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Novel tricyclic diamines 3. Synthesis of 1,4-diazaadamantane

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ABSTRACT

Synthesis of the previously unreported 1,4-diazaadamantane is described. The overall strategy involves complete saturation of a flat, aromatic heterocycle, appropriate functionalization and intramolecular double alkylation. The alkylation takes place via an iminophosphorane under anhydrous conditions, which produced superior results vs. alkylation of the corresponding primary amine.

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We have recently described the synthesis of a series of novel tricyclic diamines,[1,2,3] each of which contained one tertiary amine and one secondary amine. In each, an appropriately substituted azaindole (exemplified by **1**) was first converted to the corresponding saturated bicycle by ring hydrogenation. Appropriate functionalization (as in **2**) and intramolecular cyclization afforded the desired tricyclic diamine (exemplified by **3**, Figure 1).

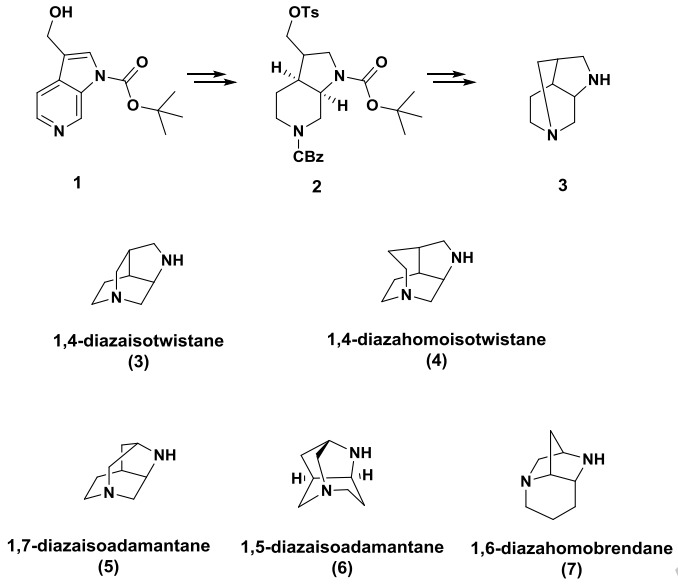

Figure 1. General approach to tricyclic diamines, represented by the synthesis of 1,4-diazaisotwistane. This figure shows the five novel tricyclic diamines prepared by this approach.

In each case, the tertiary amine was formed last from an intermediate ring-fused cyclic secondary amine. This strategy allowed for the successful creation of a several novel isomeric tricyclic diamines (**3-7**, Figure 1) in racemic form. We demonstrated that access to the homochiral amines could be achieved via chiral separation (super critical fluid chromatography, SFC) at an intermediate stage. While this was effective for our needs, it was somewhat inefficent. We were intrigued if this strategy could be extended to prepare the isomeric *achiral* 1,4-diazaadamantane (**10**, Figure 2).

The synthesis of the isomeric 1,3-diazaadamantane **8** (in which both amines are tertiary) was first reported more than sixty years ago[4] and the synthesis of 2,6-diazaadamantane **9** (in which both amines are secondary) was first reported more than forty years ago.[5] We are unaware of any literature examples of the 1,4-diazaadamantane core. There are no syntheses reported for the remaining two isomers of diazaadamantane, 1,2-diazaadamantane **11** and 2,4-diazaadamantane **12** (all other structures are degenerate with one of these five).

