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A REGIOSELECTIVE SYNTHESIS OF 8,9-DICHLORO-2,3,4,5-TETRAHYDRO-1*H*-2-BENZAZEPINE (LY134046), A POTENT PHENYLETHANOLAMINE *N*-METHYLTRANSFERASE INHIBITOR

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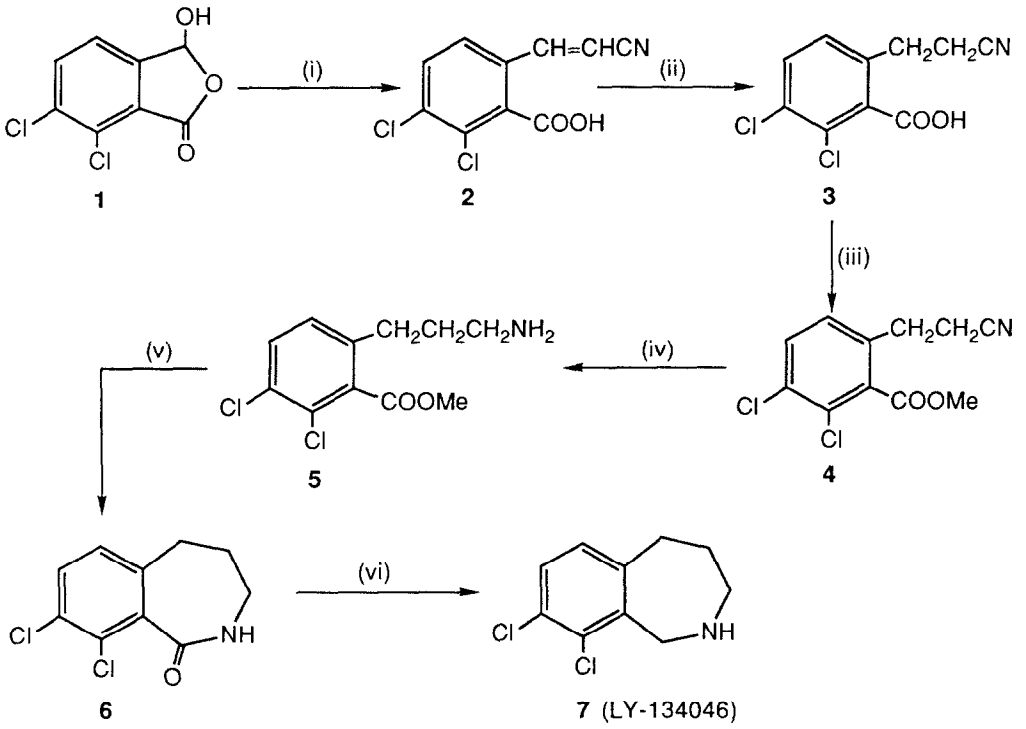
Abstract: A regioselective synthesis of 2,3,4,5-tetrahydro-1*H*-2-benzazepines substituted on the aryl and/or azepine rings is presented and used for the preparation of the title compound in overall yield of 22% from intermediate **1**.

8,9-Dichloro-2,3,4,5-tetrahydro-1*H*-2-benzazepine (LY134046) is one of the most widely studied inhibitors of the enzyme phenylethanolamine *N*-methyltransferase. The currently available methods for the preparation of this compound involve either a Schmidt reaction of 7,8-dichloro-2-tetralone[1] or a cyclopropanation-ring enlargement of 2-acetyl-7,8-dichloro-1,2-dihydroisoquinoline.[2] The use of hazardous hydrazoic acid and the chromatographic separation of the 2-benzazepine and 3-benzazepine isomers formed in the former method make it unattractive for preparation on a large scale. Similarly, the cyclopropanation-ring enlargement sequence produces a mixture of two derivatives of 2-benzazepine, only one of which can be converted into LY134046. The overall yield is less than 1% in the former case and *ca.* 9% in the latter case. Furthermore neither of these two methods is suitable for the preparation of derivatives such as 3-substituted 2-benzazepines. The other literature syntheses of 2-benzazepine utilize intramolecular electrophilic aromatic substitution as the key step,[3,4] and are not applicable for the preparation of LY134046 due to the presence of the deactivated dichlorophenyl ring. In this communication we wish to describe a regioselective synthesis of LY134046 from 6,7-dichloro-3-hydroxyphthalide.

The key intermediate 6,7-dichloro-3-hydroxyphthalide (**1**), previously prepared in our laboratory[5], and 1.0 equivalent of diethylcyanomethylphosphonate in 1,2-DME was treated with 2.0 equivalents of NaH to give a 9:1 mixture of *trans:cis* *o*-carboxycinnamonitrile **2** in 80% yield. The initial attempt to selectively reduce the double bond of this α,β-unsaturated nitrile with magnesium in methanol[6] led to simultaneous dechlorination of the aromatic ring. However, treatment of **2** with an excess of $NaBH_4$ in 2-propanol at reflux[7] for two days gave the saturated nitrile **3** in 80% yield. The esterification of **3** with potassium carbonate-methyl iodide, followed by selective reduction of the nitrile using BH_3 in THF, gave aminoester **5** as the hydrochloride salt (65%). The base (NaOMe/MeOH) catalyzed cyclization of the aminoester **5** produced the intermediate azepinone **6** in nearly quantitative yield. Lactam **6** was smoothly reduced with BH_3 in THF at reflux to the title compound in an overall yield of 22% from **1**. It is noteworthy that no chromatographic separation steps are required.

Application of the present method to the preparation of other 2-benzazepines with substituents on the aromatic ring is limited only by the availability of the starting hydroxyphthalide. Where the required hydroxyphthalide is not available, the *o*-carboxycinnamonitrile can be prepared from the corresponding anthranilic acid by the Meerwein arylation reaction.[8,9] Azepine-substituted analogs can also be prepared. For example,we have recently prepared 8,9-dichloro-3-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine by a modification of this method.[10]



(i) NaH, $NCCH_2P(O)(OEt)_2$, 1,2-DME, RT. (ii) $NaBH_4$, 2-propanol, reflux. (iii) MeI, K_2CO_3, Acetone, reflux
(iv) BH_3 in THF, RT. (v) MeONa, MeOH, reflux. (vi) BH_3 in THF, reflux.

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