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An alternative stereoselective synthesis of *trans*-(2*R*,3*R*)-3-hydroxypipecolic acid

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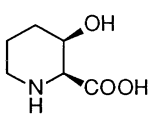
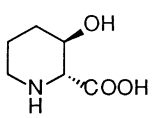
Abstract—The enantioselective synthesis of *trans*-(2*R*,3*R*)-3-hydroxypipecolic acid **1b** is presented, starting from *O*-protected methyl mandelate as chiral source. The synthesis involved a regioselective intramolecular nucleophilic substitution of an azido epoxide as the key step .

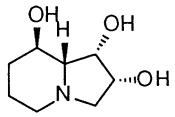
3-Hydroxypipecolic acid, a six-membered cyclic α-amino acid, is an interesting target molecule since it may be seen as a conformationally constrained serine derivative or a hydroxylated homoproline,[1] and may affect the physiological and pathological processes.[2] Moreover, this piperidine unit is found in a number of biologically important products. For example, the *cis*-isomer **1a** forms part of the structure of tetrazomine, an antitumor antibiotic,[3] while the *trans*-isomer **1b** is a precursor of (−)-swainsonine **2**, which has showed a potent and specific α-D-mannosidase inhibitory activity,[4] and it is also found in the structure of Febrifugine **3**, a potential anti-malarial agent.[5]



1a



1b



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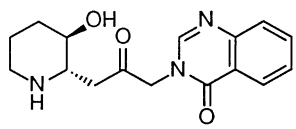

3

From a synthetical point of view, only few enantioselective synthesis of **1b** or its enantiomer have been reported.[1,3–6] In this paper, we describe a new route to *trans*-3-hydroxypipecolic acid **1b**.

Our synthesis started from the intermediate **4**, which has been prepared earlier in our laboratory[7] from *O*-protected methyl mandelate (two steps in 74% overall yield). In a first approach, **4** was hydrogenated using PtO_2 as a catalyst to give **5** (90% yield). The latter was then transformed into the selectively activated alcohol **6**. However, all attempts to cyclise **6** directly (with triphenylphosphine) or after reduction of the azide function failed. This was probably due to steric hindrance as indicated in Scheme 1.

In view of these results, we decided to modify slightly our strategy. For this purpose, compound **5** was treated in the following way (Scheme 2). The alcohol protections were removed by acidic treatment, and the triol thus obtained was transformed into the acetonide **7**. After activation of the remaining primary alcohol with methanesulfonyl chloride, the latter underwent nucleophilic displacement when submitted to an excess of sodium azide in dimethylformamide to give the azido compound **8**. Acid-promoted hydrolytic removal of the isopropylidene unit, followed by epoxidation under conditions described by Sharpless[8] gave the azido epoxide **9** in good yield.

The use of epoxide **9** was chosen because it eliminates the need for selective activation of only one hydroxyl group. As expected, when **9** was treated with triphenylphosphine in the presence of water,[9] we observed, after reduction of the azide function, an intramolecular nucleophilic displacement which took place at the benzylic position, to afford the disubstituted piperidine **10**.[10] However, the yield was rather low due probably to the formation of very polar by-prod-

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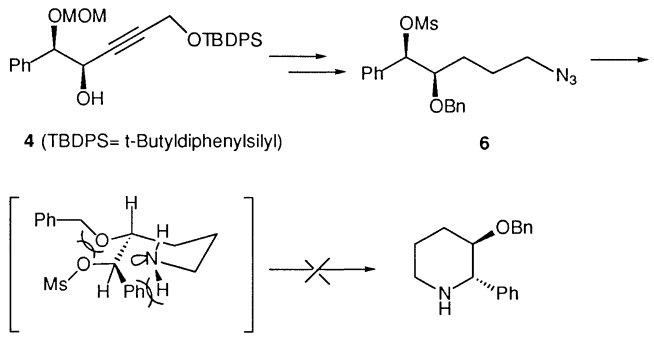
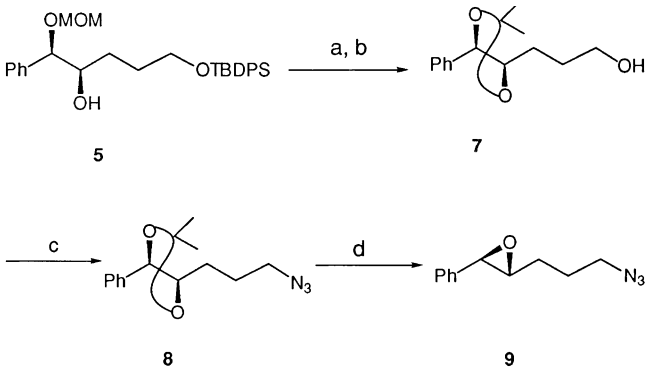


Scheme 1.



