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Chiral Azole Derivatives, 3[1]. Synthesis of the Enantiomers of the Potent Aromatase Inhibitor 1-[2-Benzofuranyl(4-chlorophenyl)methyl]-1*H*-imidazole

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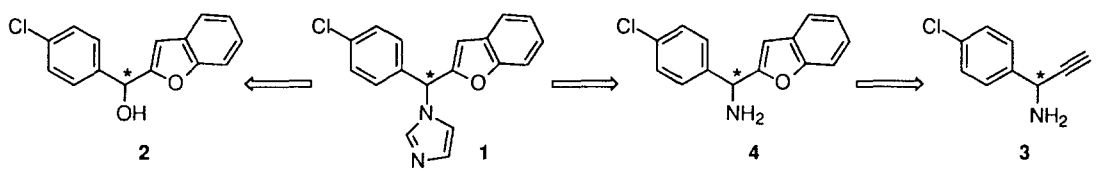
Abstract: Starting from (+)- and (-)-1-(4-chlorophenyl)-2-propynylamine, in turn obtained by CAL-mediated kinetic resolution of the corresponding racemate, a stereoselective synthesis of both enantiomers of the title compound has been achieved.
Keywords: Asymmetric synthesis; Annulation; Benzofurans; Antitumour compounds

Originally synthesised as antifungal agents,[2] substituted 1-[2-benzofuranylphenylmethyl]imidazoles have emerged as a new class of potent aromatase inhibitors, which show promise as chemotherapeutic agents for the treatment of estrogen-dependent tumors. In particular, the 4-chloro analogue **1** has been shown to be active *in vitro* (IC_{50} ± 8.6 nM) and *in vivo*.[3] Both enantiomers of **1**, obtained by fractional crystallisation of their diastereomeric dibenzoyltartrate salts,[4] proved to be potent aromatase inhibitors, with a 15-fold enantioselectivity (IC_{50} 5.3 nM *vs* 65.0 nM) in favour of the (+) form.[5]

These findings prompted us to devise a stereoselective synthesis of both (+)- and (-)-**1** starting from readily accessible precursors, which would allow the preparation of the target compounds in gram-quantity and high enantiomeric purity as well as the determination of their absolute stereochemistry.

Scheme 1.



Efforts directed toward the stereoselective transformation to **1** of enantiomerically pure alcohol **2** (Scheme 1), prepared according to a general procedure recently described by us,[6] proved to be unsuccessful, since either direct Mitsunobu substitution of **2** by imidazole derivatives, or reaction *via* the corresponding sulphonates, led to racemic compounds. Therefore, we turned our attention to the resolution of a less advanced precursor, such as **3**, and its subsequent transformation to the target **1** through heteroannulation of the triple bond to an intermediate of type **4**, followed by construction of the imidazole ring.

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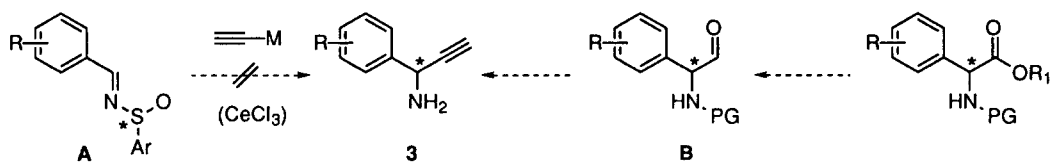
Our first approaches to homochiral **3** based on the diastereoselective addition of lithium acetylide or ethynylmagnesium bromide (even in the presence of cerium chloride) to the C=N bond of enantiopure *N*-sulphinyl benzaldimine of type A[7] (Scheme 2) proved to be unsuccessful, due to the low reactivity of these nucleophiles toward carbon-nitrogen double bonds conjugated with an aromatic ring.[8] On the other hand, synthetic transformations of the carboxyl groups of α-amino acids mostly involve conversion into *N*-protected α-amino aldehydes (B),[9] which are relatively unstable, both chemically and configurationally,[9,10] and whose preparation from the corresponding acids *via* esters or active amides is lengthy.[11] In particular, only one laborious procedure for the preparation of *N*-protected 2-phenylglycinal has been claimed so far (no experimental data).[12]

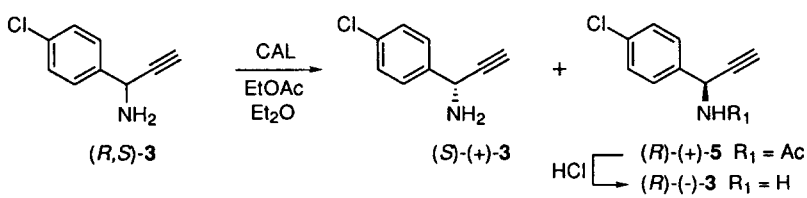
Scheme 2.



