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Synthesis of enantiopure (*S*)-7-hydroxy-3-amino-3,4-dihydro-2*H*-1-benzopyran en route to (+)-scyphostatin

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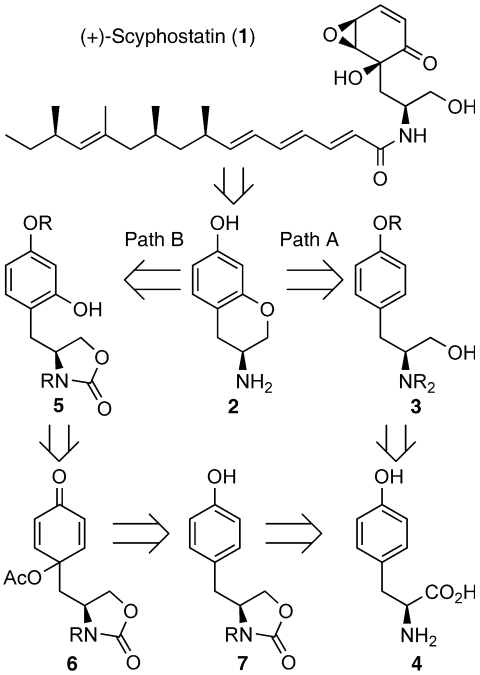
Abstract—(*S*)-7-Hydroxy-3-amino-3,4-dihydro-2*H*-1-benzopyran, a key synthetic intermediate towards the total synthesis of (+)-scyphostatin, has been prepared in >98% ee. Key synthetic steps were (i) the oxidative dearomatization of an L-tyrosine derived phenol, (ii) the transformation of the resulting *p*-quinol acetate to the corresponding resorcinol upon exposure to Thiele reaction conditions and, (iii) the direct formation of the benzopyran ring upon treatment of an *N*-Boc protected 4-(2-acetoxybenzyl)oxazolidin-2-one with sodium methoxide.

3-Aminochroman derivatives are medicinally interesting compounds as potential pharmacological tools for studying the serotonin (5-HT) receptor.[1] In addition, we have recently demonstrated that racemic 7-hydroxy-3-amino-3,4-dihydro-2*H*-1-benzopyran (**2**, Scheme 1) is the key synthetic intermediate in a diastereoselective route towards the pharmacophoric polar core of the natural product scyphostatin (**1**).[2] Preparation of this aminochroman derivative in an optically pure form should lead to the total synthesis of the natural product upon coupling with the corresponding optically active, fatty acid side chain.

Although the resolution of 3-aminochroman derivatives has been described,[1c–e] only the racemic synthesis of 7-alkoxy-3-amino-3,4-dihydro-2*H*-1-benzopyran has been reported to date.[1b,2a] Furthermore, the available synthetic methodology for the preparation of enantiomerically pure 3-aminochromans[3] is not suited for the preparation of this particular derivative. Thus, an enantiocontrolled synthesis of this compound was required and we report our results herein.

The close structural similarity of (*S*)-7-hydroxy-3-amino-3,4-dihydro-2*H*-1-benzopyran (**2**) with L-tyrosine (**4**) led us to investigate this readily available amino acid as a starting material. The recent report by Kita et al.[4] of a direct synthesis of 7-methoxy-3,4-dihydro-2*H*-1-benzopyran (**10**, Scheme 2) by PIFA-mediated cyclization of



Scheme 1. Retrosynthetic plan for (+)-scyphostatin.

Keywords: [Bis(trifluoroacetoxy)iodo]benzene; *p*-Quinol; Aminochroman.
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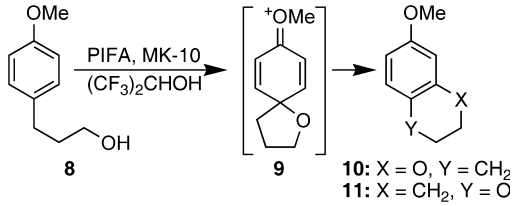


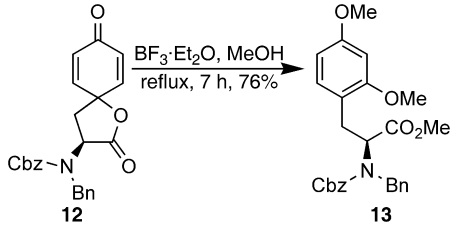
Scheme 2. Exploration of path A. PIFA = [bis(trifluoroacetoxy)-iodo]benzene; MK-10 = Montmorillonite K10.

