Tetrahedron: *Asymmetry* 20 (2009) 1262–1266

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Synthesis and axial chirality of an enantiopure aminodibenzazepinone

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ARTICLE INFO

Article history:
Received 23 March 2009
Accepted 28 April 2009
Available online 8 June 2009

ABSTRACT

A route for the synthesis of (*S*,*S*)-7-amino-5-methyl-5*H*-dibenzo[*b*,*d*]azepin-6(7*H*)-one hydrochloride is disclosed. The synthesis includes a Friedel–Crafts alkylation to form the seven-membered ring and a highly efficient classical resolution. Additional studies on the enantiopure material showed the amine to be highly resistant to racemization, which led us to investigate the unexpected stability. We propose that the inherent axial chirality contained in the dibenzazepinone works to produce an interesting chirality transfer mechanism, which accounts for the observed robustness of the stereocenter. This previously unrecognized stereochemical element exists within this specific class of molecules, and they should be drawn in a manner which displays the axial chirality.

1. Introduction

Over the course of our work on a project related to the γ-secretase inhibitor LY411575[1] **1** (Fig. 1, newly assigned biaryl stereochemistry indicated), the need for large quantities of chiral amine **2** was recognized. Amine **2** can be formed from lactam **3**. Although a number of methods have been reported for the synthesis of lactam **3**,[2] an aggressive timeline forced us to rely on proven and scalable chemistry. Upon isolation of **2** and its congeners, we noticed the unusual chiral stability of the stereocenter, as we found it difficult to racemize: a property we had planned to use to our advantage (vide infra). This led us to investigate the origin of the unusual stability, and recent publications by Natsugari[3] and Wallace[4] prompted us to disclose our own findings in this area.

2. Results and discussion

2.1. Synthesis and classical resolution

The formation of lactam **3** was accomplished by treatment of chloride **4** (prepared in four steps from commercially available 2-aminobiphenyl) with $AlCl_3$ as a neat mixture at 180–200 °C (Scheme 1; axial chirality shown). The product was isolated by way of an aqueous extraction, followed by crystallization from EtOH. This procedure reliably provided isolated yields of 39–50% (>99% purity by HPLC) on scales of up to 3 kg, without chromatography. Next, oxime installation was achieved using *t*-BuOK and *i*-AmONO. Purification and isolation consisted of extraction of the product (4:1 ratio of oxime isomers, unassigned) into an aqueous base, followed by acidification and filtration of the solid product. Oxime reduction to afford racemate **5** was then performed using Zn/AcOH in MeOH. Catalytic hydrogenation could be used, but we preferred the Zn procedure as high loadings of Pd/C were required, which tended to have a negative effect on product yield. It is noteworthy that the major geometrical isomer of the oxime was observed to undergo reduction much more rapidly than the minor isomer.[5]

We were then left to develop a robust classical resolution to afford single-enantiomer material. Earlier work had shown us that the use of (+)-DTTA[6] could accomplish this goal, but in our hands the original procedure[7] failed to produce the expected product. We eventually found that the use of seed (generated by successive recrystallization of the racemic 1:1 complex from MeOH/water) and crystallization from MeOH/water was capable of affording **6** in both high yield and high enantiomeric purity in a single operation. Karl Fisher titration, TGA, and a single-crystal X-ray structure[8] confirmed the absolute stereochemistry of **6**, and showed the salt to exist as a mono-hydrate. The presence of water appeared to be crucial to the success of this resolution, as it was found to improve yield and reproducibility. Finally, we were able to freebase the amine through a typical base wash and extraction, but the low melting nature of the freebase **7** and the desire to avoid an extraction prompted us to attempt a direct conversion to the highly crystalline HCl salt **2**. We found that treatment of a warm slurry of **6** in EtOH with concentrated HCl, followed by addition of MTBE afforded an excellent yield of **2** containing <0.06% residual DTTA. As the next synthetic operation was an amide bond formation, removal of the DTTA was absolutely critical. It is also noteworthy that a slight enhancement of ee to >99.9% was typically observed after this procedure.

