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PAPER

Synthetic approaches to a chiral 4-amino-3-hydroxy piperidine with pharmaceutical relevance†

Adrian Ortiz,* Ian S. Young, James R. Sawyer, Yi Hsiao, Amarjit Singh, Masano Sugiyama, R. Michael Corbett, Melissa Chau, Zhongping Shi and David A. Conlon

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Four synthetic strategies were evaluated towards the preparation of (−)-(3*R*,4*R*)-1-benzyl-4-(benzylamino)-piperidin-3-ol (**1**), which was constructed with control over the relative and absolute stereochemistry of the 4,3-amino alcohol moiety. The first strategy employed a novel Rh^{I} catalyzed asymmetric hydrogenation, while two other strategies exploited the existing stereochemistry in 2-deoxy-D-ribose, and the fourth explored both biocatalytic and classical resolution techniques as a means to impart enantioenrichment to racemic intermediates *en route* to targeted structure (−)-**1**.

Introduction

The piperidine **1**[1] is an advanced key intermediate utilized in the synthesis of the investigational new drug candidate, BMS-690514 (**2**, see Fig. 1), developed for treatment of non-small cell lung cancer.[1] An efficient synthesis of **1** from readily available starting materials was required in order to furnish larger quantities of BMS-690514 to support ongoing clinical studies. The initial in-house route used to prepare **1** took advantage of a well-precedented chiral pool based strategy starting from (*R*)-pyroglutamic acid (see Fig. 2).[2] While this strategy was successful in preparing **1** to support initial clinical development, it was lengthy (requiring seven multi-operational steps and three isolations) and was projected to contribute significantly to the overall cost of BMS-690514 (**2**). This complexity led us to pursue an alternative synthesis of **1**. In this article we report on the development and comparison of four alternative strategies towards this valuable intermediate.

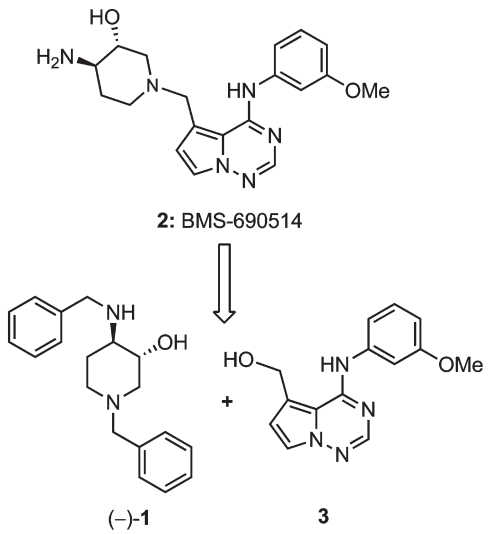


Fig. 1 Retrosynthetic analysis of drug substance **2**, and key piperidine **1**.

Results and discussion

Our first strategy sought to employ an asymmetric catalytic method for the installation of the key 4-amino-3-hydroxy moiety. Hydrogenation of keto esters is a powerful tool, providing access to the corresponding hydroxy esters.[3] In our system a *trans*-selective asymmetric hydrogenation would be required from commercially available keto ester **4** (see Scheme 1).[4] The hydrogenation of 2-hydroxycyclohex-1-ene-carboxylic acid, has been reported using Ru-BINAP catalyst with high diastereoselectivity (95 : 5) and enantioselectivity (90% ee),[5] however, this catalyst was not effective for the hydrogenation of compound **4**, giving both low diastereoselectivity (55 : 45) and enantioselectivity (70% ee).

After extensive catalyst screening, [RuCl(cymene)(*R*-C3-tunephos)]Cl **6** (1 mol%) was identified as a suitable catalyst for this transformation. Our optimized conditions for this reaction utilized a hydrogen atmosphere (50 bar, 17 h) in a mixture of EtOAc–MeOH (9 : 1) to yield the desired hydroxy ester **5** as a

Chemical Development, Bristol-Myers Squibb Company, One Squibb Drive, New Brunswick, New Jersey08903, U.S.A.
E-mail: Adrian.Ortiz@bms.com; Tel: +732-227-5816

†Electronic supplementary information (ESI) available: Experimental procedures and characterization data (^{1}H NMR, ^{13}C NMR, HRMS and IR) and copies of ^{1}H NMR and ^{13}C NMR for all new compounds. CCDC 878581 for HCl salt of **24**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25411e

