SYNTHESIS OF 5-SUBSTITUTED PIPERAZINIC ACID PRECURSORS

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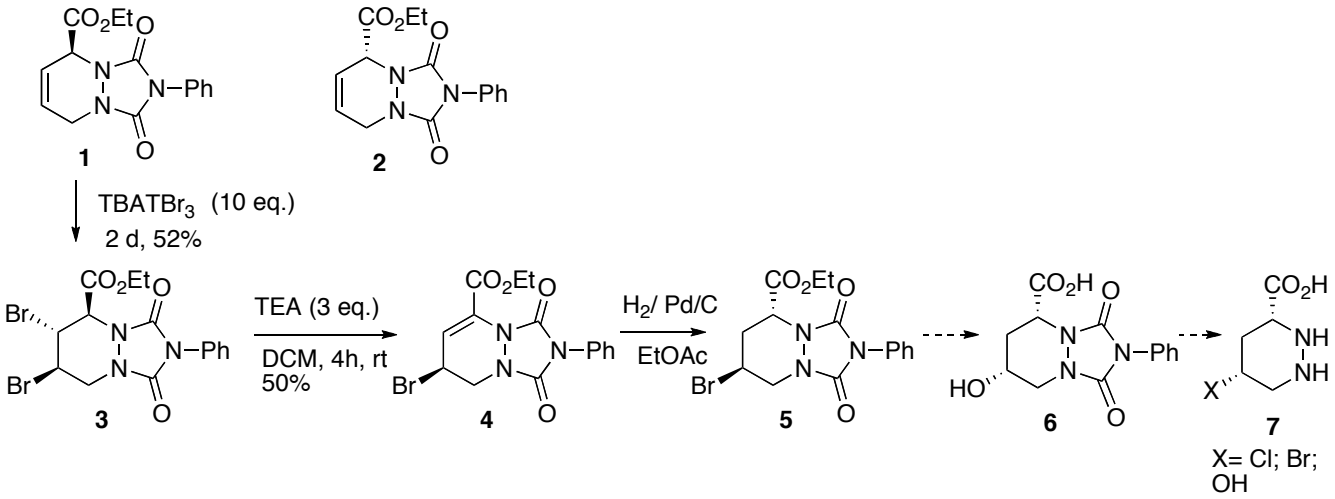
Abstract

We have recently obtained an excellent yield of the known compound **1**, the epimer **2**.[1] The sugar unit is easily cleaved under the Stoodley protocol with triethylsilane and trifluoroacetic acid.[2] With those precursors in hand we though that introduction of chloride, bromide and hydroxyl groups at the position 5 of compounds **1** and **2** would be an easy task. Those compounds are valuable synthons for the synthesis of a series of natural products like piperazinycinA, B, C or Antrimycin D with a very high anti-cancer activity.[3,4]

Treatment of the chiral alkene **1** with 10 equivalents of tetrabutylammonium tribromide lead to the dibromide compound **3** in 52% yield after 2 days at rt. When compound **3** was treated with 3 equivalents of triethylamine, compound **4** was isolated in 50% yield after 4 h at rt. Hydrogenolysis of **4** will afford the precursor **5**. The bromide group has then to be substituted by the hydroxyl group to give **6**, before removal of the urazole in the ultimate step to afford the title compounds **7**.

It is to notice that however the substitution of the halogen is needed, it can get in again after the tosylation of the hydroxyl group. The same sequence starting with antipode **2** will make possible to get the all range of 5-substituted piperazinic acids needed for the synthesis of the natural compounds referred ahead.



References:

1- Unpublished results.

2- Aspinall, I.A.; Cowley, P.M.; Stoodley, R.J. *Tetrahedron Lett.* **1994**, 3397-3400.

3- Wenhua Li, Jiangang Gan, and Dawei Ma *Angew. Chem. Int. Ed.* **2009**, *48*, 8891-8895.

4- Phillip Kennedy, Craig W. Lindsley *Tetrahedron Lett.* **2010**, *51*, 2493-2496.

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