Cyclic sulfamidates as lactam precursors. An efficient asymmetric synthesis of (-)-aphanorphine†

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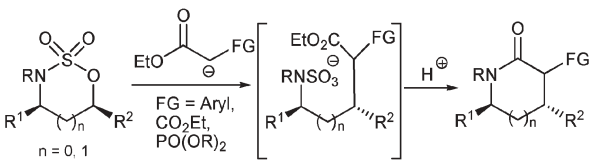
A short and efficient enantioselective synthesis of (−)-aphanorphine is described based on the use of a cyclic sulfamidate to provide a suitably functionalised lactam that allows for construction of the tricyclic 3-benzazepine scaffold.

We have recently reported synthetic entries to enantiomerically pure 5- and 6-ring nitrogen heterocycles, including lactams, based on exploiting the availability and reactivity of 1,2- and 1,3-cyclic sulfamidates towards functionalised nucleophiles.[1a,b] In particular, enolates show a high degree of flexibility providing α-functionalised lactams in good yield (Scheme 1).[1b]

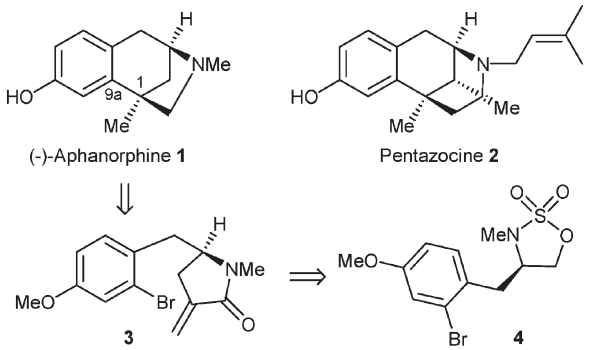


Scheme 1

It is important to define the scope and robustness of this sulfamidate-based chemistry in a broader sense, and in this paper we report on the application of this lactam methodology to a highly efficient and direct synthesis of (−)-aphanorphine **1**. Aphanorphine, first isolated from the fresh-water blue-green alga *Aphanizomenon flos-aquae*,[2] incorporates a 3-benzazepine scaffold, which is closely related to the synthetic analgesic pentazocine **2**.[3]‡ This structural feature makes aphanorphine an interesting target for synthesis and a number of groups have reported routes to both racemic and enantiomerically pure **1**.[4,5]

Our approach to aphanorphine relied on an ability to generate the C(1)–C(9a) bond to complete the 3-benzazepine array. This focussed our attention on a suitable precursor, which was the *exo*-methylene lactam **3**, available in turn from an enantiomerically pure 1,2-cyclic sulfamidate **4**.

The implementation of this strategy is outlined in Scheme 2. 2-Bromo-4-methoxybenzaldehyde **5**§ was condensed with commercially available *N*-Boc-α-phosphonoglycine trimethyl ester[7] to give the corresponding dehydroamino ester **6** in 99% yield and >99% *Z* isomer. Asymmetric reduction of **6** was accomplished



using a Rh-DuPHOS-based[8] catalyst system to give **7** in essentially quantitative yield and in 99% ee (as judged by chiral HPLC). Our aim was to use **7** to provide the requisite 1,2-cyclic sulfamidate *via* the corresponding *N*-methylated amino alcohol **10**. Attempts to reduce both the ester as well as the *N*-Boc moiety (to *N*-Me) of **7** failed because of competing debromination, but this problem was solved in an efficient manner. Reduction of **7** with $LiAlH_4$ gave alcohol **8** in 96% yield. This intermediate was then treated with NaH to effect cyclisation to the cyclic carbamate **9**, which was then methylated *in situ* with no need for isolation.¶ Once the alkylation step was judged to be complete (TLC), NaOH and MeOH were added and the intermediate carbamate was cleaved hydrolytically. This allowed us to convert **8** to **10** in 92% overall yield and in a single pot operation. The key cyclic sulfamidate **4** was then prepared in two steps (81% overall)[9] and the enantiomeric purity was confirmed as 99% ee by chiral HPLC.