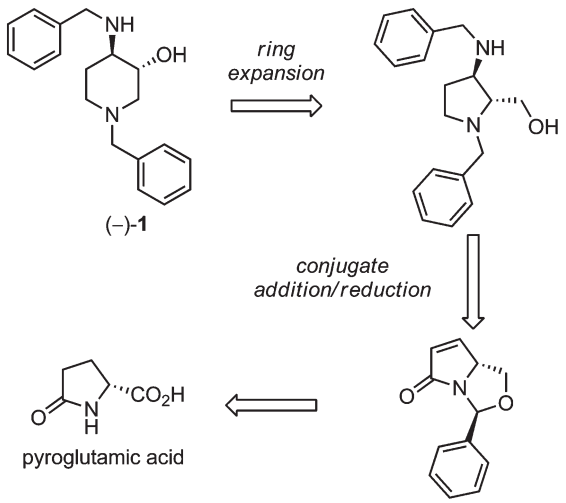
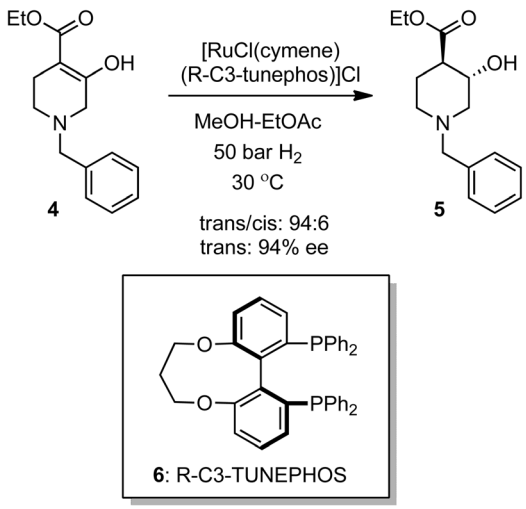
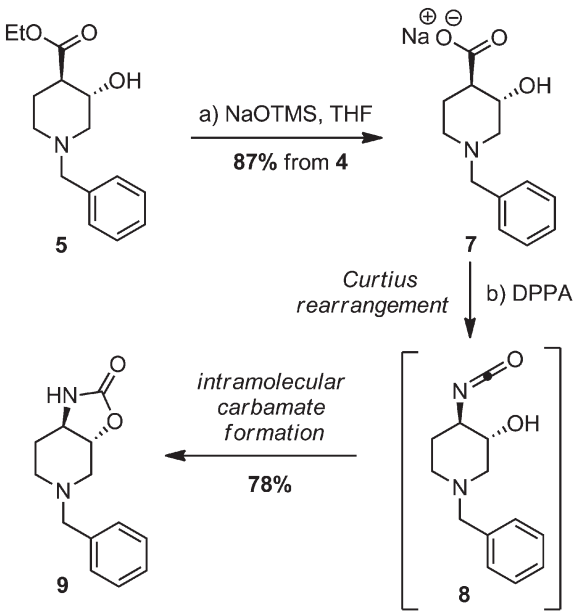


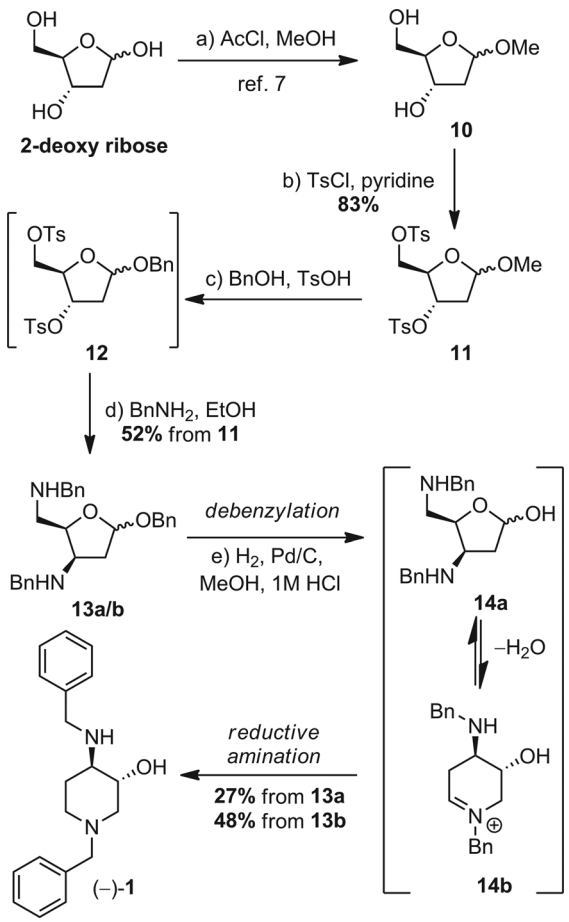
Fig. 2 Retrosynthetic analysis of **1** from initial pyroglutamic route.