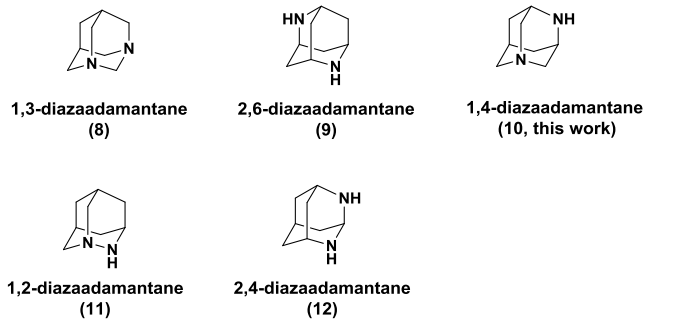

Figure 2. Isomers of diazaadamantane

Unlike the examples from the previous communications (**3-7**, Figure 1), 1,4-diazaadmantane **10**, when viewed retrosynthetically, doesn't contain any disconnections that lead to a ring fused bicycle. In every case, any single retrosynthetic disconnection leads to a bridged ring system (**14-16**). Figure 3 shows the three possible disconnections, labeled *a*, *b* and *c*. Due to symmetry, disconnections *a* and *b* are equivalent (**14** & **15**). While all three of these disconnections individually lead to bridged systems, if disconnections *a* and *b* are combined, this would lead retrosynthetically to symmetrical monocyclic piperidine **17**. This could in turn arise from ring saturation of the corresponding pyridine **19** (via **18**). This strategy would therefore continue the theme of using flat aromatic heterocycles as the initial sources for saturated tricyclic systems.

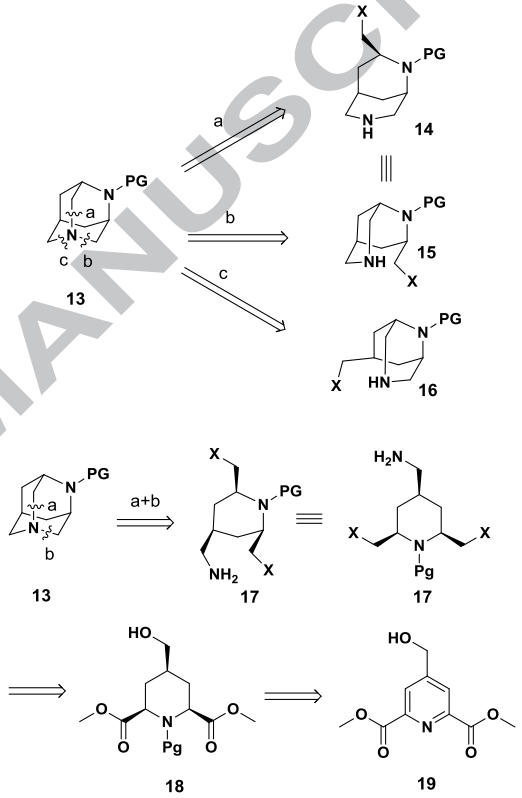

Figure 3. 1,4-diazaadamantane retrosyntheses

Synthesis began with the relatively inexpensive (~$3/gram) dimethyl 2,6-pyridinedicarboxylate **20**, which was subjected to Minisci conditions[6] according to a literature protocol to append the requisite hydroxymethyl group in hydroxymethylpyridine **19**. The yield in this transformation was only moderate, as pushing this transformation to higher conversion led to significantly decreased yields, but given the availabilty of the starting material, this was deemed acceptable. Hydrogenation proceeded in considerably higher yield than had previously been reported (76% vs 34%)[7] upon hydrogenation over palladium on carbon to afford the saturated all-cis piperidine **21**. Treatment with TsCl provided for both the protection of the piperidine nitrogen and activation of the primary alcohol in tosylate **22**. In our earlier work, final ring cyclization occurred by intramolecular alkylation of a secondary amine. In this case, a protected primary amine was required. Installation of the amine synthon was accomplished in nearly quantitative yield by treatment with sodium azide to afford azido-diester **23**. The diesters were next selectively reduced by

