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TETRAHEDRON: *ASYMMETRY*

Efficient asymmetric synthesis of ABT-594; a potent, orally effective analgesic

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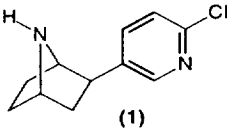
Abstract

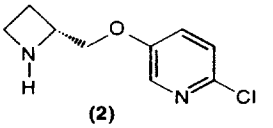
A concise asymmetric synthesis of (*R*)-2-chloro-5-(2-azetidinylmethoxy)pyridine (ABT-594) is presented in which the key intermediate *t*-butoxycarbonyl protected (2*R*)-azetidinylalcohol is obtained in three steps from the dibenzyl ester of D-aspartic acid in 44% yield and >99% ee.

The natural product (−)-epibatidine (**1**), a (chloropyridyl)azabicycloheptane alkaloid isolated from the skin of an Ecuadoran poison frog, is a non-opioid analgesic that is 200-fold more potent than morphine in mice.[1] The antinociceptive properties of epibatidine are mediated through interactions with nicotinic acetycholine receptors (nAChR),[1–3] however, it is toxic at doses only slightly higher than its effective analgesic dose.[4–6] The search for nAChR modulator compounds that exhibit a larger separation between analgesic doses and those that elicit toxic effects led to the identification of (*R*)-2-chloro-5-(2-azetidinylmethoxy)pyridine (ABT-594, **2**).[7,8] ABT-594 is 30–100 times more potent than morphine in animal models with a significantly improved therapeutic ratio and reduced side effect liabilities relative to epibatidine. In this communication we describe an efficient synthesis of enantiomerically pure ABT-594 from the commercially available dibenzyl ester of D-aspartic acid and 2-amino-5-hydroxypyridine.



(1)

(-)-Epibatidine



(2)

ABT-594

The synthesis of ABT-594 required the construction of two primary fragments, namely 2-chloro-5-hydroxypyridine **3**, and the *t*-butoxycarbonyl protected (2*R*)-hydroxymethylazetidine **4** (Scheme 1).

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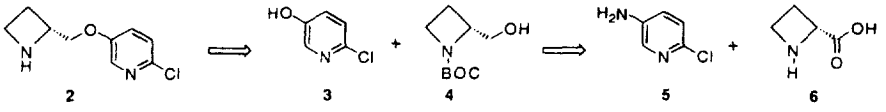
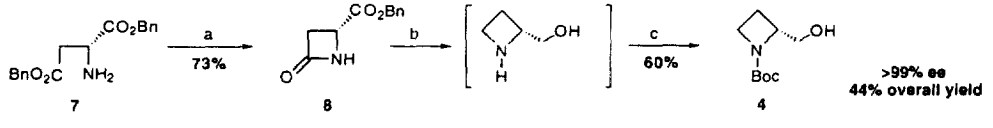
2-Chloro-5-hydroxypyridine **3** was readily produced in two steps from 2-chloro-5-aminopyridine **5** by modification of a literature method for closely related chlorohydroxypyridines.[9] In contrast, an efficient synthesis of the azetidine portion of the molecule proved to be more challenging, with known routes to appropriate (*R*)-azetidine precursors being problematic. Thus, as reported previously, a route to a protected form of **6** from D-methionine[10,11] resulted in substantial racemization in our hands.[12] In addition, a synthesis from γ-butyrolactone which required optical resolution[13,14] gave enantiomerically pure material but was lengthy and proceeded in poor overall yield. Furthermore, these routes required three additional steps to convert the protected form of azetidine carboxylic acid **6** to the desired *t*-butylcarbamate azetidinyl alcohol **4**.



Scheme 1.

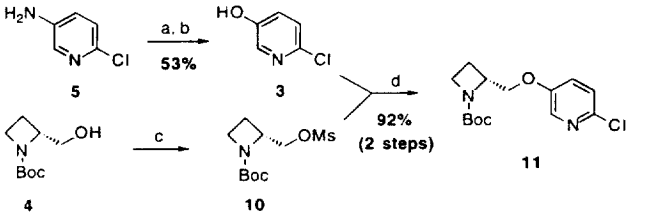
A better approach which utilized the commercially available or easily prepared dibenzyl ester of D-aspartic acid[15] **7** and proceeded through the enantiomer of a known β-lactam intermediate was then explored (Scheme 2). Treatment of **7** with trimethylsilylchloride and triethylamine in diethyl ether, removal of the triethylamine hydrochloride by filtration, followed by addition of *t*-BuMgCl (2 M in Et_2O) according to the literature precedent[16] produced the β-lactam **8** in highly variable yields (20–70%) on a small scale. The inconsistent yields were due to the high water sensitivity of the *N*-trimethylsilyl intermediate, which necessitated filtration under anhydrous conditions.[17] This proved even more difficult on a large scale and therefore modifications were explored. After some experimentation, it was discovered that filtration of the ammonium salt could be avoided if the solvent was changed to CH_2Cl_2 and two equivalents of *t*-BuMgCl were used. Using this process, the β-lactam **8** could be reproducibly formed in 70% yield. The ester and lactam carbonyls of **8** were reduced with excess lithium aluminum hydride and the resulting amine protected as the *t*-butylcarbamate to give **4** in 60% yield[18] and >99% ee as demonstrated by chiral HPLC.[19] Thus, this route to enantiomerically pure *t*-butoxycarbonyl protected (2*R*)-hydroxymethylazetidine **4** proceeds in three steps and 44% overall yield, both of which are significant improvements over previously reported syntheses.



