The total synthesis of (±)-trichoviridin

Jack E. Baldwin,* Robert M. Adlington, Ian A. O'Neil, Andrew T. Russell and Marie L. Smith

The Dyson Perrins Laboratory, South Parks Road, Oxford, UK OX1 3QY

The total synthesis of (\pm) -trichoviridin, a naturally occurring epoxy-isonitrile, is described.

We have been interested for some time in the synthesis of fungal derived isonitrile metabolites. Recently much of our effort has been directed towards the three cyclopentyl isonitriles, isonitrins A 1, B (deoxytrichoviridin) 2 and C (trichoviridin) 3 and we have reported on the successful preparation of 1 and 2 (Fig. 1).¹ Herein we disclose in preliminary form the synthesis of trichoviridin 3. The high density of functionality in 3, bearing six chiral centres on just seven skeletal carbon atoms together with the presence of the extremely rare epoxy-isonitrile functionality conspire to make this a formidable synthetic target. To date no synthesis of a naturally occurring epoxy-isonitrile has been reported.

We considered two general strategies for the generation of the epoxy-isonitrile moiety (Fig. 2). Based on our previous experience of the ease of oxidation of the isonitrile functionality with oxygen transfer reagents, strategy A appeared the more likely approach.^{1d}

After some experimentation with a model system we found that by use of 3 equiv. of dimethyldioxirane (then destruction of the excess oxidant with extra equivalents of Hünigs base) our epoxidation–dehydration protocol delivered a 74% yield of the epoxy-isonitrile 5 (Scheme 1).²

In previous reports we have detailed the conversion of the silyloxyfulvene 6 via thiooxime 7 into vinylformamide 8 in 8 steps.^{1a} Before attempting epoxidation–dehydration of 8 we addressed the outstanding problem of its purification, this being complicated by its coelution with triphenylphosphine oxide on

reverse-phase silica gel. Adoption of our new protocol which uses polymer bound triphenylphosphine facilitated isolation and led to a mixture of two compounds 8 and 9.3 The ratio of 8 and 9 was found to be variable and we were unable to separate them. On one occasion 9 was obtained as the sole product, facilitating structure determination. Treatment of the mixture with DBU furnished the desired vinylformamide 8 in 60% overall yield (Scheme 2).

Exposure of 8 to 3 equiv. of dimethyldioxirane at -40 °C followed by in situ dehydration delivered exclusively the corresponding vinylisonitrile 10, longer reaction times or higher reaction temperatures led only to decomposition of 8. In an effort to overcome this inertness to epoxidation we turned to the more reactive methyl(trifluoromethyl)dioxirane.⁴ Aware of the propensity of this compound to rearrange then hydrolyse to trifluoroacetic acid and the sensitivity of 8 to acid, we first optimised the reaction conditions on 4 finding it necessary to employ propylene oxide as an acid scavenger and to operate at -78 °C for both the epoxidation and dehydration steps, a 70% yield of 5 being obtained. Application of these conditions to 8 gave 10 in a 50% yield together with traces of two other minor isonitriles, however, on raising the reaction temperature to -40 °C these isonitriles now became the only isolable products. After chromatography two diastereoisomeric isonitriles 11 were obtained in 16 and 52% yield respectively. From their structure it appeared that the desired epoxidation had indeed taken place





Scheme 1 Reagents and conditions: i, Dimethyldioxirane (3 equiv.), CH_2Cl_2 , -40 °C, 10 min, then $Pr_{i_2}NEt$ (10 equiv.), -40 °C, 2 min, then Tf_2O (1.5 equiv.), -78 °C, 20 min



Scheme 2 Reagents and conditions: i, Polymer bound PPh₃ (3 equiv.), AcOCHO (3 equiv.), propylene oxide, CH_2Cl_2 , room temp., 24 h; ii, DBU (5 equiv.), CH_2Cl_2 , room temp., 3 h. TBDMS = *tert*-butyldimethylsilyl chloride.