Exposure of **4** to the enolate derived from triethyl phosphonoacetate served to cleave efficiently the cyclic sulfamidate and following an acidic workup, lactam **11** was isolated in 84% yield as an inconsequential mixture of diastereoisomers. Exposure of **11** to HCHO gave the desired *exo*-methylene lactam **3** in 74% yield. This intermediate is set up to establish the key C(1)–C(9a) bond of **1** under radical or (reductive) Heck reaction conditions. Both processes were studied in detail, but under a range of Heck conditions, no cyclisation occurred.[10] Pd-mediated oxidative addition did occur but we only observed the product of C–Br reduction. Consequently it is unclear whether the Heck cyclisation takes place, or if it does occur this step may be reversible. The alternative aryl radical pathway was, however, successfully implemented. Exposure of **3** to Bu_3SnH (PhH, AIBN, reflux) resulted in cyclisation to give **12**‖ in 62% yield (see below). Reduction of the lactam moiety of **12** gave (+)-*O*-methyl aphanorphine **13** ($[\alpha]_D^{20}$ + 8.3 (*c* 0.5, $CHCl_3$); lit. $[\alpha]_D^{28}$ + 8.1 (*c* 1.2, $CHCl_3$),[5h] $[\alpha]_D^{20}$ + 9.4 (*c* 0.3, $CHCl_3$),[5j] $[\alpha]_D^{20}$ + 8.7 (*c* 1.06, $CHCl_3$)[5n]), which constitutes a formal synthesis of (−)-aphanorphine **1**.

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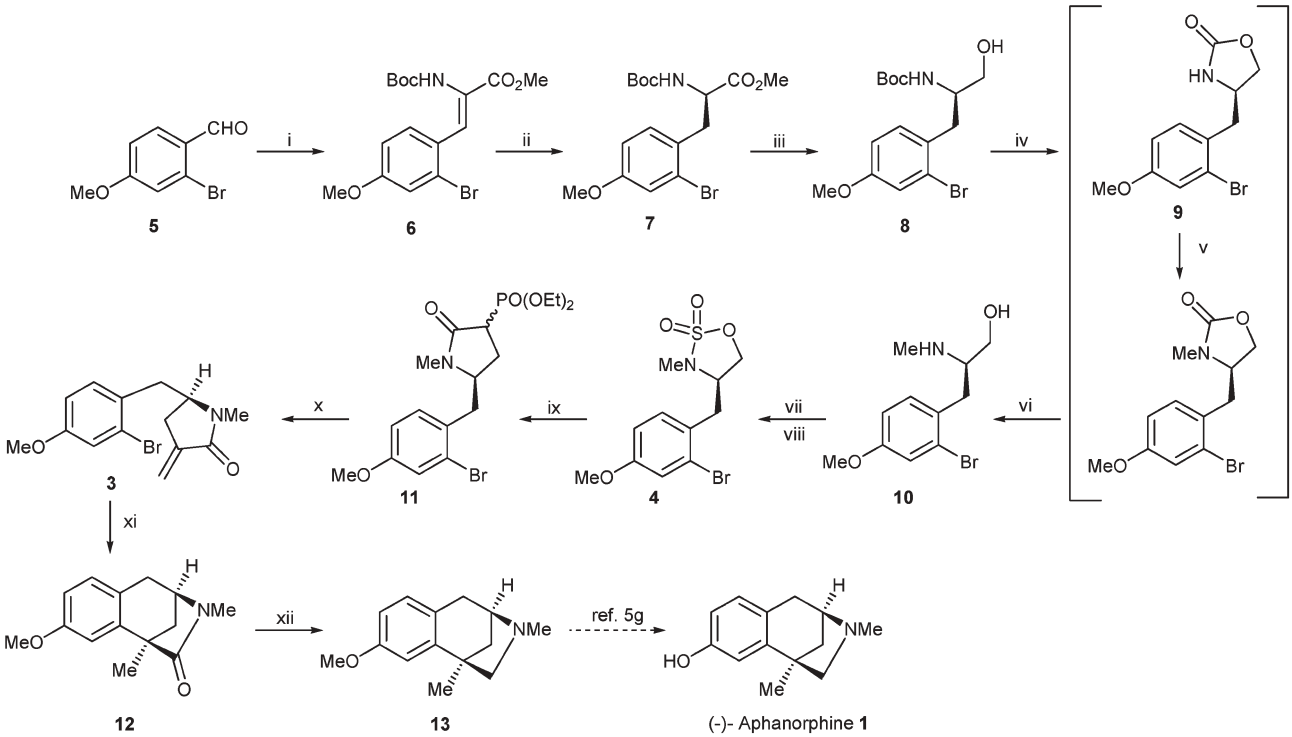
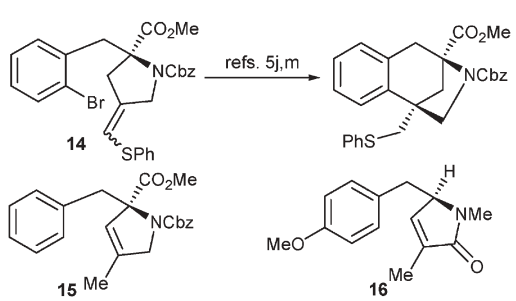
† Electronic Supplementary Information (ESI) available: Full experimental details and spectroscopic data. See DOI: 10.1039/b510761j