2.2. Atropisomerism and axial chirality

With the successful development of a classical resolution, we had hoped to be able to employ a dynamic kinetic resolution

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doi:10.1016/j.tetasy.2009.04.016

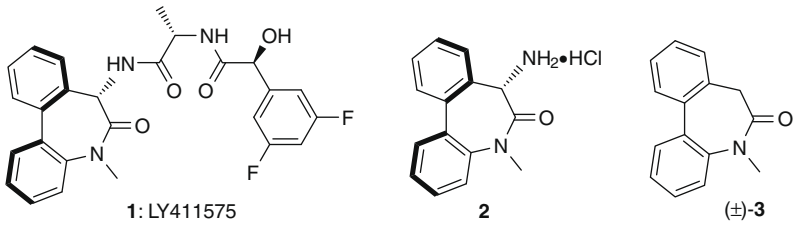
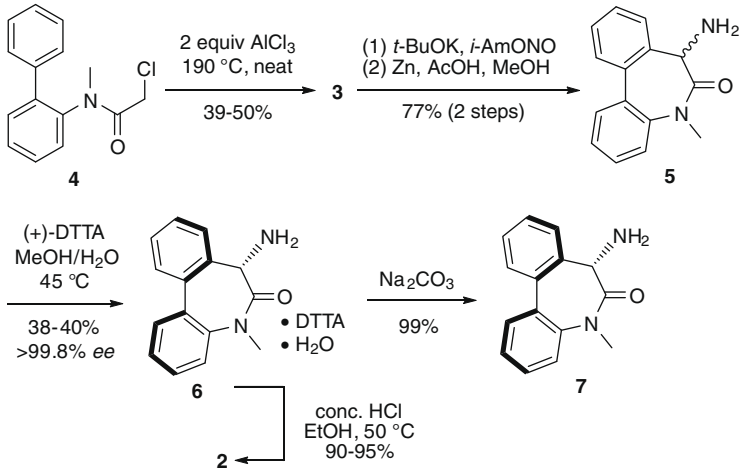
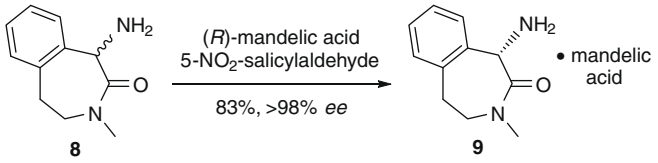


Figure 1. LY411575 and congeners.



Scheme 1. Synthesis and resolution of **5**.

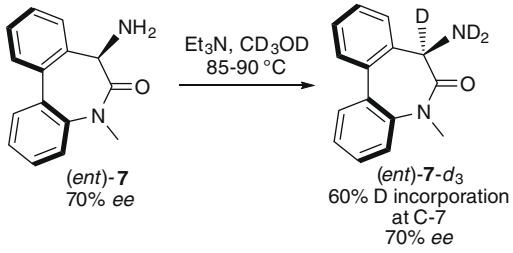
(DKR) in order to increase the yield. A similar DKR was previously utilized with great success, as shown in Scheme 2.[9] This DKR relies on the facile racemization of the stereocenter (catalyzed by an electron-deficient, non-enolizable aldehyde), and a slight difference in solubility of the diastereomeric salts. Our efforts toward this goal were immediately blocked by the inability to demonstrate the racemization of **7** either by aldehyde catalysis, or by heating with amine bases. In stark contrast, amine **8** is racemized simply upon freebasing.[9] This anomalous observation encouraged us to investigate the dibenzo system in more detail.



Scheme 2. Dynamic kinetic resolution.

We felt that enolization should be possible because the crystal structure of **6** clearly showed that the enolizable proton, at least in the solid state, was in the proper geometrical configuration with respect to the carbonyl for deprotonation. There was some question as to whether enolization would be prevented by the potentially large amount of ring strain introduced by the formation of a sixth sp^2 center in the seven-membered ring. This question was addressed by the experiment shown in Scheme 3. Scalemic amine (*ent*)-**7** was heated in CD_3OD in the presence of Et_3N. NMR and MS analysis clearly showed the incorporation of deuterium α to the carbonyl, *without racemization by HPLC*. With the destruction of the stereogenic center, one would expect the deuteration to occur equally from either face, resulting in a racemic product.

