Tetrahedron Letters 59 (2018) 751–754

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Novel tricyclic diamines 2. Synthesis of 1,7-diazaisoadamantane, 1,5-diazaisoadamantane and 1,6-diazahomobrendane

Ivar M. McDonald [a,*], Robert Mate [a], Alicia Ng [b], Hyunsoo Park [b], Richard E. Olson [a]

[a] Bristol-Myers Squibb Drug Discovery, Wallingford, CT 06492, USA
[b] Bristol-Myers Squibb, Drug Product Science & Technology, Princeton, NJ 08543, USA

ARTICLE INFO

Article history:
Received 12 September 2017
Revised 5 January 2018
Accepted 10 January 2018
Available online 11 January 2018

Keywords:
Diazaisoadamantane
Diazahomobrendane
Tricyclic diamine
Intramolecular cyclization
Azaindole synthesis

ABSTRACT

Three novel tricyclic diamines (1,7-diazaisoadamantane, 1,5-diazaisoadamantane and 1,6-diazahomobrendane) were prepared. A flexible synthetic strategy was employed which used flat, aromatic azaindoles as the starting materials. The requisite azaindoles were prepared by a tandem Sonogashira coupling/intramolecular cyclization reaction. Ring saturation, appropriate functionalization and intramolecular alkylation provided the three novel tricyclic diamines cores.

In the previous communication,[1] we described the synthesis of 1,4-diazaisotwistane (**3**) and 1,4-diazahomoisotwistane (**6**) employing a strategy wherein an appropriately substituted azaindole (**1** or **4**) was first converted to the corresponding saturated bicycle (**2** or **5**) by ring hydrogenation followed by appropriate functionalization and intramolecular cyclization (Fig. 1).

These two tricyclic diamines were initially pursued as interesting ring-constrained isosteres of 3-aminoquinuclidine. We envisioned the methods used to construct these tricyclic diamines could be extended to allow for the formation of additional, potentially useful, novel tricyclic diamines starting with isomeric substituted azaindoles.[2] As depicted in Fig. 2, a route starting with an azaindole with hydroxymethyl functionality at C-2 (**4**), rather than C-3 as in azaindole **1**, would potentially afford the novel 1,7-diazaisoadamantane core **9** (named and numbered after the corresponding all carbon analog, isoadamantane, Fig. 2).

Our efforts began with the attempted Boc-protection of the known 2-hydroxymethylazaindole (**10**).[3] Unfortunately, this was unsuccessful, with mixtures of *N*- and *O*-Boc-protected compounds obtained. This complication could be eliminated by the incorporation of a protecting group on the free hydroxyl. Thus, the literature method used to prepare the unsubstituted azaindole **10** was modified to incorporate a benzyl ether protecting group. Sonogashira coupling of Boc-protected 3-amino-4-iodopyridine **11** with benzyl propargyl ether **12** afforded alkyne **13** in good yield. Treatment of *ortho*-amino-alkynylpyridine **13** with DBU promoted cyclization to azaindole **11** according to the method of Harcken et al.[2] This proceeded with concommitant loss of the *tert*-butoxycarbonyl group to give azaindole **14**. The *tert*-butoxycarbonyl moiety was then reinstalled on the azaindole **14** without difficulty to afford azaindole **15** (Scheme 1).

We were pleased to notice that the fully-protected azaindole **15** matched a minor impurity in the crude mixture of **13** from Sonogashira coupling. In fact, we found that by conducting the Sonogashira coupling at elevated temperatures (80 °C rather than rt) the cyclization to azaindole **15** proceeded during the course of the Sonogashira coupling, without loss of the *tert*-butoxycarbonyl group, thus removing the two steps associated with cyclization and reprotection (Scheme 2).

