



An efficient stereoselective and stereodivergent synthesis of (2*R*,3*R*)- and (2*R*,3*S*)-3-hydroxypipelicolic acids

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Abstract

Asymmetric syntheses of (2*R*,3*R*) and (2*R*,3*S*)-3-hydroxypipelicolic acids are reported featuring a key diastereoselective addition of Büchi's Grignard reagent to the chiral serinal L-5. Based on conformational analysis, a stereocontrolled reduction of piperidin-3-one (15) to *cis* 2,3-disubstituted piperidine (16) is also described. © 2000 Elsevier Science Ltd. All rights reserved.

Chiral, non-racemic piperidines are common structural units found in many biologically and medicinally important natural and non-natural products. It is thus not surprising that many new asymmetric synthetic methods have been developed.¹ Among them, chiral auxiliary based approaches developed by the groups of Husson,² Meyers,³ and Comins,⁴ respectively, are notable examples. Interestingly, the synthesis of 3-hydroxy-piperidine derivatives,⁵ such as, 3-hydroxypipelicolic acid (1 and 2),⁶ (+)-prosopphylline (3),⁷ Febrifugine (4)⁸ etc. (Fig. 1) are less developed and their asymmetric syntheses have been accomplished only very recently. Our group⁹ and Pedrosa et al.¹⁰ have recently synthesized a new serinal: L-(*N,N*-dibenzylamino)serine (TBDMS) aldehyde (5). The predictable and high diastereofacial selectivity of nucleophilic addition to the aldehyde function constitutes the main advantage of this synthon.¹¹ As part of a program directed at synthesizing alkaloids using the enantiopure L-5 and D-5 as chiral building blocks, we report in this letter an efficient synthesis of both (2*R*,3*R*) and (2*R*,3*S*)-3-hydroxypipelicolic acids (1 and 2) from L-5.

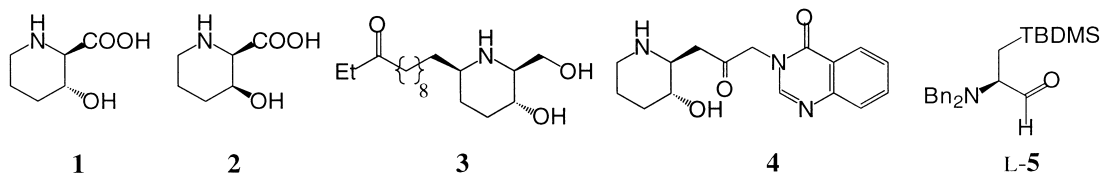
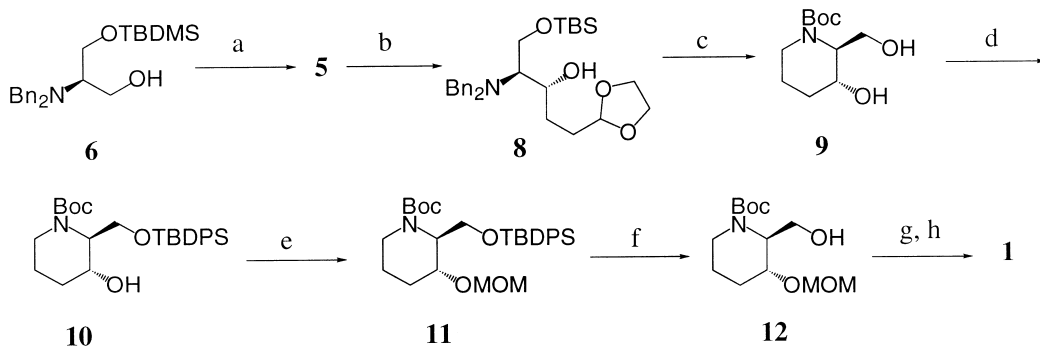


Figure 1.