It was obvious from the crystal structures of **6** and an additional downstream compound that there was a significant dihedral angle



Scheme 3. Deuterium incorporation.

of ~30° between the two benzene rings. The biaryl stereochemistry in **6** matched that of the downstream compound, and was assigned to be (*S*). This led us to the conclusion that the barrier to the rotation about the axis is significant, suggesting that perhaps this axial chirality could play a role in the stability of the stereogenic center at C-7. Examination of lactam **3** supported this hypothesis. One clue came from the ^1H NMR of **3**, as the C-7 methylene protons appear as a diastereomeric pair of doublets. Next, we were surprised when we discovered that **3** could be resolved by chiral HPLC into separate enantiomers. Upon preparative separation of **3** (enantiomers not assigned) we discovered that single enantiomer material racemized upon standing at ambient temperature in heptane/*i*-PrOH. This inspired us to carefully monitor the racemization, as kinetic and thermodynamic data could be derived from the decay. The ee of a freshly separated sample of the first eluting isomer was monitored at 15 min intervals. The findings are illustrated in Figure 2 and indicate that the barrier for rotation about the biaryl bond[10] to be 22.34 kcal/mol, which is in good agreement[11] with the recently found value of 23.4 kcal/mol.[3] The discrepancy may point toward some solvent effect, as Natsugari's results were obtained in toluene, and ours in *i*-PrOH/heptane. While we were not surprised

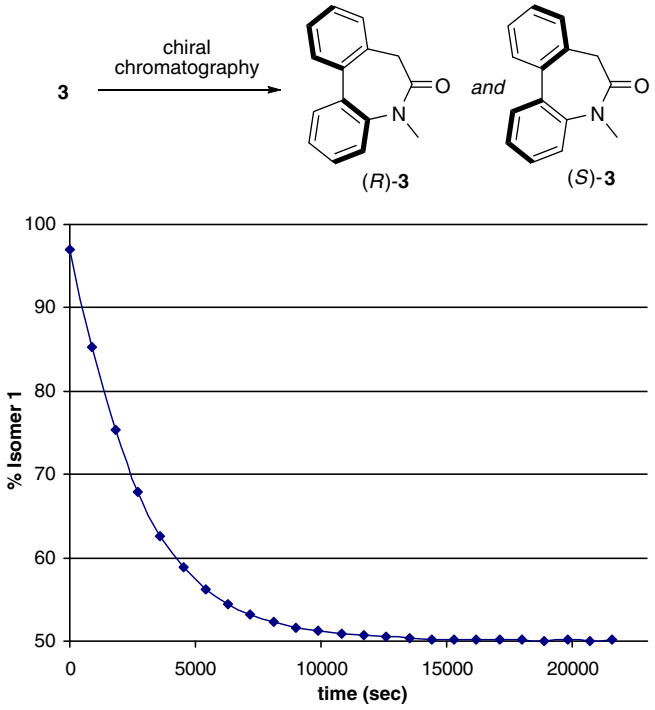


Figure 2. Separation and decay of **3** enantiomers.

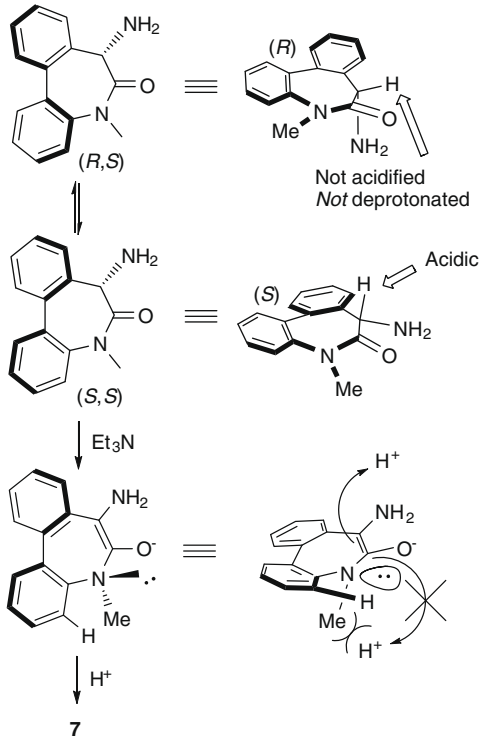


Figure 3. Proposed explanation for stereochemical stability of **7**.