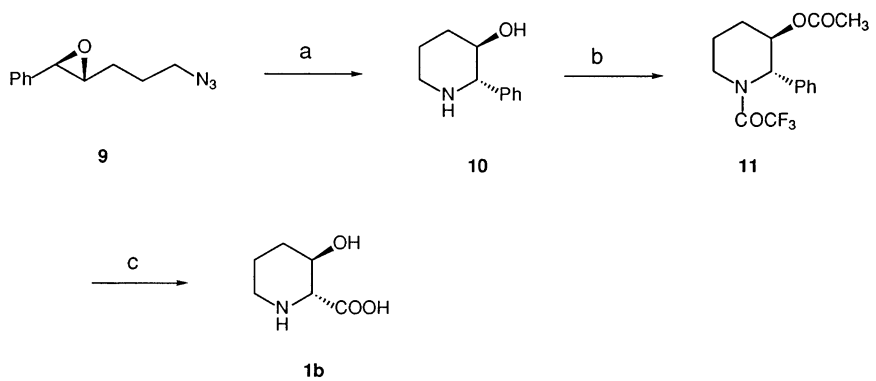
Scheme 2. (a) MeOH/HCl, rt, 90%; (b) $CuSO_4$, acetone, PPTS, 92%; (c) MsCl, NEt_3, DMAP; then NaN_3, DMF, 60°C, 82%; (d) THF/10% HCl (2/1), reflux (12 h); then $MeC(OMe)_3$, Me_3SiCl (CH_2Cl_2/0°C) and K_2CO_3, MeOH, 76%.

ucts resulting from the opening of the epoxide by triphenyl phosphine, and attempts to increase it by modifying the experimental conditions (amount of triphenylphosphine or water, the use of $LiClO_4$ as catalyst[11]) were unsuccessful. The next steps for the transformation of **10** into **1b** were accomplished in the following way:[12] complete protection by treatment with trifluoroacetic anhydride, selective deprotection of the hydroxyl group with K_2CO_3 in THF, and protection as the acetate, yielding **11** (Scheme 3). Oxidation and deprotection finally gave the target compound **1b,**[13] with spectral data identical to those already described.

In conclusion, we have developed a new practical access to *trans*-3-hydroxypipecolic acid. The latter is obtained with a high stereoselectivity, starting from methyl (*R*)-(−)-mandelate, a commercially available material.

References

1. Battistini, L.; Zanardi, F.; Rassu, G.; Spanu, P.; Pelosi, G.; Fava, G. G.; Ferrari, M. B.; Casiraghi, G. *Tetrahedron: Asymmetry* **1997**, *17*, 2975–2987.
2. Sugisaki, C. H.; Carroll, P. J.; Correia, C. R. D. *Tetrahedron Lett*. **1998**, *39*, 3413–3416.
3. Scott, J. D.; Tippie, T. N.; Williams, R. M. *Tetrahedron Lett*. **1998**, *39*, 3659–3662.
4. Ferreira, F.; Greck, C.; Genêt, J. P. *Bull. Soc. Chim. Fr*. **1997**, *134*, 615–621.
5. Jourdant, A.; Zhu, J. *Tetrahedron Lett*. **2000**, *41*, 7033–7036 references cited therein.
6. (a) Horikawa, M.; Busch-Petersen, J.; Corey, E. J. *Tetrahedron Lett*. **1999**, *40*, 3843–3846; (b) Agami, C.; Couty, F.; Mathieu, H. *Tetrahedron Lett*. **1996**, *37*, 4001–4002.
7. Haddad, M.; Imogai, H.; Larchevêque, M. *J. Org. Chem*. **1998**, *63*, 5680–5683.
8. Kolb, H. C.; Sharpless, B. *Tetrahedron* **1992**, *48*, 10515–10530.
9. Knouzi, N.; Vaultier, M.; Carrié, R. *Bull. Soc. Chim. Fr*. **1985**, *5*, 815–819.
10. (2*S*,3*R*)-2-Phenylpiperidin-3-ol **10**: $[\alpha]_D^{22}=-23$ (*c* 1.5, MeOH); mp 143–144°C dec. ^1H NMR (400 MHz, $CDCl_3$): δ 1.35–1.50 (1H, m), 1.65–1.85 (2H, m), 2.08–2.18 (1H, m), 2.2–2.4 (2H, m), 2.66 (1H, dt, $J=3.6$ and 11.5 Hz), 2.97–3.07 (1H, m), 3.34 (1H, d, $J=9$ Hz), 3.6 (1H, ddd, $J=4.4$, 9 and 10.6 Hz), 7.15–7.45 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.9, 33.0, 46.5, 69.0,



Scheme 3. (a) $P(Ph)_3$ (1.5 equiv.), H_2O (2 equiv.), THF, 48 h, 38%; (b) 1. $(CF_3CO)_2O$, NEt_3; 2. K_2CO_3 (2 equiv.), THF; 3. $(CH_3CO)_2O$, NEt_3, 80%; (c) 1. $RuCl_3{\cdot}H_2O$, $NaIO_4$; 2. K_2CO_3, MeOH, 60%.

72.3, 128.1, 128.7, 140.6; MS (CI, NH_3) m/z 178 (MH^+, 100%).
11. Chini, M.; Crotti, P.; Flippin, L. A.; Macchia, F. *J. Org. Chem.* **1991**, *56*, 7043–7048.
12. Haddad, M.; Larchevêque, M. *Tetrahedron: Asymmetry* **1999**, *10*, 4231–4237.
13. Spectral data for **1b**: $[\alpha]_D^{22}=-13$ (*c* 0.45, 10% HCl), lit.[4] $[\alpha]_D^{22}=-14$ (*c* 0.4, 10% HCl); mp 232°C dec. ^1H NMR (400 MHz, D_2O): δ 1.54 (2H, m), 1.81 (2H, m), 2.93 (1H, m), 3.18 (1H, m), 3.45 (1H, d, $J=7$ Hz), 3.98 (1H, m). ^{13}C NMR (50 MHz, D_2O): δ 18.3, 28.1, 42.4, 61.9, 65.9, 172.0; MS (CI, NH_3) m/z 146 (MH^+).