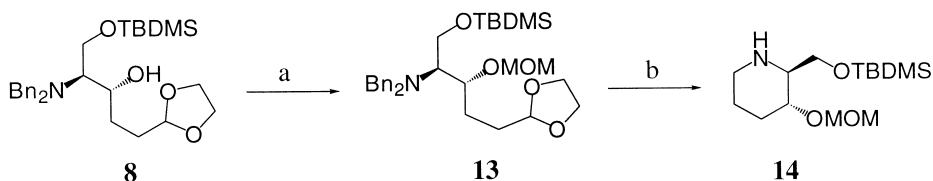
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Swern oxidation of serinol L-6 gave the aldehyde L-5 which, without purification, was reacted with Büchi's Grignard reagent¹² to give the amino diol **8** in excellent yield and diastereoselectivity (*anti:syn* = 15:1). The major stereomer was assumed to be *anti* according to Felkin–Anh model¹³ and this is corroborated by the obtention of final compound. Catalytic hydrogenation (3N HCl, ^tBuOH–THF, Pd/C, H₂) followed by *N*-protection as *tert*-butoxycarbamate gave piperidine **9** in 80% overall yield. A series of four reactions, namely, hydrogenolysis of the *N*-benzyl function, hydrolysis of the acetal, imine formation and reduction of the imine took place under these hydrogenolysis conditions. It was found that the reaction consistently gave high yields of the desired compound **9** when the hydrogenation was carried out in a mixture of ^tBuOH–THF instead of MeOH. Selective oxidation of the primary alcohol under various conditions¹⁴ failed to give the desired β-hydroxy carbonyl compound. Consequently, a straightforward three-step sequence was applied to convert the diol into the primary alcohol **12**. Jones' oxidation of **12** followed by simultaneous removal of MOM ether and *N*-Boc functions under acidic conditions gave then (2*R*,3*R*)-3-hydroxypipercolic acid (**1**)¹⁵ whose physical and spectroscopic data are in full agreement with those reported in the literature (Scheme 1).

Alternatively, the secondary hydroxyl group of compound **8** was protected as its MOM ether immediately after its formation to give the fully protected amino diol **13**. Hydrogenolysis of **13** in MeOH (3N HCl, 10% Pd/C) gave directly the piperidine **14** as its hydrochloride salt in 50% yield (Scheme 2). Partial deprotection of TBDMS and MOM ethers under these acidic conditions were nevertheless unavoidable.

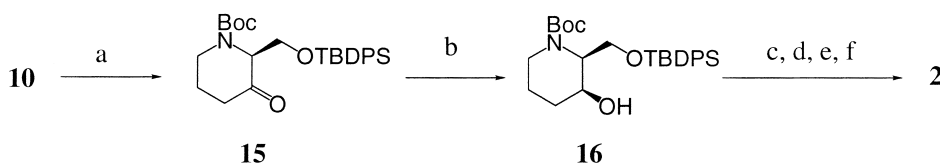


Scheme 1. Reagents and conditions: (a) (COCl)₂, DMSO, CH₂Cl₂, –78°C, then Et₃N; (b) 2-(2-bromomethyl)-1,3-dioxolane (**7**), Mg, THF, 86% then **5**; (c) (i) H₂, 10% Pd/C, 3N HCl, THF:^tBuOH (1:1); (ii) Boc₂O, H₂O, dioxane, 1N NaOH, 80%; (d) TBDPSCl, DMF, imidazole; (e) MOMCl, Hunig's base, CH₂Cl₂, reflux, 90%; (f) HF (48%), pyridine, THF, 85%; (g) CrO₃/H₂SO₄, 2.67 M, acetone, 0°C; (h) 6N HCl, 80°C, 2 h, 75%



Scheme 2. Reagents and conditions: (a) MOMCl, Hunig's base, CH₂Cl₂, rt, 90%; (b) Pd/C, MeOH, 3N HCl, 50%