3-(4-methoxyphenyl)propan-1-ol (**8**) indicated that the direct conversion of a suitable tyrosinol derivative (**3**) to the desired 3-aminochroman might be feasible (Path A, Scheme 1). The reaction mechanism suggested by the authors for this transformation involved the formation of spiro-intermediate **9** and subsequent rearrangement via C–O bond migration to yield **10**. Unfortunately, in our hands, 3-(4-methoxyphenyl)propan-1-ol (**8**) failed to provide any 7-methoxy-3,4-dihydro-2*H*-1-benzopyran (**10**)[5] employing the published experimental procedure.[4] Instead, the known[6] isomeric 6-methoxy-3,4-dihydro-2*H*-1-benzopyran (**11**) was obtained in a 40% yield presumably via formation of spiro-intermediate **9** and subsequent rearrangement via C–C bond migration, as it is usually observed upon treatment of such oxaspirodienones with acids.[7]

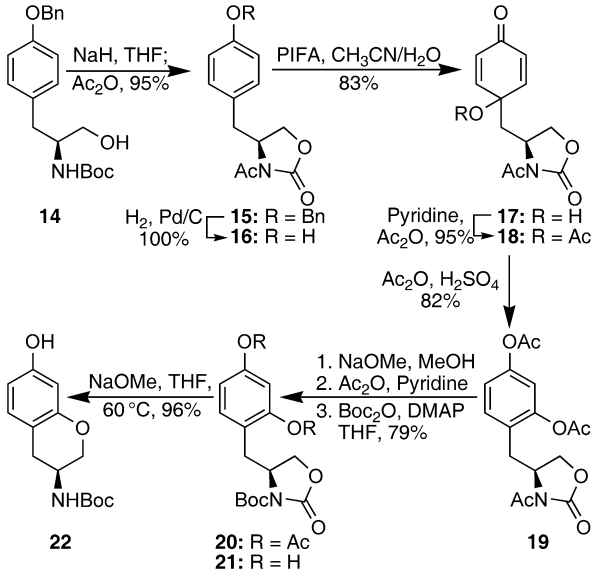
On the other hand, successful alkoxylation *meta* to the hydroxyl group of L-tyrosine by refluxing a solution of dienone lactone **12** in methanol in the presence of $BF_3{\cdot}Et_2O$ has been reported (Scheme 3).[8] However, the optical purity of the product **13** was compromised (88% ee) under the reaction conditions, presumably due to the sensitivity of the α-amino acid moiety. In an effort to overcome this drawback, *p*-quinol acetate **6** (Path B, Scheme 1) was targeted with the hope that the tertiary acetoxy group will retain the observed preference of spirolactone **12** to aromatize via C–O bond scission while incorporation of the amino function in an oxazolidinone ring will protect it from racemization.

Therefore, to access *p*-quinol acetate **6**, tyrosinol derivative **14** was prepared as previously described[9] in >99% ee. Treatment of **14** with NaH in THF at room temperature resulted in intramolecular cyclization of the resulting alkoxide onto the *N*-Boc-protecting group to form the oxazolidinone anion, which was trapped in situ by the addition of Ac_2O (Scheme 4).

Thus, oxazolidinone **15** was obtained in one step and in 95% yield. Subsequent hydrogenolysis of the benzyl protecting group furnished phenol **16** in a quantitative



Scheme 3. Reported *meta* alkoxylation of L-tyrosine.

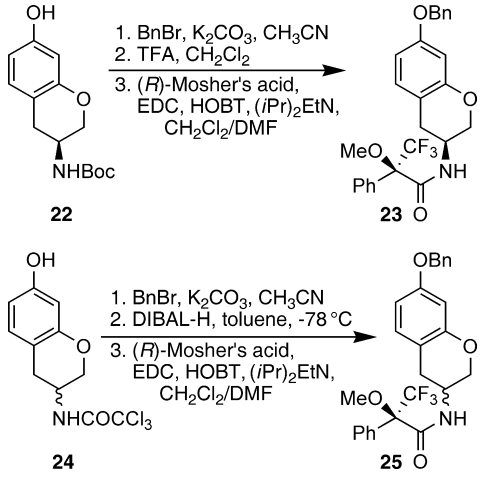


Scheme 4. Synthesis of (*S*)-7-hydroxy-3-amino-3,4-dihydro-2*H*-1-benzopyran.