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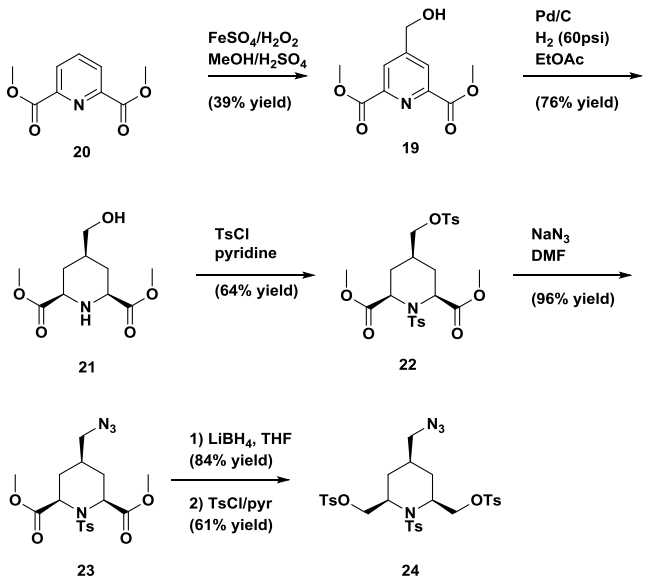
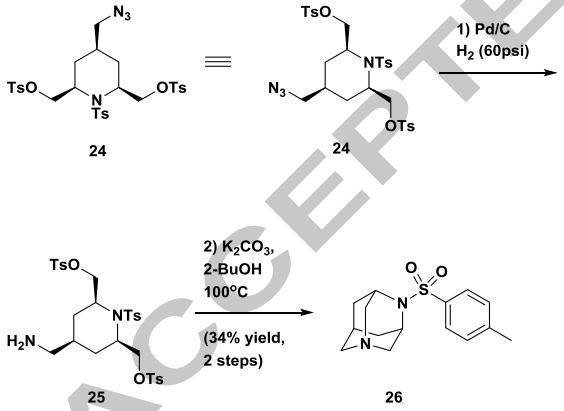
treatment with lithium borohydride and the resultant diol was doubly activated as the bis-tosylate **24**.



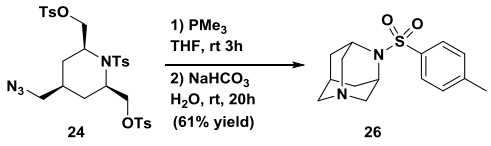
Scheme 1. First approaches to 2-hydroxymethyl azaindole core

With bis-tosylate **24** in hand, we were prepared to attempt the key intramolecular bis-cyclization. In the event, hydrogenation of azide **24** over palladium on carbon appeared to efficiently reduce the azide to the corresponding amine. Upon heating **25** in the presence of base, the amine was successfully cyclized to afford the desired tosyl-protected 1,4-diazaadamantane **26**. This cyclization was considerably less efficient than we had observed in our earlier tricyclic diamine syntheses as it required more forcing conditions and afforded significantly lower yields.



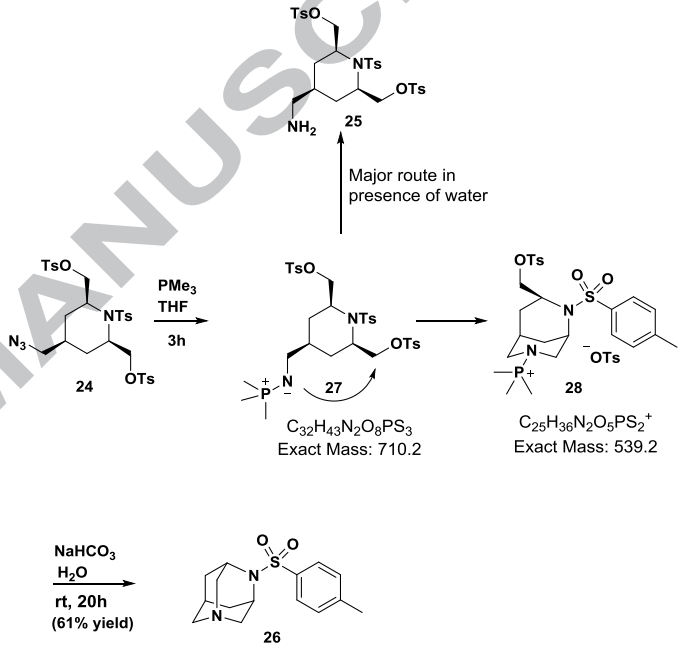
Scheme 2. Cyclization to form 1,4-diazaadamantane core

While we were pleased that we had succeeded in our attempts to prepare this novel tricyclic system, we were disappointed in the poor efficiency in the key step and set out to optimize this transformation. Unfortutately, we were unable to improve upon the yield of this compound via the cyclization of **25**.