Scheme 1 Preparation of **5** by asymmetric hydrogenation.



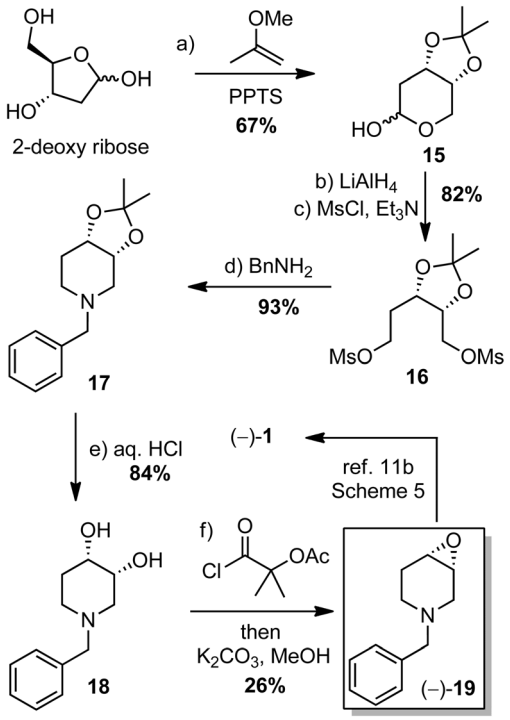
Scheme 2 Synthesis of carbamate derivative **9**.



Scheme 3 Synthesis of **1** in enantiomerically pure form from 2-deoxy-D-ribose.

94 : 6 *trans* : *cis* mixture and in 94% ee. The crude product **5** was saponified and isolated as its sodium salt (**7**, NaOTMS, THF, 87% over the two steps, see Scheme 2). Curtius rearrangement (DPPA, *t*-BuOH, 80 °C) proceeded smoothly with *in situ* trapping of the intermediate isocyanate, to afford cyclic carbamate **9** (78%). An interesting advantage in the formation of **9** is that the oxazolidinone simplifies the protecting group strategy for the eventual coupling with fragment **3**. Despite the success of the asymmetric reduction approach, we unfortunately encountered difficulties in finding commercial sources to provide ligand **6** and therefore continued to pursue alternative strategies.

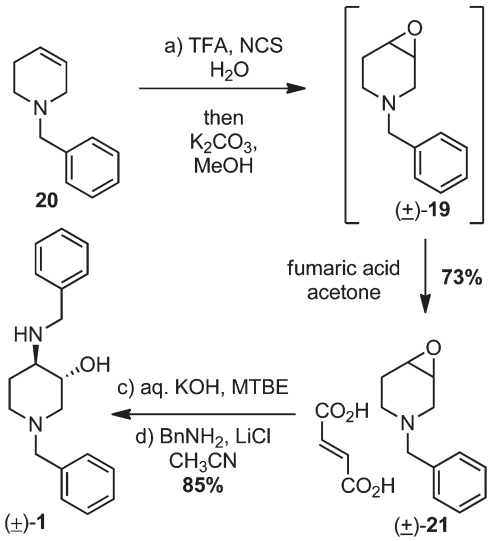
The second strategy investigated was based on a literature precedent for the preparation of chiral 3,4-substituted piperidines.[6] The ring expansion of a 2-deoxy-D-ribose derivative was examined as an avenue to access **1** (Scheme 3). Formation of the methyl glycoside **10** (1.25 : 1 mixture of anomers) was conducted at 0 °C (AcCl, MeOH) to minimize competing formation of the hexose sugar (<8%).[7] Subsequent transformation to its bis-tosylate derivative (**11**, 83%) yielded a substrate suitable for glycoside exchange, *via* treatment with an excess of benzyl alcohol in the presence of catalytic TsOH, thus providing **12** as a



Scheme 4 Synthesis of epoxide (−)-**19** from 2-deoxy-D-ribose.

