Pergamon

Tetrahedron Letters 43 (2002) 8519–8522

TETRAHEDRON LETTERS

# Studies toward a synthesis of AI-77-B

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Received 18 July 2002; revised 30 August 2002; accepted 20 September 2002

**Abstract**—Utilising an intermediate prepared by an intramolecular acylnitroso Diels–Alder reaction, a suitably protected right hand part of AI-77-B was synthesised in racemic form. A modified procedure for introducing an Aoc (*tert*-amyloxycarbonyl) protecting group is discussed. 

As part of our interest in the synthesis of the gastroprotective agent AI-77-B[1] we recently reported an intramolecular acylnitroso Diels–Alder reaction with a cleavable tether,[2] related type II Diels–Alder chemistry has been reported by Shea[3] and an asymmetric version has been described by Craig.[4] We detailed the application of this reaction to the synthesis of compound **3** and herein we describe the conversion of **3** into racemic **1**, a fragment suitably protected to allow coupling to the dihydroisocoumarin part of AI-77-B (Fig. 1).

Hydrolysis of **3** proceeded smoothly by treatment with alcoholic KOH to give crude **4**. In the light of reports on the successful Boc protection of related substrates it was disappointing that treatment of **4** with $Boc_2O$ under a variety of conditions failed to deliver the desired N-Boc derivative.[5] Use of AdocF was similarly ineffectual. In as much as nucleophilicity and basicity run in parallel, the p$K_a$ data reported by Bols[6] for the protonated forms of the azasugars **7** and **8** point to the oxazine nitrogen having a poorly nucleophilic character. To assess the extent of the problem and working from previous experience[2] **4** was reacted with Z-Cl in a two phase system to afford the desired protected compound **5**. The location of the Z-group on the nitrogen was secured by the oxidation of the primary alcohol to aldehyde **6** (Scheme 1).

