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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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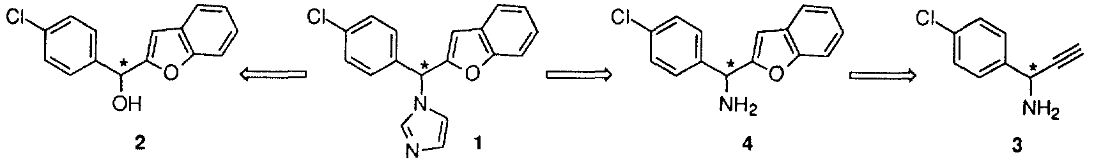
Abstract: Starting from (+)- and (-)-1-(4-chlorophenyl)-2-propynylamine, in turn obtained by CAL-mediated kinetic resolution of the corresponding racemate, a stereoselective synthesis of both enantiomers of the title compound has been achieved.
Keywords: Asymmetric synthesis; Annulation; Benzofurans; 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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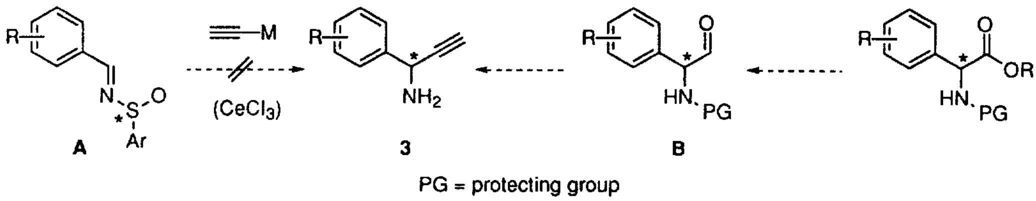
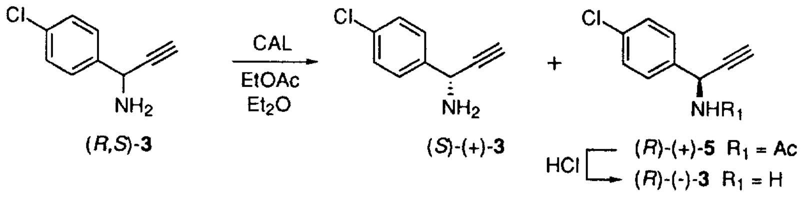
Our first approaches to homochiral 3 based on the diastereoselective addition of lithium acetylide or ethynylmagnesium bromide (even in the presence of cerium chloride) to the C=N bond of enantiopure *N*-sulphinyl benzaldimine of type A[7] (Scheme 2) proved to be unsuccessful, due to the low reactivity 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.



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.

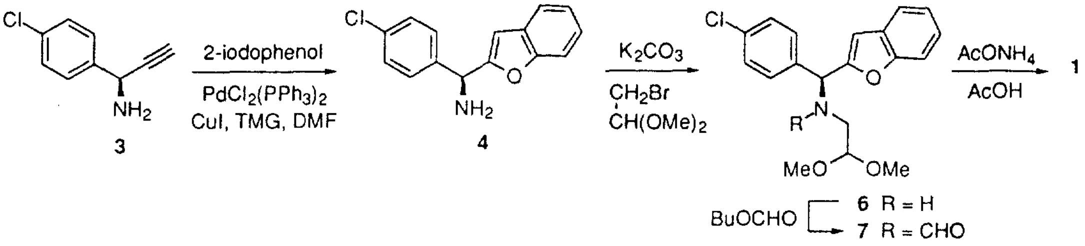
Scheme 3.



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 ([α^{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** ([α^{23}_D] +10.9)[17] and (*R*)-**4** ([α^{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** ([α^{23}_D] +16.8)[17] and (*S*)-**1** ([α^{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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REFERENCES AND NOTES

1. For part 2, see: Corelli, F.; Summa, V.; Brogi, A.; Monteagudo, E.; Botta, M. *J. Org. Chem.* **1995**, *60*, 2008.
2. Pestellini, V.; Giannotti, D.; Giolitti, A.; Fantò, N.; Riviera, L.; Bellotti, M. G. *Chemioterapia* **1987**, *6*, 269.
3. Whomsley, R.; Fernandez, E.; Nicholls, P. J.; Smith, H. J.; Lombardi, P.; Pestellini, V. *J. Steroid Biochem. Mol. Biol.* **1993**, *44*, 675.
4. Pepper, C.; Smith, H. J.; Barrell, K. J.; Nicholls, P. J.; Hewlins, M. J. E. *Chirality* **1994**, *6*, 400.
5. Lombardi, P.; Pestellini, V. Personal communication.
6. Botta, M.; Summa, V.; Corelli, F.; Di Pietro, G.; Lombardi, P. *Tetrahedron: Asymmetry* **1996**, *7*, 1263.
7. Davis, F. A.; Reddy, R. E.; Portonovo, P. S.; Chiu, Y. *J. Org. Chem.* **1996**, *61*, 440.
8. (a) Yamazaki, T.; Mizutani, K.; Kitazume, T. *J. Org. Chem.* **1995**, *60*, 6046. (b) Denmark, S. E.; Weber, T.; Piotrowski, D. W. *J. Am. Chem. Soc.* **1987**, *109*, 2224.
9. Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.
10. Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487.
11. Katritzky, A. R.; Cheng, D.; Li, J. *J. Org. Chem.* **1998**, *63*, 3438 and references cited therein.
12. Braun, M.; Opdenbusch, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 578.
13. (a) Sánchez, V. M.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry* **1997**, *8*, 37. (b) Reetz, M. T.; Schimossek, K. *Chimia* **1996**, *50*, 668. (c) Öhrner, N.; Orrenius, C.; Mattson, A.; Norin, T.; Hult, K. *Enzyme Microb. Technol.* **1996**, *19*, 328.
14. (a) Waldinger, C.; Schneider, M.; Botta, M.; Corelli, F.; Summa, V. *Tetrahedron: Asymmetry* **1996**, *7*, 1485. (b) Messina, F.; Botta, M.; Corelli, F.; Schneider, M. P.; Fazio, F. *J. Org. Chem.* **1999**, *64*, 3767.
15. Racemic propargylamine **3** was readily prepared in 58% overall yield by hydrolysis of the acetamide **5**, in turn obtained from the corresponding propargylic alcohol *via* Ritter reaction using the procedure described by Hacksell for the synthesis of similar compounds (see ref. 16).
16. Nilsson, B. M.; Hacksell, U. *J. Heterocycl. Chem.* **1989**, *26*, 269.
17. Measured in chloroform solution, *c* 1.0.
18. The structures of the new compounds were determined by FAB-MS and ^{1}H NMR spectroscopy. All the new compounds gave satisfactory (± 0.4% of the theoretical values) elementary analyses.
19. (a) Wu, M.-J.; Pridgen, L. N. *J. Org. Chem.* **1991**, *56*, 1340. (b) Rossi, D.; Calcagni, A.; Romeo, A. *J. Org. Chem.* **1979**, *44*, 2222.
20. For examples of annulation of achiral propargylamines both in solution and on solid support, see: Fancelli, D.; Fagnola, M. C.; Severino, D.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2311.