Analysis of ^1H NMR spectrum of piperidine **9** indicated that it adopted in solution a *trans* diaxial conformation exclusively as evidenced by the coupling constant ($J_{\text{H}2-\text{H}3} = 1.5$ Hz). Computational studies (Macromodel, version 5.5, force field MM2) also showed that the *trans* diaxial conformer was more stable than the *trans* diequatorial one. Such a conformational preference is understandable assuming the partial double bond character of the C–N carbamate bond which causes the A^{1,3} strain in the *trans* diequatorial conformation.¹⁶ This conformational analysis led us to develop a synthesis of (2*R*,3*S*)-3-hydroxypipercolic acid based on the assumption that reduction of ketone **15** might be highly stereoselective to give *cis* 2,3-disubstituted piperidine **16**. Indeed, reduction of ketone **15** with sodium borohydride afforded a single diastereomer whose ^1H and ^{13}C spectra are in accord with the assigned configuration and are different from that of **10**. Following the same route described for the synthesis of **1**, compound **16** was converted to (2*R*,3*S*)-3-hydroxypipercolic acid (**2**) in 52% overall yield (Scheme 3).



Scheme 3. Reagents and conditions: (a) $(\text{COCl})_2$, DMSO, CH_2Cl_2 , -78°C , then Et_3N , 96%; (b) NaBH_4 , MeOH, 0°C , 88%; (c) MOMCl, Hunig's base, CH_2Cl_2 , reflux, 89%; (d) HF (48%), pyridine, THF, 75%; (e) $\text{CrO}_3/\text{H}_2\text{SO}_4$, 2.67 M, acetone, 0°C ; (f) 6N HCl, 80°C , 2 h, 78%

The high diastereoselectivity observed in the reduction of **15** can be rationalized on the basis of Felkin's torsional strain model which disfavors the equatorial attack of hydride.^{13,17} The presence of the *N*-Boc function in the six-membered ring should flatten the molecule and decrease the 1,3-diaxial steric interactions, further increasing the axial selectivity (Fig. 2).

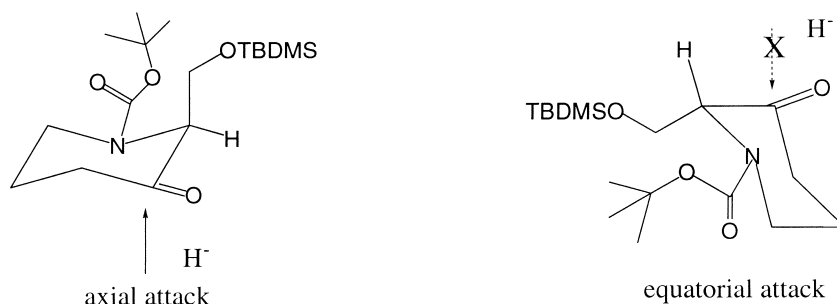


Figure 2.

In summary, we have described a highly stereoselective and stereodivergent synthesis of both the (2*R*,3*R*) and (2*R*,3*S*)-3-hydroxypipercolic acids from the common serinal (**L-5**) with 39 and 29% overall yield, respectively. Since its antipode **D-5** is easily available, the chemistry developed here can be applied to the synthesis of other two diastereomeric hydroxypipercolic acids.

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- Compound **1**: $[\alpha]_D^{25} = 14$ (*c* 0.4, 10% aqueous HCl), lit.⁶ $[\alpha]_D^{25} = 14$ (*c* 0.4, 10% aqueous HCl); mp 231°C; IR (KBr) ν 3404, 3051, 2983, 1742 cm^{-1} ; ¹H NMR (D₂O, 200 MHz) δ 1.61 (m, 2H), 1.91 (m, 2H), 2.98 (ddd, *J* = 10.4, 8.7, 3.5 Hz, 1H), 3.27 (m, 1H), 3.52 (d, *J* = 7.0 Hz, 1H), 4.06 (ddd, *J* = 10.4, 7.2, 3.2 Hz, 1H); ¹³C NMR (D₂O, 50.3 MHz) δ 20.1, 29.9, 44.1, 62.8, 67.6, 173.6; MS (CI) *m/z* 146 [M+]⁺.
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