Intrigued by this transformation, we examined the reaction in more detail. Subjecting isolated alkyne **13** to the Sonogashira reaction conditions with warming (80 °C) provided smooth cyclization to azaindole **15** (Scheme 2). Furthermore, when the palladium was omitted, the cyclization occurred with similar efficiency, but the transformation did not occur in the absence of copper (not shown). Both of these observations suggested that the cyclization was indeed copper-promoted. The cyclization was aided by elevated temperatures, but if the reaction temperature was raised higher than 80 °C, an impurity, which was consistent with loss of the *tert*-butoxycarbonyl group, began to grow in significance. Similar observations have previously been made for the synthesis of

* Corresponding author.
E-mail address: ivar.mcdonald@bms.com (I.M. McDonald).

https://doi.org/10.1016/j.tetlet.2018.01.028
0040-4039/

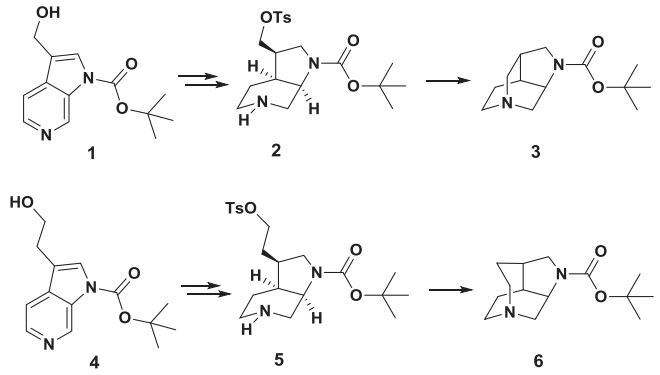


Fig. 1. Strategy for preparation of 2,6-diazaisotwistane.

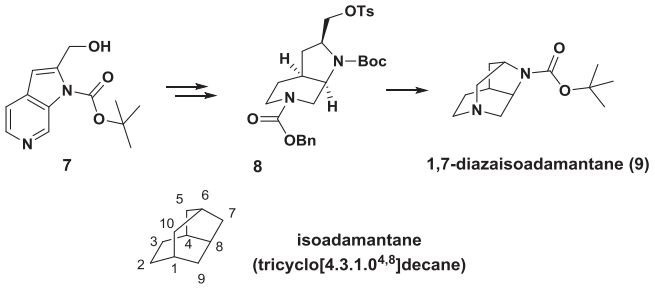
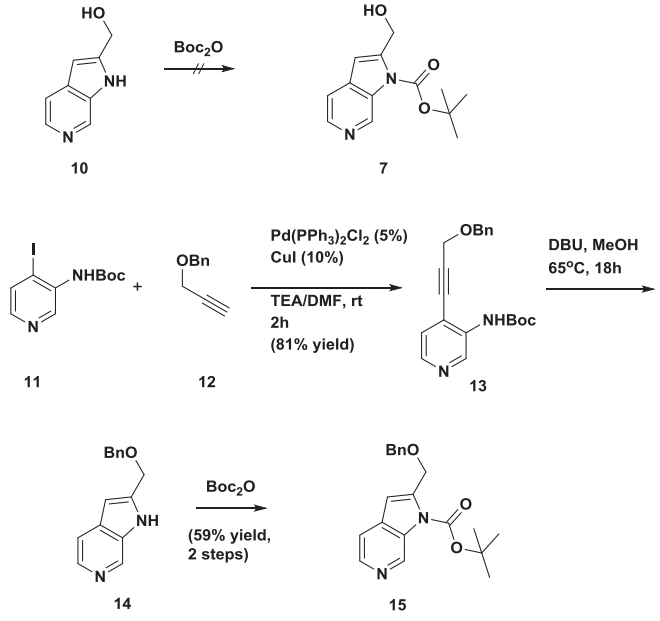
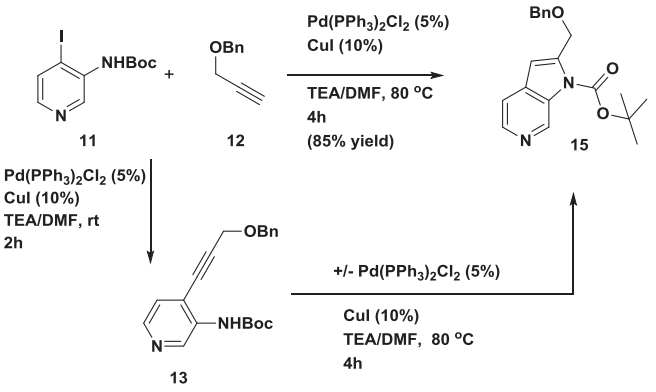


