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A regioselective reductive cleavage of benzylidene acetal: stereoselective synthesis of *N*-Boc-protected *cis*-(2*R*,3*S*)-3-hydroxy pipecolic acid

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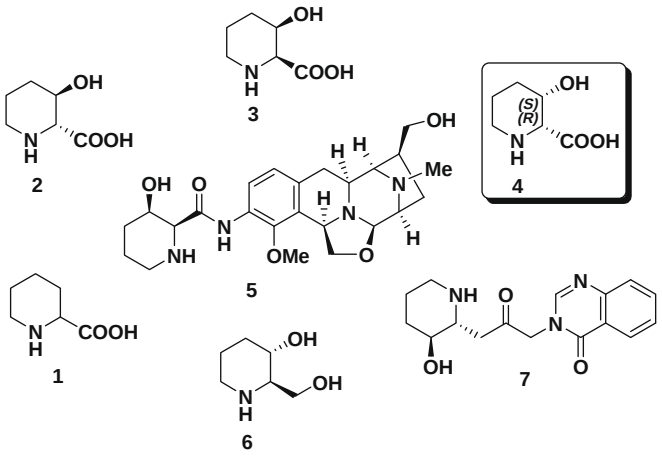
ABSTRACT

A stereoselective synthesis of *N*-Boc-protected *cis*-(2*R*,3*S*)-3-hydroxy pipecolic acid, starting from D-glucose is described. The key step in the overall synthesis is a highly regioselective reductive cleavage of benzylidene acetal **13** leading to hydroxymethyl piperidine derivative **14**.

Functionalized piperidines are important class of compounds present in various natural products, pharmaceuticals, and synthetic intermediates.[1] In particular, hydroxylated piperidine alkaloids, frequently found in living organisms, display wide spectrum of biological activities by mimicking carbohydrate substrates in a variety of enzymatic processes.[2] Selective inhibition of a number of enzymes involved in the binding and processing of glycoproteins has rendered piperidine alkaloids as important tools in the study of biochemical pathways.[3] Pipecolic acid **1**, a widespread natural non-proteinogenic amino acid, is an important subunit present in several bioactive molecules such as immunosuppressant FK506,[4] anticancer agent VX710,[5] oxytocin antagonist L-365209,[6] antifungal antibiotic demethoxyrapamycin,[7] and antitumor antibiotic sandramycin.[8] In recent years stereoisomeric 3-hydroxypipecolic acids (**2–4**) have gained considerable attention due to their wide spectrum of biological activities and also as important intermediates in the preparation of several pharmaceutically important molecules. For example, cis-isomer **3** is an important constituent of a naturally occurring antitumor antibiotic tetrazomine **5**,[9] whereas the *trans*-isomer **2** is a valuable precursor in the synthesis of potent α-D-mannosidase inhibitor (−)-swainsonine.[10] 3-Hydroxy pipecolic acid has also been extensively studied by incorporating its structural motif in the design and synthesis of novel molecules with diverse biological activities such as immunosuppressants,[11] enzyme inhibitors,[12] NMDA antagonists,[13] antitumor,[14] and anti-HIV agents.[15] Moreover, the conformationally constrained core of the 3-hydroxy pipecolic acid has been exploited in ligand-binding studies involving biologically significant peptides and peptidomimetics.[16] In addition, the hydroxymethyl analogue, 4-deoxy fagomine (**6**) is the key constituent in (+)-febrifugine (**7**), a potent antimalarial agent and also an important intermediate in the synthesis of biologically active molecules such as κ-opioid receptor agonist and GABA receptor binders.[17]



As a consequence of its biological significance, stereoisomeric 3-hydroxy pipecolic acid has become an important target for many synthetic organic chemists and several synthetic strategies have been reported in the literature.[18] Surprisingly, among the four possible stereoisomers of 3-hydroxypipecolic acid, the synthesis of cis-(2*R*,3*S*)-enantiomer **4** is the least documented.[19] The potential application of hydroxy pipecolic acids coupled with our continued interest on the regioselective cleavage of benzylidene acetals to highly functionalized chiral intermediates has inspired us to develop a new strategy for the synthesis of this class of molecules.[20] In this Letter, we report a stereoselective synthesis of *cis*-(2*R*,3*S*)-3-hydroxy pipecolic acid (**4**) starting from D-glucose through regioselective reductive cleavage of benzylidene acetal.

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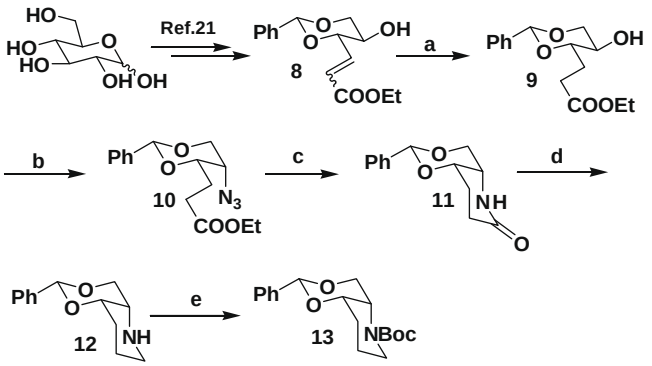


Scheme 1. Synthesis of benzylidene acetal **13**. Reagents and reactions conditions: (a) H_2, Pd/C, EtOH, rt, 1 h, 95%; (b) DPPA, DEAD, Ph_3P, THF, 71%; (c) H_2, Pd/C, EtOH, rt, 95%; (d) $LiAlH_4$, dry ether, rt, 3 h, 88%; (e) Boc_2O, CH_3CN, rt, 6 h, 88%.