that the rotational barrier for the system was low, an explanation for the chiral stability of amine **7** was still lacking. Had the atropisomers of **3** been stable, we had hypothesized that the seven-membered ring was acting as a chiral auxiliary (similar to BINOL), enforcing a diastereoselective deuteration. The thermodynamic findings led us to believe that the biaryl bond in **7** is most likely relatively free to rotate, and therefore **7** should racemize.

An additional piece of information was gathered by an observation made during the reduction of the intermediate oxime to afford **5**. If the biaryl portion was stereogenic, one might expect us to obtain two diastereomers from a non-selective reduction. In fact, the reduction of the oxime (H_2, Pd/C or Zn/AcOH) affords a single, racemic diastereomer of **5**. We surmise that (1) the reduction was completely diastereoselective, that is, only one face of the oxime enantiomers was reduced, or (2) the unobserved diastereomer is thermodynamically unstable and rapidly converts to the observed compound. If the axial-like amine isomer was initially formed, then the reaction conditions can promote thermodynamic equilibration and the formation of a single racemic diastereomer. Since no diastereomer of **5** or any related compound has ever been observed, we feel that the energy gained by this potential isomerization must be significant.

The lingering question of racemization still remained. A model that may offer some explanation was examined. We believe that a synergistic relationship exists between the relative configurations of the biaryl and those of C-7 (Fig. 3). After careful examination of a structural model, it was realized that even if the biaryl portion is free to rotate, its motion has a profound effect on the overall conformation of the azepinone, and that *only one of the diasteromers can be deprotonated* by the base, in this case (*S*,*S*). A simple explanation would be that once the acidic (*S*,*S*)-diastereomer is deprotonated, reprotonation is *much* faster than a rotation about the biaryl bond, and racemization is kinetically disfavored. Furthermore, once C-7 is deprotonated, the heterocyclic nitrogen may partially lose its amide character and become more tetrahedral. This would force the attached methyl group to slide beneath the plane of the molecule. Nitrogen inversion should not be a factor, as the A strain[1,3] between the methyl group and the *o*-proton should impose a severe barrier. The methyl group is now positioned in a pseudo-axial configuration, but the lack of other axial-like substituents prevents this from being a destabilizing interaction. The axial methyl group effectively transfers the stereochemistry of the nitrogen by completely shielding the bottom face of the enolate, forcing deuterium (or other electrophiles as observed by Natsugari) to approach from the top face, therefore retaining the overall stereochemistry of the system. This is very similar to the 'memory of chirality' concept popularized by Kawabata and Fuji,[12] but is complicated by the presence of the chiral biaryl and its probable role in determining the reaction outcome. The system may also very well fit into Seebach's definition of a 'self-regenerating stereocenter'.[13,14]

3. Conclusion

A kilo-scale synthesis of enantiopure **2** has been demonstrated. We discovered the extraordinary stability of the C-7 stereocenter and sought out an explanation. We believe that the biaryl portion of this azepinone system contains a previously unrecognized axis of chirality, and this most likely plays an important role in the robustness of the C-7 stereocenter either by way of enforcing a kinetically controlled protonation, or through an interesting chirality-transfer mechanism. We have assigned an additional stereochemical element to all molecules of this class, including **1**. Further investigations into the system, as well as the potential use of **7** and related derivatives as stable asymmetric catalysts are currently underway and will be reported in due course.