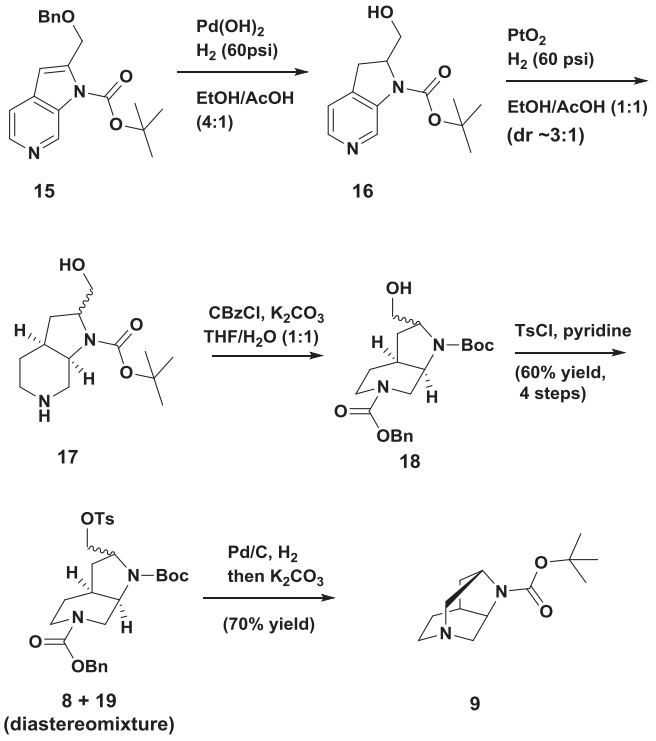
Fig. 2. Strategy for preparation of 1,7-diazaisoadamantane.



Scheme 1. First approaches to 2-hydroxymethyl azaindole core.



Scheme 2. Revised approach to 2-hydroxymethyl azaindole **15**.



Scheme 3. Synthesis of racemic Boc-1,7-diazaisoadamantane (**9**).

5-azaindoles,[4] however in that case, the authors state that they prefer the two-step procedure (via an intermediate similar to alkyne **13**), while in this work, we found the one-step procedure to be preferable.

With azaindole **15** in hand, the synthesis proceeded in a manner analogous to that previously reported for diazaisotwtistane synthesis. (Scheme 3)[1] Thus, hydrogenation over palladium hydroxide accomplished reduction of the azaindole to azaindoline, followed by hydrogenolysis of the benzyl protecting group to yield **16**. The pyridine ring was saturated by hydrogenation over platinum oxide to afford the per-hydro bicycle **17** as a mixture of two disastereomers. Both diastereomers had the same *cis*-configuration at the ring fusion, but differed in the configuration of the pendant hydroxymethyl group, with the major diastereomer containing the all-*cis* configuration.[5] Protection of the secondary amine of **17** as the benzyl carbamate (**18**) was followed by activation of the primary alcohol as the corresponding tosylate. This was obtained as a mixture of diastereomers **8** and **19**. Both had the *cis*-stereochemistry at the ring fusion, but while isomer **8** had an all-*cis* configuration with the tosyl group oriented toward the concave side of the bicycle as is required for subsequent cyclization; diastereomer **19** had the tosylate on the convex side and was unable to undergo intramolecular cyclization. Upon unveiling the secondary amine by hydrogenolysis of the benzyl carbamate, intramolecular nucleophilic attack took place to afford the tricyclic *N*-boc-1,7-diazaisoadamantane **9**.

The racemic diastereomixture of **8** and **19** could be separated into four components by chiral supercritical fluid chromatography (SFC). The individual enantiomers of diastereomer **8** (**8a** and **8b**)