1.3 : 1 mixture of anomers. The excess benzyl alcohol was difficult to remove from the product at this stage. Therefore, the crude bis-tosylate **12** was directly subjected to displacement with $BnNH_2$, providing chromatographically separable cascade precursors **13a/b** in 52% combined yield from **11**.[8] Interestingly, the rate of product formation for each anomer (**13a/b**) was different under hydrogenative conditions (H_2, Pd/C); the more polar anomer had a diminished rate for *–O*-Bn removal, resulting in a reduced yield of (−)-**1** (27%). Extended reaction times (4.5 h), significantly increased *–N*-Bn removal. However, the less polar anomer reached greater than 90% conversion in 2 h, to produce compound (−)-**1** in 48% yield, and >99.9% enantiomeric excess. This reaction has not been optimized with respect to hydrogen pressure, catalyst, or acid, and the major by-products are the *–N*-benzyl cleaved compounds and the methyl glycosides of the starting material. Although high quality **1** was prepared using this strategy, the differential reactivity of **13a/b** reduced the attractiveness of this approach.

A third strategy utilizing 2-deoxy-D-ribose as a chiral building block was also explored (Scheme 4). It has previously been reported[6] that the *N*-Boc derivative of **18** could be converted to the corresponding epoxide by treatment with Moffatt's reagent.[9] In our case, the *N*-benzyl substrate had yet to be utilized in such a transformation, and as will be observed (*vide infra*[11]), an *N*-alkyl substituent is required to obtain a high degree of regioselectivity in the epoxide opening with benzylamine. To this end, 2-deoxy-D-ribose was protected as its isopropylidene derivative **15** (2-methoxypropene, PPTS) in 67% yield. Reduction of **15** ($LiAlH_4$) afforded the corresponding diol, which after conversion to the bis-mesylate **16** (82%, 2 steps), was displaced with benzylamine to give piperidine **17** (93%). The isopropylidene moiety was cleaved under acidic conditions (aq. HCl) to furnish

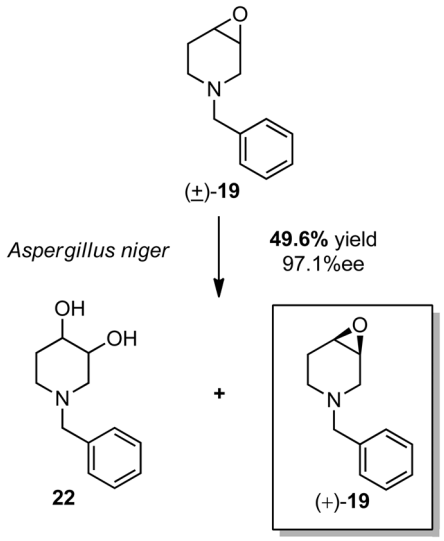


Scheme 5 Synthesis of racemic (±)-**1** from tetrahydropyridine **20**.

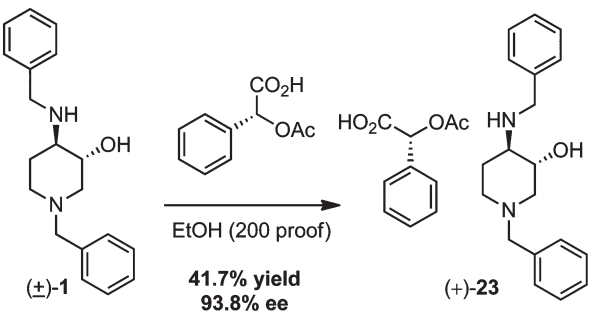
cis-diol **18** (84%). Subsequent treatment with Moffatt's reagent and basic hydrolysis (K_2CO_3, MeOH), resulted in ring closure, and delivered epoxide (−)-**19** in 26% yield and >99.9% ee. Enantiomerically pure epoxide (−)-**19** required only regioselective opening with benzylamine to complete the synthesis of **1** (see Scheme 5).[10] Despite the perceived advantages of using 2-deoxy-D-ribose to prepare **1**, this route suffered from unattractive low yields.

The final strategy towards **1** focused on the development of a simple racemic synthesis to epoxide **19** as a key intermediate. We hoped to take advantage of a recent report detailing the highly regioselective opening of 3,4-epoxy piperidines by nitrogen nucleophiles in the presence of lithium salts.[11] This report thus rendered regioselectivity a non-issue, and left enantioenrichment *via* resolution as the key step still requiring development. The synthesis of **1** began with epoxidation of *N*-benzyl 1,2,5,6-tetrahydropyridine (**20**, see Scheme 5) utilizing a two-step procedure (TFA–H_2O then NCS),[12] to circumvent potential *N*-oxide formation. Thus, the regioisomeric chlorohydrins were treated with base (K_2CO_3, MeOH) to provide racemic epoxide **19**. The 3,4-epoxy piperidine **19** was isolated as its fumaric acid salt **21** in high yield, 73% (from **20**). A salt break (aq. KOH) followed by Li^+-mediated, regioselective (>20 : 1) epoxide opening with $BnNH_2$ (LiCl, CH_3CN)[11b] afforded (±)-**1** as a crystalline solid (85%). It has been previously shown[11b] that lithium chelation between both the oxygen and the basic piperidine nitrogen (*i.e.* *N*-Bn rather than *N*-Boc) is required to achieve the desired regioselectivity.