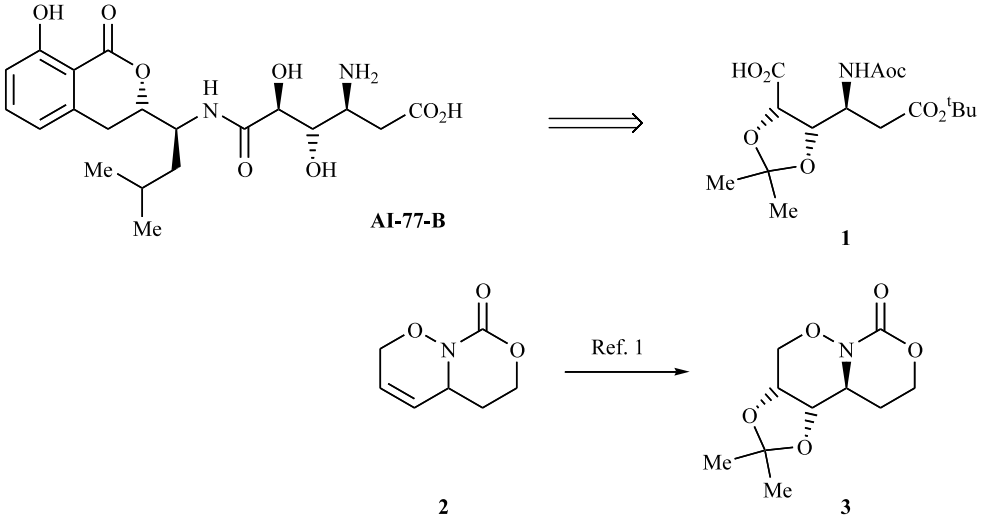


**Figure 1.**

*Keywords*: AI-77-B; Aoc protecting group; $Mo(CO)_6$; Sharpless oxidation; Widmer's reagent.
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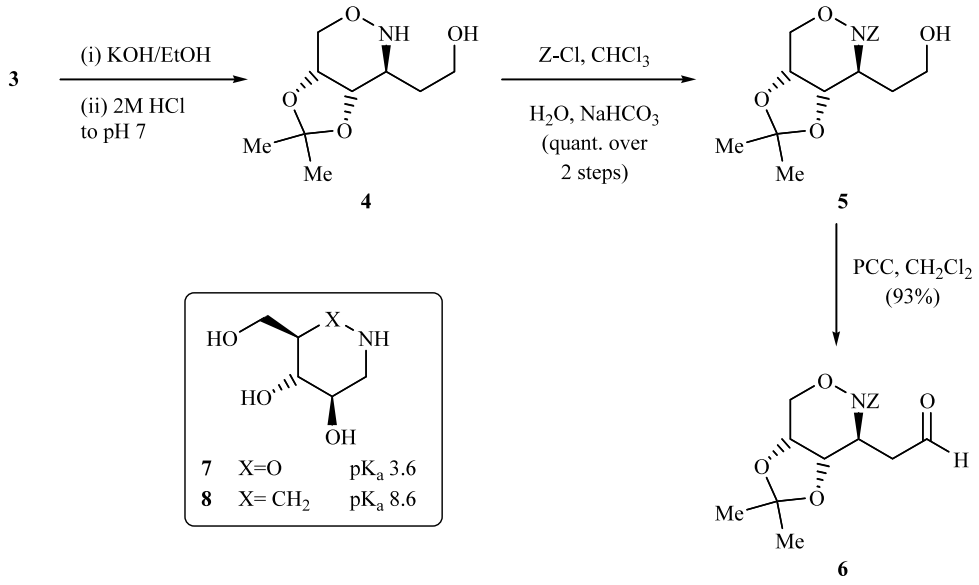
PII: S0040-4039(02)02082-8



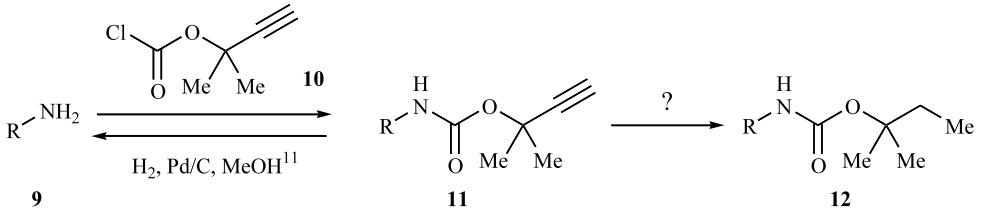

**Scheme 1.**

However, the subsequent chemistry planned for the synthesis (especially saponification of **17**[7] and global acid catalysed deprotection at the end of the synthesis) mandated a bulky, acid labile protecting group. Whilst BocCl could have been employed its marked instability made this inconvenient. Thus a more stable chloroformate was sought and a proposal by Carpino et al. of a two step protocol to introduce an Aoc (*tert*-amyloxycarbonyl) group seemed interesting (Scheme 2).[8] Recognising that the instability of BocCl originates from the stability of the *tert*-butyl cation it was proposed that substituting a methyl group ($\chi$ 2.3)[9] by a more electron withdrawing acetylene ($\chi$ 3.3)[9] should stabilise **10**. Whilst the formation of urethanes such as **11** was reported, no method for their saturation to give **12** was given.[10] The subsequent report by Southard et al. on the facile hydrogenolysis of such urethanes to recover the amines **9** gave us some concern.[11]

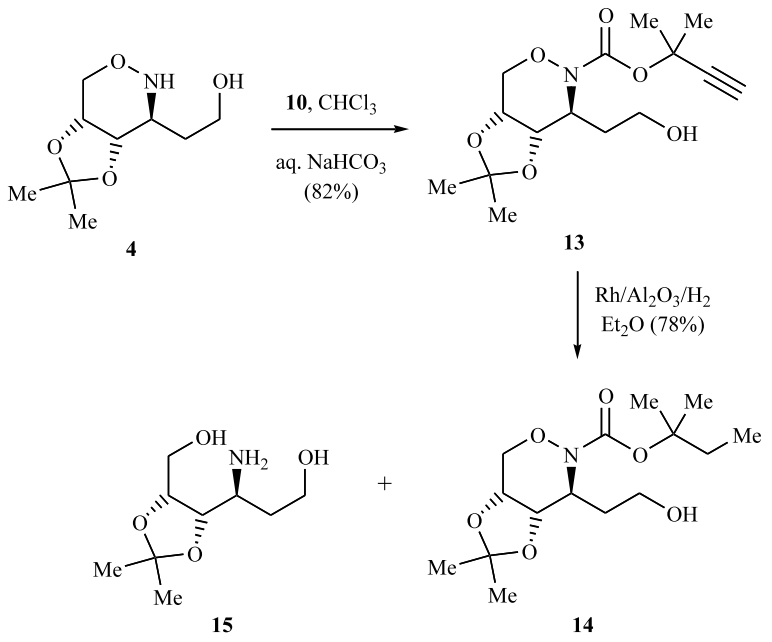
Treatment of 1,1-dimethylprop-2-yn-1-ol with triphosgene in $CH_2Cl_2$ afforded **10**. Whilst this compound could be distilled we found that simply concentrating the solution to about half its original volume in vacuo (to remove any residual phosgene) then adding it directly to oxazine **4** was simplest (storage of **10** in the freezer at ca. −20°C for more than a day allowed significant decomposition to occur). By this method **13** was prepared in 82% yield. As expected, attempted hydrogenation of **13** over Pd/C in MeOH afforded significant quantities of **4** (**14**:**4**, 0.9:1). By contrast hydrogenation of **13** over $Rh/Al_2O_3$ in $Et_2O$ afforded a 78% yield of **14**.[12] However, the reaction was dependant on the batch of catalyst with the worst ratio being **14**:**15**, 3.2:1, with **14** being obtained in 65% yield (Scheme 3).