Scheme 3. Improved synthesis of 1,4-diazaadamantane core

During the course of these experiments however, we attempted alternative conditions for the reduction of the azide functionality, specifically by Staudinger reduction of azide **24** as an alternative to hydrogenation. Initial efforts (Ph_3P or Me_3P in wet THF) led to poor results, but to our surprise, when trimethylphosphine was used in anhydrous THF, complete consumption of the starting material was observed within a few hours, and when the reaction mixture was subsequently treated with aqueous sodium bicarbonate, with the intention of freeing the primary amine, the tosyl-protected 1,4-diazaadamantane **26** was instead obtained in significantly improved yield. Surprisingly, this occurred without the need to warm the reaction mixture. This unexpected result warranted further mechanistic investigation. Attempts to follow this transformation by ^{1}HNMR or ^{31}PNMR were unsuccessful, as there were a number of components present which were difficult to identify.



Scheme 4. Possible mechanism for 1,4-diazaadamante synthesis via iminophosphorane

product	M+H	r.t.	t=5min	t=70min	t=4h	t=21h
26	293	1.56min	0.03	0.06	0.09	0.31
28	539,M+	2.37min	0.30	0.48	0.46	0.22
25	637	2.65min	0.26	0.13	0.12	0.10
27	711	2.79min	0.17	0.28	0.28	0.33
24	663	3.76min	0.25	0.05	0.05	0.05

Table 1. LC/MS data from reaction monitoring of iminophosphorane cyclization. All data is normalized to the sum of the five components shown here, and reported as detected by UV at 220nm.

In a follow-up experiment, the reaction was repeated under the same conditions, but with regular LC/MS monitoring, which provided insight into the experiment.

Table 1 summarizes the LC/MS data obtained in this experiment, and Figure 4 shows overlaid LC/MS traces at the 5 minute (black) and 21 hour (red) timepoints. As a caveat, the data is represented as the area percentage observed by UV detection at 220nm; the results do not take into account differences in the extinction coeffiecients in the various components. Additionally, the results are normalized to the sum of these five components, thus removing other minor unassigned peaks as well as a major

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non-ionizing , UV-active peak (at rt=0.46 min) which was consistent with the tosylate counterion.

Within 5 minutes, three quarters of the starting material was consumed with four new components present. The expected primary amine **25** was present (*m/z*= 637.3 for M+H). A second major component was consistent with the intermediate iminophosphorane **27** (*m/z*= 711.3 for M+H). We were surprised that iminophosphorane **27** appeared to survive chromatography in the presence of water/methanol +0.01% TFA, although it may be the case that the primary amine (**25**) which is observed was an artifact due to decomposition of the iminophosphorane during the quenching & LC/MS analysis conditions. More surprising was the observation that the main component was consistent with bridged bicycle **28**, in which the iminophosphorane partially cyclized to form a bridged bicyclic piperidinyl phosphonium ion (observed *m/z*= 539.3, consistent with M+ for **28**). While we did not find precedent for this type of transformation, this structure was generally consistent with the observed reactivity. At the 5 minute time-point, small amounts of tricyclic product **26** were already observed.

At approximately one hour, almost all of the starting material was consumed and nearly half of the total was monocyclized **28**. At this time, the amount of amine **25** observed was significantly decreased compared to the 5 minute time point, and the fully cyclized tricycle **26** was increased.

Whereas in the earlier reaction, the mixture was quenched after 3h, when complete consumption of the starting material was observed, this time the reaction was allowed to age overnight, as it appeared that there was a significant amount of iminophosphorane **27** remaining. Surprisingly, a significant amount of solid material had crystallized from the reaction mixture after aging overnight. These were collected and identified as the *p*-TsOH salt of tricycle **26**. In this case, where the aqueous workup was omitted, the yield was decreased from the previous example (42% vs. 61% yield).

