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Resolution and assignment of the absolute stereochemistry of a *trans*-2,3-diarylpyrrolidine LTB_4 inhibitor intermediate

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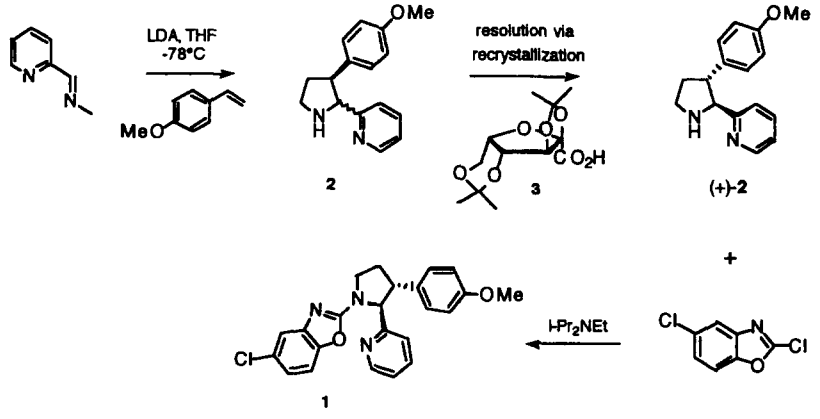
Abstract: 1,3-Cycloaddition of an azaallyl anion with 4-methoxystyrene furnishes the corresponding racemic *trans*-pyrrolidine. Resolution of both enantiomers was accomplished by fractional crystallization with the inexpensive diacetone-2-keto-L-gulonic acid. The absolute stereochemistry was determined by single crystal X-ray analysis of the corresponding sulfonamide. © 1997 Elsevier Science Ltd. All rights reserved.

During the preclinical evaluation of a pyrrolidine-based LTB_4 inhibitor (**1**, BIRZ-227), a supply of each enantiomer of the drug candidate was required in a short time frame. The initial chromatographic isolation of milligram quantities suggested that the (+)-isomer was the more active one. Rather than work out an asymmetric synthesis, it was decided that a classical resolution could furnish multigram quantities of the desired products in the least time. In addition, the absolute stereochemistry of each enantiomer was unknown and required determination.

Synthetic Scheme



Synthesis of the *trans*-diaryl pyrrolidine **2** using an azaallyl cycloaddition strategy furnished the desired compound in 85% yield as a 95:5 mixture of trans/cis isomers.[1] Chromatographic purification on silica gel allowed for isolation of pure racemic **2**. After surveying the most common chiral carboxylic acids for use as a resolving partner, we discovered that the infrequently utilized and inexpensive diacetone-2-keto-L-gulonic acid (**3**, (−)-DAG) proved to be a suitable reagent for the resolution of both enantiomers.[2] Acid **3** is an intermediate in the production of ascorbic acid and is available in ton quantities as the monohydrate and was used as such.

Treatment of one equivalent of racemic **2** with a slight excess (1.15 equiv.) of (−)-DAG in boiling isopropanol furnished off-white needles (enriched (+)-amine salt) upon slow cooling to ambient temperature.[3] The solids were collected by filtration and the mother liquors were concentrated to furnish the corresponding (−)-amine salt as a fluffy solid. Chiral HPLC analysis[4] of the

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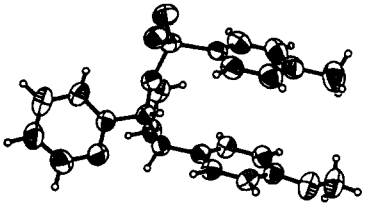
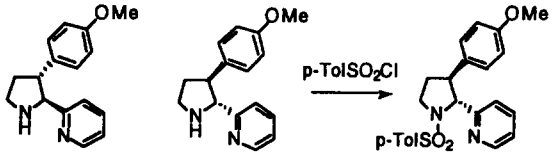


Figure 1. ORTEP diagram of 4.

corresponding free base of each salt indicated each fraction was enriched to 60% e.e. Subsequent recrystallization (twice) of each diastereomeric pair from isopropanol/methanol 4:1 (84% e.e.), then final recrystallization from hot acetone and liberation of the free base with aqueous sodium hydroxide furnished the pyrrolidines (+)-**2** and (−)-**2** in >98% e.e. as determined by chiral HPLC analysis and ^{1}H-NMR analysis of the corresponding (S)-Mosher amides.[5] The yield (based on 50%) for the desired (+)-**2** was 35% and the isolation of (−)-**2** was less efficient furnishing that enantiomer in 19% yield.



(+)-2
$[\alpha]_D$=+167.11
(c 1.2, CH_2Cl_2)
(2S,3R)

(-)-2
$[\alpha]_D$=-166.12
(c 0.98, CH_2Cl_2)
(2R,3S)

4

Conversion of (−)-**2** to the corresponding sulfonamide **4**, followed by recrystallization from diethylether furnished colorless plates suitable for X-ray analysis. The structure and absolute stereochemistry are illustrated in Figure 1.

In summary, we have confirmed that (−)-DAG is a useful resolving agent for the 2,3-*trans*-diarylpyrrolidine **2** and found a method that allowed for the rapid preparation of gram quantities of BIRZ-227; in addition, the absolute configuration of the enantiomers has been assigned.

References

1. Experimental details for the preparation of racemic-**1** and **2** can be found in: Pal, K.; Behnke, M.; Adams, J. EP 0657451A; For a general synthesis and absolute stereochemistry of similar *cis*-pyrrolidines see: Pal, K.; Behnke, M.L.; Tong, L *Tetrahedron Lett.* **1993**, *34*, 6205.
2. The use of (−)-DAG as a resolving agent was made popular by the Hoffmann–LaRoche group. For an overview see: Mohacsi, E.; Leimgruber, W. *Organic Synthesis* **1976**, *55*, 80.
3. Brossi; A.; Teitel, S. *J. Org. Chem.* **1970**, *35*, 3559.
4. HPLC analysis was accomplished using a 0.46 × 25 cm Chiracel-OD column with 9:1 hexanes/isopropanol containing 0.5diethylamine (1.0 mL/min, 254 nm). T_R (+)-**2**=9.4 min; T_R (−)-**2**=8.3 min.
5. Diagnostic signals for ^{1}H-NMR (270 MHz, $CDCl_3$): (+)-**2** 5.13 ppm d, J=6.5 Hz; (−)-**2** 4.98 ppm d, J=6.5 Hz.

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