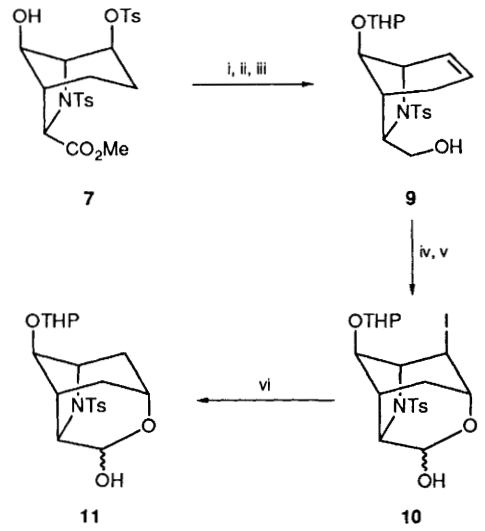
Scheme 1 *Reagents, conditions and yields*: i, cyclohexa-1,3-diene, toluene, heat, (80%); ii, *m*-CPBA, CH_2Cl_2, heat, (89%)

† The structure **1** is not to be confused with des-alaninylactinobolin, also referred to as 'actinobolamine'.[5]

‡ Tosyl imine **3** was prepared *in situ* from toluene-*p*-sulphonylisocyanate and methyl glyoxylate.[8] A manuscript reporting the addition reactions of this imine is in preparation.



Scheme 2 *Reagents, conditions and yields*: i, TsOH, PhH/CH_2Cl_2, heat; ii, 85–92%

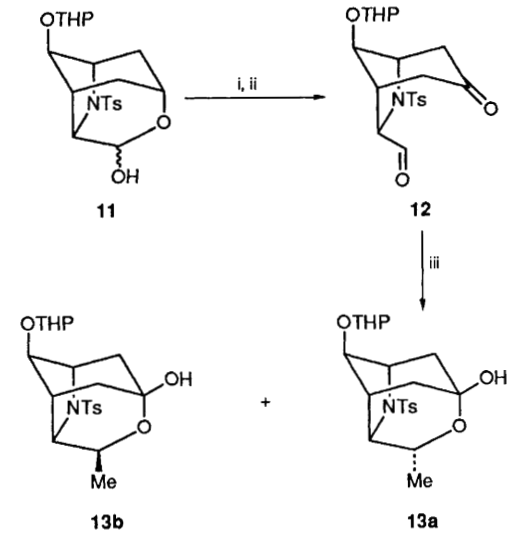


Scheme 3 *Reagents, conditions and yields*: i, 3,4-dihydro-2*H*-pyran, TsOH, CH_2Cl_2, 0 °C; ii, DIBAL, CH_2Cl_2, 0 °C; iii, $KOBu^t$, dimethyl sulphoxide (DMSO), (82%); iv, Swern oxidation[14]; v, I_2, DMSO/H_2O, (84%); vi, Bu_3SnH, azoisobutyronitrile, toluene, heat, (97%)

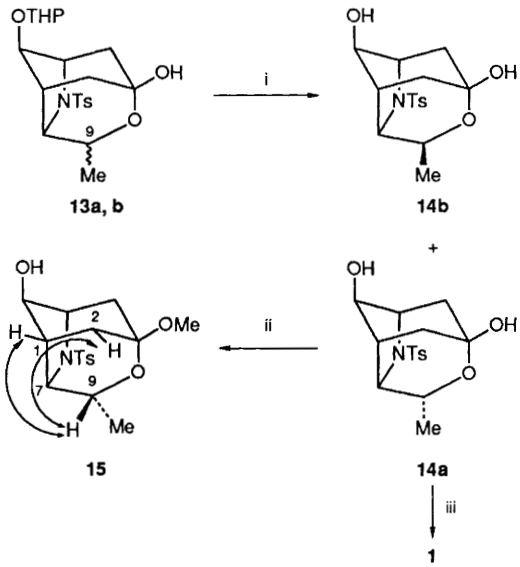
inium hydride (DIBAL) reduction of the ester to a primary alcohol and potassium t-butoxide elimination of the tosylate functionality (Scheme 3). Construction of the tricyclic hemi-acetal **11** was accomplished by Swern[14] oxidation to the aldehyde, followed by iodoacetalisation to give the iodo-acetal **10**, and subsequent reductive removal of iodine.[15]

DIBAL reduction of the tricyclic hemi-acetal **11** followed by Swern oxidation gave the corresponding dicarbonyl compound **12**, which underwent chemo- and stereo-selective Grignard addition to give the required diastereoisomer **13a** as the major product (Scheme 4). Removal of the THP protecting group, followed by separation of the diastereoisomers by HPLC gave *N*-tosylactinobolamine **14a** and its C(9) epimer **14b** (5:1 as determined by HPLC) (Scheme 5). Both **13a,b** and **14a,b** were found to be an equilibrium mixture of hydroxy-ketone and hemi-acetal forms in solution.

The stereochemistry of the C(9) centre was confirmed by NOE measurements in the ^1H NMR spectrum of *N*-tosylactin-



Scheme 4 *Reagents, conditions and yields*: i, DIBAL, CH_2Cl_2; ii, Swern oxidation, (92%); iii, MeMgBr, tetrahydrofuran (THF), −30 °C, (81%)



Scheme 5 *Reagents, conditions and yields*: i, TsOH, THF, heat, (92%); ii, TsOH, MeOH, (99%); iii, sodium naphthalenide, dimethoxyethane, −70 °C, (99%)

obolamine methyl acetal **15**, prepared from *N*-tosylactinobolamine **14a**. Irradiation of the C(9) proton gave a strong NOE to the C(2) equatorial proton and also to the C(1) proton. In addition, irradiation of the methyl group of C(9) resulted in an NOE to the C(7) proton only, thus providing evidence that the stereochemistry at C(9) is consistent with that of actinobolamine. Furthermore the absence of vicinal coupling between the C(7) and C(9) protons in **14a** is consistent with Munk's observations in related compounds.[1]

Deprotection of the nitrogen was carried out efficiently using sodium naphthalenide[16] to afford (±)-actinobolamine§ whose spectral data and that of several precursors are consistent with that of natural actinobolamine§ whose spectral

§ All new compounds gave satisfactory spectroscopic and/or analytical data.

data and that of several precursors are consistent with that of natural actinobolamine and its derivatives.[1]

In summary the highly efficient construction of 6-azabicyclo[3.2.1]octane **7** has led to the first synthesis of (±)-actinobolamine. There are relatively few methods for construction of this ring system which have been useful in total synthesis.[17–19] The methodology outlined above should be valuable in the preparation of a variety of naturally occurring alkaloids bearing this skeleton. Work is currently being undertaken to exploit this chemistry in the synthesis of such alkaloids.

We thank the SERC for supporting this work, and Merck Sharp and Dohme (Harlow) and Pfizer (Sandwich) for generous financial assistance.

Received, 3rd July 1990; Com. 0/02988B

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