With **14** in hand the N–O bond was reduced with $Mo(CO)_6$ in aqueous acetonitrile as described by Miller, with **16** being obtained in 84% yield.[13] Oxidation of both hydroxyls to the carboxyl oxidation level was achieved simultaneously under Sharpless conditions.[14] As anticipated the oxidation to the γ-lactam proved slow, taking around 3 days to complete. The crude was treated directly with Widmer's reagent to afford the *tert*-butyl ester **17** in 44% yield from **16**.[15] Finally, hydrolysis of the γ-lactam to give **1** proceeded smoothly in 83% yield on reaction with LiOH (Scheme 4).[16,17]

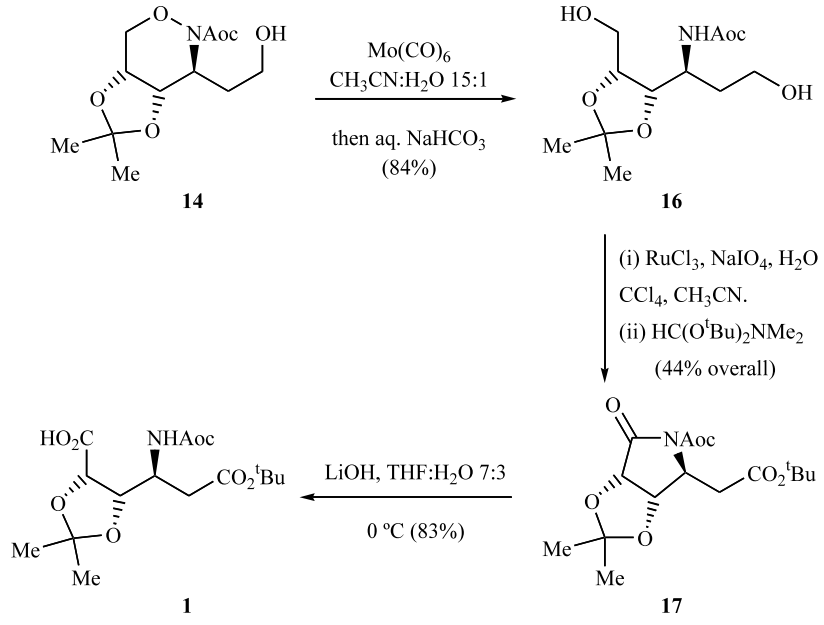
In summary we have developed an intramolecular acylnitroso Diels–Alder reaction with a cleavable tether and successfully applied it to a synthesis of the right-hand half of AI-77-B in racemic form. During the course of this synthesis we have developed a new protocol for the introduction of Aoc protecting groups.




**Scheme 2.**




**Scheme 3.**




**Scheme 4.**

## Acknowledgements

The authors would like to thank the EPSRC for a studentship to G.D. and Zeneca for financial assistance from the Zeneca Strategic Fund.

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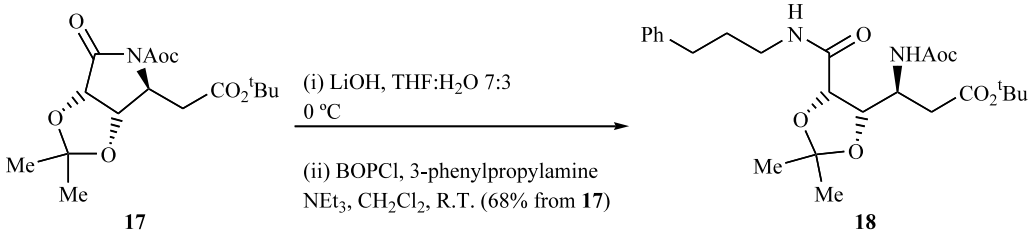
17. We were unable to obtain satisfactory mass spectral data on **1** and so derivatised it with 3-phenylpropylamine to give **18** which was fully characterised.




**17** **18**