4. Experimental

4.1. General

Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere with solvents and reagents used without

purification or drying. Reverse-phase HPLC conditions: Analysis was run on ACE-3 phenyl column (75 × 3 mm) with solvent system consisting of (A) water (with 0.1 mL TFA/L) and (B) HPLC grade acetonitrile. Detection was run at 217 and 260 nm with column temperature = 45 °C and a flow rate of 1.5 mL/min. The gradient was as follows: t(0) 90% A 10% B gradient to t(11 min) 20% A 80% B; t(11.01 min) 90% A 10% B. Chiral HPLC conditions: analysis was run on Chiralpak AD-H column (150 × 4.6 mm) packed with Amylose tris-(3,5-dimethylphenylcarbamate) coated on 5 μm silica gel, solvent was isocratic: methanol containing 0.2% Et_2NH. Detection was run at 260 nm, with column temperature at 30 °C and a flow rate of 0.6 mL/min. NMR spectra were acquired using Varian instruments and software. Chemical shifts (δ) are reported in ppm, and spectra were referenced to the residual solvent signal. Melting points were collected on Büchi melting point apparatus and are uncorrected. Optical rotations were obtained on a Jasco DIP-370 polarimeter.

4.1.1. (*S,S*)-7-Amino-5-methyl-5*H*-dibenzo[*b,d*]azepin-6(7*H*)-one (2*S*,3*S*)-2,3-bis(4-methylbenzoyloxy)succinate hydrate 6

Seed material of **6** was developed by precipitation of a 1:1 mixture of **5** and (+)-DTTA in MeOH by the addition of water. The solid was then successively recrystallized from MeOH/water until the ee of the freebased amine was >99%.

In a 22 L RBF fitted with internal temperature probe, glycol-cooled condenser, addition funnel, and heating mantle, amine **5** (600 g, 2.52 mol) was dissolved in MeOH (8 volumes, 4.8 L). Water (6 volumes, 3.6 L) was then added. The solution was heated to 50 °C. While the amine solution was heating, (+)-DTTA (0.9 equiv, 876 g) was placed in a 5 L flask and dissolved (with gentle heating) in MeOH (6 vols relative to amine, 3.6 L). This solution was then transferred to the addition funnel. When the amine solution had reached 50 °C, the (+)-DTTA solution was slowly added, so as to maintain the salt solution temperature close to 50 °C (approximate addition time: 45 min). When the addition was completed, the addition funnel was rinsed with a small amount of MeOH (<100 mL). The solution was stirred 1 h at 50 °C, then the internal temperature was lowered to 40 °C, and seed was introduced (2 g). It was evident that the seed held, and a large amount of precipitate was observed to form within 15 min. The temperature was increased to 45 °C, and the slurry was stirred overnight. The following morning, the temperature was lowered to 40 °C and stirring was continued; at the end of the second day, the temperature was lowered to 35 °C, and the slurry was stirred over a second night. The following morning, heating was discontinued, and the internal temperature lowered to about 30 °C, at which point the slurry was filtered and rinsed with 1:1 MeOH/water (2 L) to afford **6** as snow-white crystals. The solid was dried in vacuo at 35 °C overnight to afford **6** (631 g, 0.982 mol, 39%). Karl Fischer analysis indicated the presence of one molecule of water (2.7% by weight).

Mp 156.1–163.7 °C; $[\alpha]_D^{23} = -22.5$ (*c* 1.07, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.81 (d, 4H, *J* = 8.4 Hz), 7.67 (d, 2H, *J* = 7.2 Hz), 7.61-7.50 (m, 5H), 7.44 (ddd, 1H, *J* = 2.4, 6.0, 8.8 Hz), 7.30 (d, 4H, *J* = 8.0 Hz), 5.64 (s, 2H), 4.64 (s, 1H), 3.28 (s, 3H), 2.36 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 168.3, 167.7 (2C), 164.7 (2C), 143.8 (2C), 139.8, 134.4, 134.2, 132.1, 129.8, 129.3, 129.2 (4C), 129.2 (4C), 128.5, 128.4, 128.3, 126.6 (2C), 126.0, 122.9, 122.2, 71.3 (2C), 52.8, 35.7, 21.1 (2C); chiral HPLC of freebase: t_R = 5.68 min (desired isomer) ee > 99.9%.