(a) *i.* TMSCl, Et_3N, CH_2Cl_2; *ii.* t-BuMgCl; (b) LAH, THF; (c) BOC_2O, THF

Scheme 2.

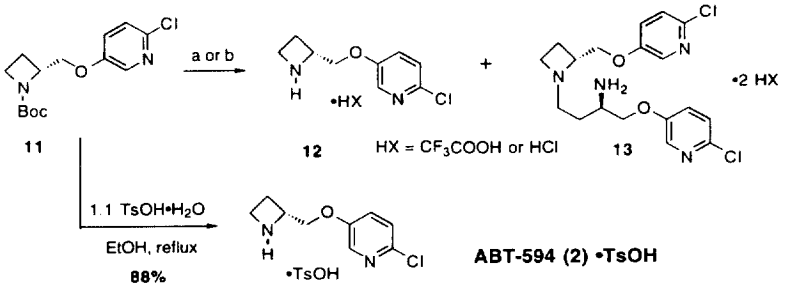
Synthesis of 2-chloro-5-hydroxypyridine **3** and coupling of the primary fragments is shown in Scheme 3. Treatment of 2-chloro-5-aminopyridine **5** with boron trifluoride etherate and *t*-butylnitrite generated the diazonium salt which was decomposed in acetic anhydride[9] to give 2-chloro-5-acetoxypyridine. This acetate was then subjected to potassium carbonate in methanol to produce 2-chloro-5-hydroxypyridine **3** in 53% overall yield for the two steps, a considerable improvement over published syntheses.[8,20] In earlier accounts, the ether forming step to produce compounds such as **11** were always carried out under Mitsunobu conditions.[8,12] This was due in part to a report in which the tosylates of *N*-*t*-butoxycarbonyl prolinol underwent intramolecular cyclization and loss of *t*-butyl to generate the fused 5,5-bicyclic carbamate under basic conditions.[21] However, this undesired reaction appears to be slow with the azetidinyl alcohols and we were able to mesylate **4** to give **10** followed by coupling with **3** in the presence of NaOH in DMF to produced **11** in 92% yield for the two steps.



a) *i* $BF_3{\cdot}OEt_2$, *t*-BuONO, CH_2Cl_2/DME; *ii* Ac_2O, Δ;
b) K_2CO_3, MeOH; c) MsCl, Et_3N, THF; d) KOH, DMF, 80 °C

Scheme 3.

Removal of the *t*-butylcarbamate of **11** using trifluoroacetic acid followed by chromatographic purification provided the free amine of ABT-594 in moderate yield on a small scale (60–80%) and gave a significant byproduct on a large scale which proved difficult to remove. In addition, it was discovered that the initially selected salt forms of ABT-594 (mono or bishydrochloride salts) were hygroscopic and partially decomposed after the absorption of water to give significant quantities of the same byproduct. This undesired material was identified as dimer **13** which presumably resulted from the addition of **12** to the 4-position of another azetidine (Scheme 4). Therefore, it was critically important to find a stable, non-hygroscopic salt form and to remove the *t*-butoxycarbonyl group under conditions which prevented dimer formation. After generating and examining several salt forms, it was found that the tosylate salt provided the desired properties.[22] Subsequently, it was discovered that deprotection and salt formation could be accomplished in a single step by heating **11** in ethanol with a slight excess of *p*-toluenesulfonic acid hydrate. After allowing the reaction to cool and addition of ethyl acetate, crystalline toluenesulfonic acid salt of ABT-594 was produced in 88% yield. This exceptionally efficient sequence produced pure final product in 81% overall yield from *t*-butoxycarbonyl protected (2*R*)-hydroxymethylazetidine **4**.



a) TFA, CH_2Cl_2; b) i. HCl, EtOH/Et_2O, ii. absorption of H_2O by mono or bis-hydrochloride salts

Scheme 4.

In conclusion, the synthesis of ABT-594 from readily available starting materials was accomplished in six steps, in 36% overall yield and with an enantiomeric excess >99%. This route includes a concise synthesis of a protected form of (2*R*)-hydroxymethylazetidine **4** from the dibenzyl ester of D-aspartic acid, an improved construction of 2-chloro-5-hydroxypyridine **3**, and an efficient assembly and final deprotection sequence.

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18. Alternatively, removal of the benzyl group of **8** by hydrogenation (Pd/C, 4 atm hydrogen, THF) followed by LAH reduction produced **4** in 45–55% yield. Although lower yielding, this process eliminated the need for separation of benzyl alcohol by flash silica gel chromatography.
19. Chiralpak AD column, 90:10 hexane:EtOAc (1.0 mL/min) at 210 nm. Michael Fitzgerald and Michael Rasmussen (D45L) are gratefully acknowledged for developing the method and running the analyses.
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22. Dr. Devalina Law of Abbott Laboratories (Pharmaceutics, D4P3) is gratefully acknowledged for evaluation of the physical properties of the different salts of ABT-594.