Scheme 2 *Reagents and conditions:* i, BocNHCH(PO(OMe$_2$))CO$_2$Me, *N*,*N*,*N*′,*N*′-tetramethylguanidine, CH_2Cl_2 (99%); ii, [((*R*,*R*)-Et-DuPHOS)Rh(COD)]BF_4 (1.5 mol%), H_2 (5 bar), MeOH (100%); iii, $LiAlH_4$, THF, 0 °C (96%); iv, NaH, THF; v, NaH, MeI, THF; vi, NaOH, MeOH, reflux, 2 h (92% from **8**); vii, $SOCl_2$, imidazole, Et_3N, CH_2Cl_2, 0 °C; viii, $RuCl_3$ (0.15 mol%), $NaIO_4$, H_2O, EtOAc, 0 °C (81% from **10**); ix, $(EtO)_2OPCH_2CO_2Et$, KO*t*-Bu, THF, 40 °C then 5 M HCl (84%); x, NaH, paraformaldehyde, THF (74%); xi, Bu_3SnH–AIBN (added over 1.5 h), PhH, reflux (62% + 18% of **16**); xii, $LiAlH_4$, THF (93%).

The radical-mediated cyclisation of **3** to give **12** merits comment (Scheme 3). Previously, Ishibashi[5j,m] described a related approach to **1** based on construction of the C(1)–C(9a) bond. However, this required the presence of a thio-substituted radical acceptor (as in **14**) to promote the radical cyclisation step. In the *absence* of this thio residue, although this was only reported in the desmethoxy series, a major pathway observed corresponded to intramolecular 1,5-hydrogen atom abstraction *i.e.* leading to **15**. In our approach, there is no requirement for additional activation of the *exo*-methylene moiety to achieve an efficient cyclisation. We do, however, also observe the product (**16**) of a formal 1,5-hydrogen atom abstraction. Interestingly, the amount of **16** does increase if the Bu_3SnH–AIBN component is added over a shorter period.** This suggests that **16** could also arise *via* a direct isomerisation of the *exo*-alkene to the *endo*-isomer.



Scheme 3

In summary, we have described a novel entry to (−)-aphanorphine **1** based on exploiting the reactivity of cyclic sulfamidates as progenitors of substituted, α-functionalised lactams. The route outlined in Scheme 2 is highly efficient, and the conversion of **5** to *O*-methyl aphanorphine **13** proceeds in an overall yield of 25.4%, which compares very favourably with existing synthetic approaches to (−)-aphanorphine **1**.

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Notes and references

‡ Pentazocine and naloxone (Talwin nX®) are prescribed together, with naloxone reducing the dependence and morphine-like side effects of pentazocine. Interestingly, and despite the co-occurrence of saxitoxin and neosaxitoxin with aphanorphine in *Aphanizomenon flos-aquae,* this plant material is also marketed as a food supplement and nutraceutical.

§ 2-Bromo-4-methoxybenzaldehyde **5** was prepared as described by Durst[6a] using Comins' methodology[6b] for directed *ortho*-lithiation of aryl aldehydes.

¶ The intermediacy of the cyclic carbamate **9** is inferred, but this species has not been isolated.

‖ Intermediate **12** was reported in racemic form by Funk, who also described the lactam reduction and *O*-demethylation. Spectroscopic data obtained for lactam **12** matched that reported by Funk (see ESI).[4b] We converted **12** to (+)-*O*-methyl aphanorphine **13**, which constitutes a formal synthesis of (−)-aphanorphine **1**; the *O*-demethylation step has been reported by a number of groups in yields ranging from 57–86%.

** This observation does not exclude participation of the 1,5-hydrogen atom abstraction pathway, but the ratio of **12** to **16** would not be expected to depend on the concentration of Bu_3SnH if intramolecular abstraction was the only source of **16**. In our hands, *exo*-methylene lactams related to **3**

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are prone to C=C migration. Use of TMS_3SiH failed to give an improved yield of **12**.

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