PG = protecting group

Therefore, based on recent literature reports on the enzyme-catalysed resolution of amines[13] and on our previous experience in this area,[14] we decided to explore the possibility of resolving racemic **3**[15] *via* an acyltransfer reaction using the lipase from *Candida antarctica* (CAL). Accordingly, a mixture of (±)-**3** (2 mmol), EtOAc (8 mmol) and lipase B from *Candida antarctica* (immobilized form NOVOZYM 435) (100 mg) in Et_2O (5 mL) was stirred at rt, while monitoring the reaction by GC on a FS-cyclodex BETA I/P column, until the desired conversion (ca. 50%) was achieved (Scheme 3). Following the usual work-up, compounds (+)-**3** ($[\alpha^{23}_D]$ +28.6)[17] and (+)-**5** ($[\alpha^{23}_D]$ +80.3)[17] were easily purified by flash chromatography (43% and 40% yield, respectively). The enantiomeric excess (ee), determined again by chiral GC, was ≥ 98% for both enantiomers.[18] In no case was a loss of ee due to the work-up and silica gel chromatography observed.

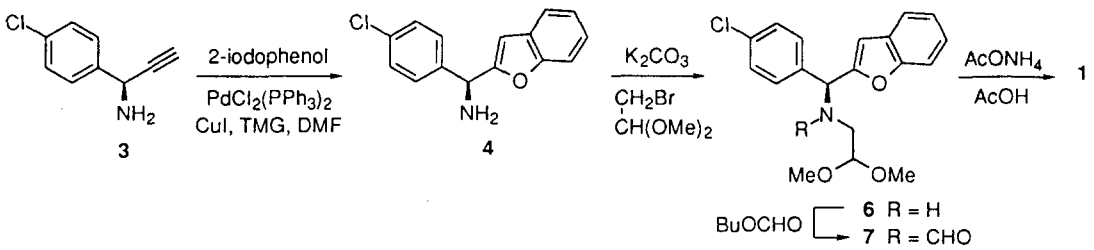
Scheme 3.



In order to assign the absolute configurations of (+)-**3** and (+)-**5**, the propargylamine (+)-**3** was subjected to hydrogenation of the triple bond with concurrent hydrogenolysis of the chlorine atom (H_2, Ra/Ni) leading to (-)-1-phenylpropylamine. Comparison of its specific rotation with reported data for (*R*)-(+)-1-phenylpropylamine[19] established the *S*-configuration for **3** and, consequently, the *R*-configuration for the amide

5. This result is in perfect agreement with the reported preference of CAL for the acylation of (*R*)-amines.[13] Chemical hydrolysis of acetamide (*R*)-**5** with 3.0 N aqueous HCl (70 °C, 17 h) afforded amine (*R*)-**3** without loss of enantiomeric purity ($[\alpha^{23}_D]$ -27.5).[17]

Scheme 4.



With both enantiomers of **3** in hand, we investigated their heteroannulation reaction to give **4**, employing the same procedure we have used before for the preparation of homochiral aryl 2-benzofuranyl carbinols.[6] Thus, (*R*)-**3** and (*S*)-**3** were reacted with 2-iodophenol ($PdCl_2(PPh_3)_2$, CuI, TMG, DMF, 40 °C) to provide (*S*)-**4** ($[\alpha^{23}_D]$ +10.9)[17] and (*R*)-**4** ($[\alpha^{23}_D]$ -10.7),[17] respectively, in 68-71% yields (Scheme 4: for simplicity only the reaction from (*R*)-**3** is shown). It is important to point out that, unlike propargylic alcohols, the corresponding propargylamines have not as yet found very extensive application in palladium-mediated heteroannulation reactions and, to the best of our knowledge, the reaction here reported is the first example involving homochiral α-arylpropargylamines.[20] Subsequent alkylation of **4** with bromoacetaldehyde dimethyl acetal (K_2CO_3, DMF, 120 °C) to **6**, followed by acylation in refluxing butyl formate, afforded the intermediates **7**, which were cyclised to the final imidazole compounds (*R*)-**1** ($[\alpha^{23}_D]$ +16.8)[17] and (*S*)-**1** ($[\alpha^{23}_D]$ -17.4)[17] in 40-45% overall yield for the three steps. HPLC analysis on a Lichrospher 100 RP-18 column (5 μm, 250 x 4 mm) eluting with 0.05 M phosphate buffer (pH 7.5)/acetonitrile 55/45 (flow rate: 1 mL/min) in comparison with the chromatogram of racemic **1** gave an ee of 97.5% for both enantiomers, thus demonstrating the complete stereospecificity of the reaction sequence.

In summary, we have developed a practical method for the synthesis, in good chemical yield and high enantiomeric purity, of both enantiomers of the potent aromatase inhibitor 1-[2-benzofuranyl(4-chlorophenyl)methyl]-1*H*-imidazole (**1**) and have assessed their absolute configuration. A further merit of this preparation, which involves as the key steps the unprecedented enzyme-catalysed resolution of racemic 1-(4-chlorophenyl)propynamine (**3**) into (*S*)-(+)-**3** and (*R*)-(-)-**3** as well as further elaboration of both enantiomers through palladium-mediated heteroannulation, resides in its potential use for the synthesis of analogs of **1** with different substituents on the aromatic rings and/or different heterocyclic moieties. Studies in this area are in progress in our laboratories and will be reported in due course.

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