4.2. X-ray acquisition for 6

A single crystal was mounted on a thin filament and cooled to 100 K. Data were collected using a CuK radiation source (=1.54178 Å) and a Bruker diffractometer equipped with a 3-circle goniometer and SMART 6000CCD area detector.[15] Cell refinement and data reduction were performed using the SAINT program V7.56a.[16] The unit cell was indexed, having monoclinic parameters of *a* = 12.8949(2) Å, *b* = 7.56270(10) Å, *c* = 15.7273(3) Å, and *b* = 95.4530(10)°. The cell volume of crystal structure was 1526.79(4) Å.[3] The calculated density of the structure is 1.398 g/cm^3 at 100 K. The structure was solved by direct methods.[16] All atomic parameters were independently refined. The space group choice, that is *P*21, was confirmed by successful convergence of the full-matrix least-squares refinement on (F^2)[17] with a final goodness-of-fit of 1.021. The final *R* indices [$I > 2\sigma(I)$], R_1 = 0.0363, wR_2 = 0.0896 and the largest difference peak and hole after the final refinement cycle were 0.189 and −0.211 (e A^{-3}), respectively.

4.2.1. (*S,S*)-7-Amino-5-methyl-5*H*-dibenzo[*b,d*]azepin-6(7*H*)-one hydrochloride 2

A 1 L flask equipped with overhead stirrer, nitrogen inlet, and thermocouple was charged with **6** (40.0 g, 62.2 mmol) and ethanol (120 mL, 3 vols) was used to rinse all the solid into the flask. The mixture was stirred as 37% HCl (7.9 mL, 96.5 mmol) was added to a single portion. A solution was formed within 5 min. The solution was stirred and warmed to 50 °C. After 2 h at 50 °C, the reaction was cooled to 40 °C. MTBE (400 mL) was added over 1 h at 40 °C. A light tan solid began to form after ~370 mL had been added (mixture became cloudy after ~320 mL). Heating was discontinued, and the slurry was allowed to cool slowly. Once the temperature reached 23 °C, the solid was filtered through a polypropylene pad and washed with MTBE (2 × 40 mL). The solid was dried at 50 °C in vacuo overnight to afford **2** (16.55 g, 97%) as a tan powder. The isolated compound **2** was 99.95 area % by HPLC with 0.05% DTTA impurity. ^{1}H NMR analysis revealed that the product was contaminated with EtOH and water (potency not determined).

Mp decomposed over 215 °C; $[\alpha]_D^{23} = -90.6$ (*c* 0.97, water); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (br s, 3H), 7.73–7.69 (m, 2H), 7.67–7.57 (m, 4H), 7.53 (d, 1H, *J* = 8.0 Hz), 7.47 (dt, 1H, *J* = 2.0, 8.0 Hz), 4.74 (br s, 1H), 3.30 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.6, 139.6, 134.2, 132.1, 131.9, 129.9, 129.5, 128.8, 128.8, 128.6, 126.3, 123.1, 122.2, 52.6, 35.7; HPLC t_R = 2.42 min.

4.3. Procedure for chiral separation of 3

Compound **3** (500 mg) was dissolved in $CHCl_3$ (2 mL) and 2-propanol (3 mL), then heptane (15 mL) was added for a single 20 mL injection over a 8 × 33 cm (20 μm) Chiralpak AS column. The system was eluted isocratically using 3:1 heptane/2-propanol with a flow rate of 375 mL/min, with detection at 260 nm. Both isomers were collected, and the first eluting (isomer 1) was sampled without further dilution. Isomer 1 was held at ambient temperature (296 K) and sampled analytically every 15 min over 6 h. Analytical HPLC conditions: Chiralpak AS-H 4.6 × 150 mm (5 μm) column eluting isocratically with 3:1 heptane/2-propanol containing 0.2% dimethylethylamine. Flow rate = 0.6 ml/min, detect at 260 nm. t_R = 6.6 min (isomer 1) and 11.4 min (isomer 2).

Acknowledgments

We thank Dr. Greg Stephenson and Mr. Benjamin Diseroad for X-ray analysis; Mr. Matthew Voss, and Mr. Joseph Phillips for experimental assistance; and Mr. Greg Rener and Mr. Thomas Gunter for HPLC support. Additionally, we thank PharmaCore Inc. and Asymchem Laboratories Inc. for assistance during scale-up activities.

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