yield. Direct oxidative dearomatization of **16** towards *p*-quinol acetate **18** by treatment with [bis(acetoxy)iodo]benzene (PIDA) in glacial acetic acid proved to be problematic furnishing the product in only a moderate yield (35–40%) contaminated with varying amounts of the corresponding *p*-quinol **17**. On the other hand, the two-step procedure of oxidizing **16** with PIFA in wet acetonitrile to obtain *p*-quinol **17** followed by acetylation with Ac_2O in pyridine was more efficient and reproducible, yielding quinol acetate **18** in a 79% overall yield.

Thus, the stage was set for the crucial *meta*-functionalization of the phenol ring. Gratifyingly, rearrangement of **18** under the conditions of the Thiele reaction,[10] acetic anhydride in the presence of sulfuric acid, furnished resorcinol **19** in a good yield (82%). At this point it should be noted that, subjecting the free quinol **17** to the same conditions resulted in poorer yields (31%) of the desired product.

With all the required functionality present in **19** we turned our attention to the formation of the benzopyran ring. For this transformation we planned to exploit the oxazolidinone moiety as a leaving group in an intramolecular nucleophilic attack by the neighbouring phenol.[11,12] For this feat to be accomplished it was deemed necessary to activate the oxazolidinone by replacing the acetyl with a *tert*-butoxycarbonyl protecting group. Thus, methanolysis of the acetyl protecting groups, followed by selective reacetylation of the phenols and *N*-*tert*-butoxycarbonyl protection of the oxazolidinone furnished **20** in a good overall yield (79%). Treatment with K_2CO_3 in a 1:1 mixture of methanol/THF afforded the free resorcinol **21**. Upon treatment of **21** with 2 equiv of NaH in THF at 60 °C we observed the formation of benzopyran **22** in a very good overall yield (83%). Alternatively, the direct treatment of **20** with sodium methoxide in THF at 60 °C for 3 h



Scheme 5. Confirmation of the optical purity of (*S*)-**22**.

furnished (*S*)-7-hydroxy-3-amino-3,4-dihydro-2*H*-1-benzopyran **22** in one step and in an excellent yield (96%). That this direct transformation was even successful is noteworthy given the well-documented reactivity of *N*-*tert*-butoxycarbonylated 2-oxazolidinones towards methanolic bases to yield acyclic *N*-protected 1,2-amino alcohols.[13] Presumably, intramolecular attack of the phenoxide onto the 5-position of the oxazolidinone ring is favoured over intermolecular attack of a methoxide onto the cyclic carbamate carbonyl moiety.

In order to confirm the optical purity of **22** it was converted into Mosher amide **23** (Scheme 5). The enantiomeric excess of **23** was confirmed to be >98% via chiral HPLC analysis over Chiralpak® AD (Daicel Chemical Industries, LTD) stationary phase in comparison with a sample of the corresponding racemic amide **25** prepared from the known benzopyran **24**.[2b]

In conclusion, (*S*)-7-hydroxy-3-amino-3,4-dihydro-2*H*-1-benzopyran has been prepared in a high optical purity by an efficient synthetic route employing readily available and inexpensive reagents. This paves the way for an alternative total synthesis of the natural product scyphostatin.[14] In the process, a new method was developed for the preparation of 2-hydroxytyrosine derivatives[8,15] and a novel approach for the direct cyclization of 4-(2-hydroxybenzyl)-2-oxazolidinones to 3-aminobenzopyrans was established. Both, 2-hydroxytyrosine derivatives[15,16] and 3-aminobenzopyrans,[1] are medicinally interesting classes of compounds.

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Supplementary data

Spectroscopic data and experimental procedures for compounds **15**–**20** and **22**. Copies of the ^{1}H NMR, HSQC and HMBC spectra of **11**. Copies of the ^{1}H NMR and ^{13}C NMR spectra of compounds **15**–**20** and **22**, **23** and **25**. HPLC chromatograms of compounds **23** and **25**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.006.

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