Taken together, these results suggest the reaction proceeds by intial iminophosphorane formation (**27**), followed by intramolecular alkylation of the iminophosphorane nitrogen. Iminophosphoranes have been shown to be strongly nuclephilic at nitrogen, participating in both intra-[8] and intermolecular[9] alkylations. The resultant monocycle **28** can slowly cyclize to the tricyclic **26**, either in the presence or absence of water, although it appears in the aqueous conditions the yield is significantly improved. In this mechanism, the amine **25** could be rationalized as occuring through iminophosphorane decomposition either through adventitious water or as an artifact of the LC/MS analysis. Unanswered in this proposal however is the question of why significant amounts of iminophosphorane **27** remained after 21 hours when the initial cyclization of iminophosphorane **27** to bicycle **28** had occurred very rapidly within the first 5 minutes. As our mechanistic insights are essentially based solely on LC/MS analysis, we cannot at this time rule out other possibilities as to the course of this reaction.

The structure of tricycle **26** was confirmed by single-crystal X-ray analysis of the compound as its *p*-TsOH salt (Figure 5).

With tricycle **26** in hand, protected as the tosamide, the final step was to deprotect the sulfonamide. In the event, reaction of sulfonamide **26** with lithium naphthalenide accomplished deprotection of this group. Isolation of the free 1,4-diazaadamantane **10** from the reaction mixture was challenging, so instead the resultant free amine was trapped with di-tert-butyldicarbonate to provide the Boc-protected 1,4-diazaisoadamantane **29**. This material was isolated in a straightforward manner, and could be deprotected to afford the free 1,4-diazaadamantane **10** as a TFA salt without purification.

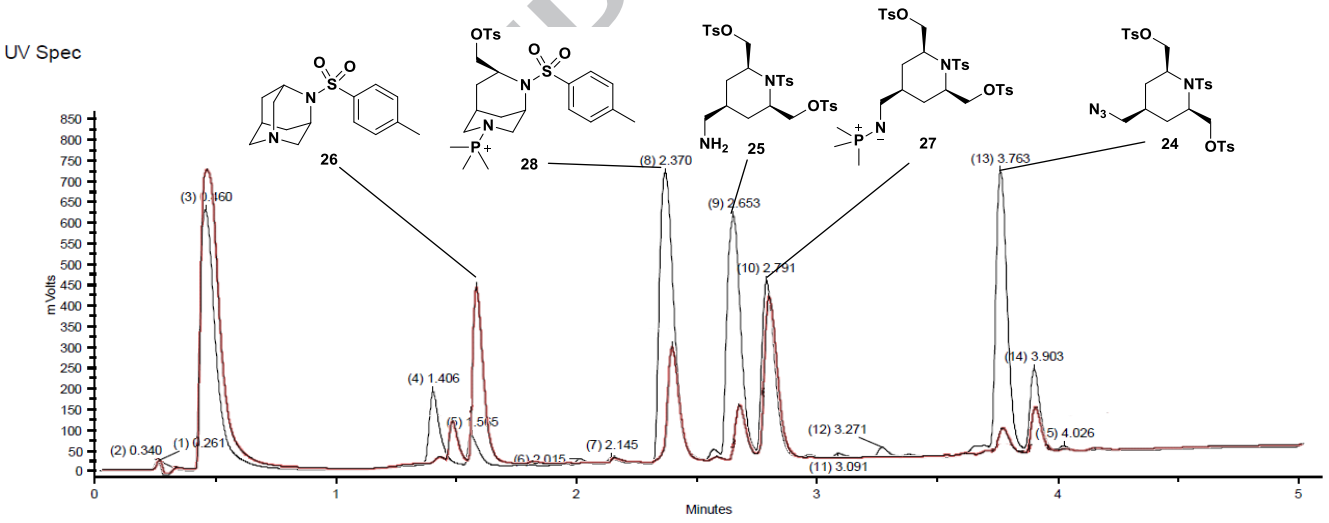

Figure 4. LC/MS traces for aliquots removed from the reaction at 5 minutes (black trace) and 21 hours (red trace). Detection by UV monitoring at 220nm.