Scheme 3 Reagents and conditions: i, Dimethyldioxirane (3 equiv.), CH_2Cl_2 , -40 °C, 10 min, then Pr_2NEt (10 equiv.), 2 min, then Tf_2O (1.5 equiv.), -78 °C, 20 min



Scheme 4 Reagents and conditions: i, Methyl(trifluoromethyl)dioxirane (2 equiv.), 1,1,1-trifluoroacetone, -78 °C, CH₂Cl₂, propylene oxide, 10 min, then Prⁱ₂EtN (10 equiv.), 1 min, then Tf₂O (1.5 equiv.), -78 °C, 20 min



Scheme 5 Reagents and conditions: i, Amberlyst A-26 Br₃⁻ form (1 equiv.), propylene oxide (10 equiv.), CH_2Cl_2 , room temp., 2 h, in the dark; ii, Methyl(trifluoromethyl)dioxirane, propylene oxide, -20 °C, CH_2Cl_2 ; iii, P(OEt)₃ (10 equiv.), room temp., 1 h; iv, tetrabutylammonium fluoride (1.15 equiv.), 0 °C, THF

but had been followed by rapid ring-opening of the epoxide followed by an Amadori-type rearrangement, trapping of the tertiary alcohol by 1,1,1-trifluoroacetone accompanying this process (Scheme 4). A related ring opening of an epoxy-enamine has been reported by Adam.⁵ Faced with the apparent instability of this epoxy-formamide we elected to change to strategy B.[†]

Accepting the previously noted lability of isonitriles towards oxidation to isocyanates it was necessary to protect this functionality and we found that the well established addition of halogens to isonitriles was the most promising.^{6,7} In particular bromination of **10** with a polymer bound bromine reagent (Amberlyst A-26 Br₃- form) was found to be consistent, high yielding and facilitated isolation of the dibromoimine **12**.‡

Before attempting epoxidation we established that the reaction could be reversed. Treatment of **12** with triphenylphosphine led to complete decomposition whilst use of triethylphosphite returned **10** smoothly and in high yield (82% over two steps).⁸ The success of these latter conditions is interesting in the light of the reported tendency of trialkyl phosphites to react at the carbon atom of dichloroimines in a manner reminiscent of the Arbuzov reaction.⁸ Successive treatment of dibromoimine **12** with excess methyl(trifluoromethyl)dioxirane then triethylphosphite (10 equiv.) led, after chromatography, to a single stereoisomer of **13** in 19% yield from **10** (Scheme 5).§,¶

Finally, exposure of 13 to TBAF (1.15 equiv.) gave crystalline (\pm)-trichoviridin 3 in 68% yield after chromatography. The identity of 3 was confirmed by ¹H NMR (500 MHz) of a mixed sample of synthetic 3 with authentic material, ¹³C NMR, a high resolution mass spectrum, IR spectra and comparison of TLC data.

Footnotes

 \dagger Thiooxime 7 is synthesised as a 6:1 mixture of epimers at the exocyclic centre and can be separated at this stage by low temperature crystallisation. This change of strategy allows us to delay the separation until the vinylisonitrile 10, a more yield efficient process. For simplicity only the major isomer of 7 and 8 are shown.

‡ Use of this reagent (available from Fluka, cat. no. 16055) for the preparation of dibromoimines was developed by Dr D. Chen of these laboratories during work on a related project.

§ Due to the complexity of the ¹H NMR of the intermediate epoxydibromoimine it is not possible to say with certainty that the other diastereoisomeric epoxide is not formed then selectively decomposes.

¶ Professor A. G. M. Barrett (Imperial College) has informed us that he has developed a related strategy for the synthesis of epoxy-isonitriles. We thank him for communicating his results to us prior to publication.

|| We thank Nippon-Roche for kindly providing an authentic sample of trichoviridin.

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