With a simple synthetic strategy to racemic **1** in place, we explored potential avenues for its enantioenrichment. Initially, we focused on the resolution of racemic epoxide (±)-**19**, as resolution earlier in the synthetic sequence had the potential to increase the efficiency of our route. We were encouraged by the work of Grishna and coworkers on the biotransformations of *N*-benzyl 1,2,5,6-tetrahydropyridines to their corresponding *trans*-diol intermediates (*i.e.* **20** → **22**).[13] We therefore, investigated the potential to perform a microbial resolution of racemic epoxide (±)-**19**. A significant screening of microbes was



Scheme 6 Biocatalytic/kinetic resolution of racemic epoxide (+)-**19**.



Scheme 7 Classical resolution of (±)-**1**.

conducted (see Scheme 6)[14] which interestingly, resulted in only the undesired enantiomer [*i.e.* selective hydrolysis of (−)-**19** over (+)-**19**]. The optimized conditions, [yielding (+)-**19**] utilized *Aspergillus niger* SC 16295 to provide selective hydrolysis of (−)-**19** while leaving epoxide (+)-**19** largely intact (49.6% yield, 97.1% ee).[15]

An alternative enantioenrichment strategy focused on a classical resolution of racemic intermediate (±)-**1**. It was discovered, after a high throughput crystallization screen, that treatment of (±)-**1** with R-*O*-acetyl mandelic acid (1.0 eq.)[16] in EtOH (200 proof) generated the desired diastereomeric salt [(+)-**23**] in 41.7% yield and 93.8% ee (Scheme 7). Unambiguous confirmation for the absolute stereochemistry present in **23** was provided by single crystal X-ray crystallographic analysis (see Fig. 3).[17] This final route provided the target structure (**1**) in 26% overall yield, and required only two chemical transformations and a classical resolution.

Conclusion

In summary, four strategies have been demonstrated on lab scale with the potential to prepare benzyl-protected piperidine **1** in enantiomerically pure form. Each route is characterized by apparent advantages and limitations, and exploits differing strategies for achieving enantioenrichment. A preliminary evaluation of these four routes was conducted in terms of safety, cost, ease of intermediate isolation, availability of starting material, and overall yield, with the final route, employing a classical resolution, being selected for further optimization. The implementation of this route on a kilogram scale is currently under investigation in our laboratories and will be reported in due course.

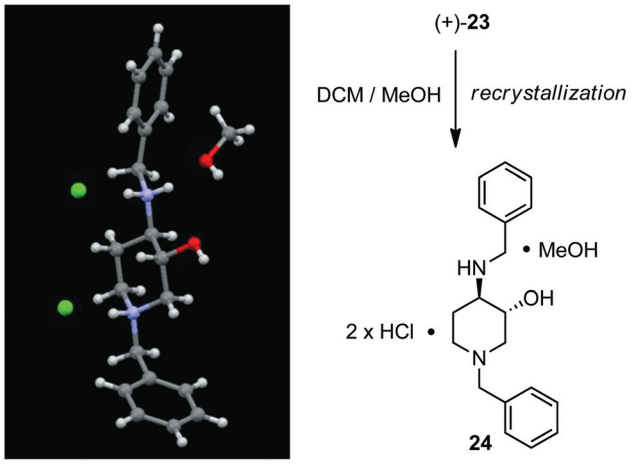


Fig. 3 X-ray derived ORTEP of bis-HCl salt **24**.

Acknowledgements

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Notes and references

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10 The conversion of **19** to **1** has been established both in this article (see Scheme 5) and previously in the literature (ref. 11*b*).
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14 See ESI† for a condensed list of the microbes examined.
15 The absolute stereochemistry of (+)-**19** was determined by its conversion to (+)-**1** (LiCl, $BnNH_2$) and then comparison of both chiral HPLC and optical rotation data to that of the known compound. See ESI.†.
16 A high throughput crystallization screen of epoxide (±)-**19** yielded ≤30% ee.
17 Bis-HCl salt **24** (MeOH co-solvate) was serendipitously prepared from (+)-**23** while attempting its recrystallization (from MeOH–CH_2Cl_2) to generate crystals appropriate for single crystal X-ray analysis.