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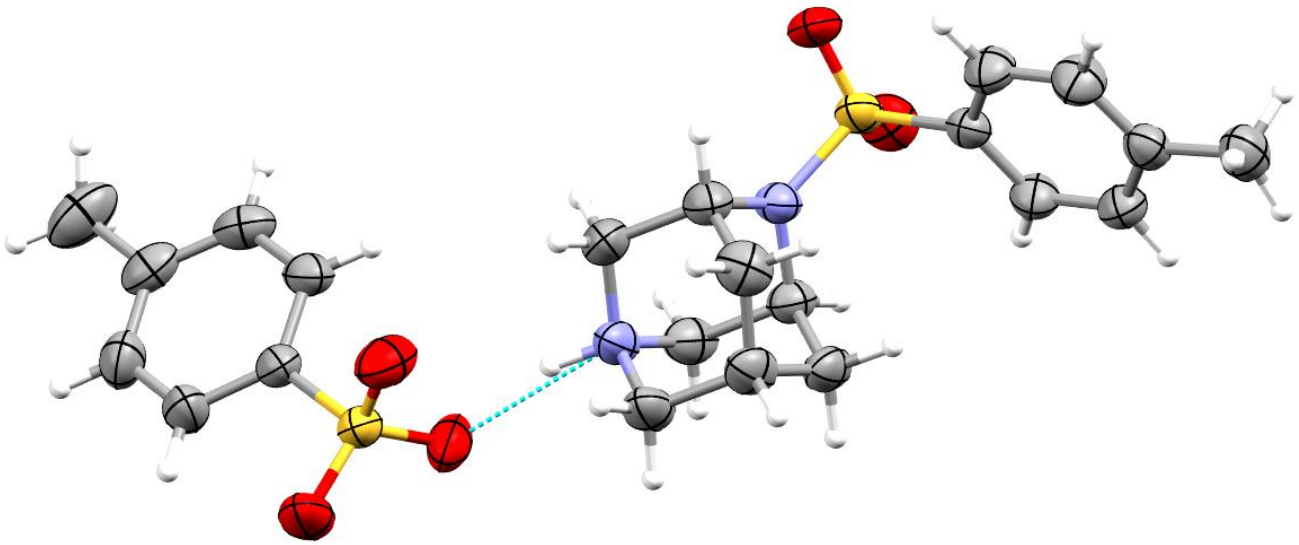

Figure 5. ORTEP of X-ray crystal structure of 1,4-diazaadamantane **26**.

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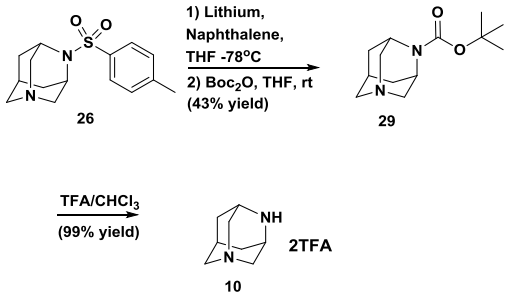

Scheme 5. Deprotection of sulfonamide **26**.

In summary, we prepared a new diazaadamantane isomer, 1,4-diazaadamantane (**10**), which contains one secondary amine and one tertiary amine. This complements the five new tricyclic diamines (**3**-**7**) described in the previous two communications in this series. Notably, this has the advantage of being achiral. The synthesis was accomplished by a route which drew inspiration from the synthesis of these other tricycles, that is the synthesis began by derivitization and saturation of a flat, aromatic heterocycle, followed by intramolecular cyclization. In this case, this double cyclization took advantage of an unexpected iminophosphorane-driven intramolecular bis-alkylation to form the novel 1,4-diazaadamantane. The use of this amine, in addition to the other tricyclic diamine cores from the previous two communications in this series in the course of a medicinal chemistry project will be reported in a forthcoming publication.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at

Highlights

- Novel 1,4-diazaadamantane was prepared.
- Synthesis relies on saturation of trisubstituted pyridine followed by intramolecular cyclization.
- Final ring closure appears to proceed via iminophosphorane displacement of a tosylate.