The key intermediate benzylidene acetal **13**, required for the regioselective reductive cleavage study, was prepared from D-glucose as shown in Scheme 1. Following the literature procedure, D-glucose was readily converted to the corresponding olefin ester **8** in a few steps.[21] Catalytic hydrogenation of compound **8** over Pd/C followed by azidation of the corresponding hydroxy ester **9** under Mitsunobu reaction conditions provided the azido derivative **10** in 71% yield. Azido ester **10** on catalytic hydrogenation over Pd/C and in situ cyclization furnished the lactam **11** in good yield. Reduction of amide **11** with $LiAlH_4$ followed by *N*-Boc protection of the resultant amine **12** with $(Boc)_2O$ gave the corresponding *N*-Boc-protected benzylidene acetal **13** in good yield.

The crucial regioselective reductive cleavage of benzylidene acetal **13** was studied with different Lewis and Brønsted acid catalysts and the results are summarized in Table 1.[22] Among the catalysts screened, $EtAlCl_2$ in combination with Et_3SiH was found to be the most efficient reagent system to bring about this transformation to give the requisite hydroxymethyl-piperidine derivative **14** in excellent yield with high degree of regioselectivity.[23] Interestingly, the acid labile *N*-Boc-protecting group was found to be very stable under the reaction conditions.[20b] Among the solvents screened, DCM was found to be the most effective medium to realize the regioselective reductive cleavage of benzylidene acetal **13** leading to **14** in excellent yield. Intriguingly in all the cases studied, regardless of the nature of the catalyst, the reductive cleavage resulted in the formation of hydroxymethyl derivative **14** as the only regioisomeric product (Scheme 2).

A plausible mechanism for the regioselective reductive cleavage of benzylidene acetal is shown in Scheme 3, which can be rationalized on the basis of sterics. It is anticipated that the catalyst would preferentially coordinate with oxygen atom 'a' of the benzylidene acetal instead of oxygen atom 'b' due to sterics. This would favor the cleavage of carbon-oxygen 'a' bond leading to oxonium ion intermediate (**13b**), which on further reduction in the presence of Et_3SiH would furnish hydroxymethyl-piperidine derivative **14**.

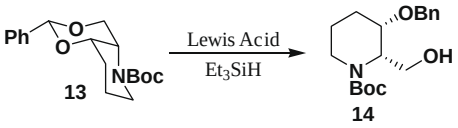
Moreover, the regioselectivity of the benzyl ether **14** was further unambiguously confirmed by single crystal X-ray analysis of the corresponding carbamate **15** (Fig. 1),[24] which was readily prepared by the reaction of alcohol **14** with sodium hydride in dry THF (Scheme 4).

The oxidation of alcohol **14** to the corresponding acid **16** was achieved in good yield using $RuCl_3$–$NaIO_4$ reagent system (Scheme 5).[25] Finally, the benzyl ether **16** on catalytic hydrogenation with $Pd(OH)_2$ furnished the corresponding *N*-Boc-protected *cis*-(2*R*,3*S*)-3-hydroxy pipecolic acid **17** in 70% yield. The spectral data of compound **17** were found to be comparable with the literature values except the sign of rotation.[18a]

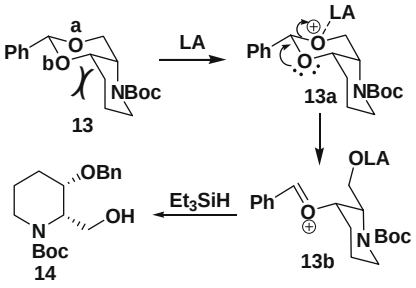
Table 1
Regioselective reductive cleavage of the benzylidene acetal **13** to the corresponding alcohol **14**

S.No.	Acid	Temp. (°C)	Time (h)	Conversion (%)	Yield[a] (%)
1	$EtAlCl_2$	−78	1	86	99
2	$BF_3.OEt$	−78	1.5	66	58
3	$TiCl_4$	−78	2	84	57
4	$InCl_3$	0–rt	1.5	52	46
5	DIBAL-H	0–rt	3	76	32[b]
6	CF_3COOH	−78	2.5	80	50
7	Triflic acid	−78	1	76	47

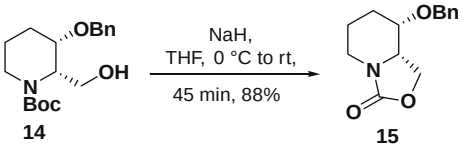
[a] Refers to pure isolated product based on recovered starting material.
[b] Reaction was carried out in the absence of Et_3SiH.



Scheme 2. Regioselective reductive cleavage of benzylidene acetal **13**.



Scheme 3. A plausible mechanism for the regioselective reductive cleavage of benzylidene acetal **13**.



Scheme 4. Synthesis of cyclic carbamate **15**.

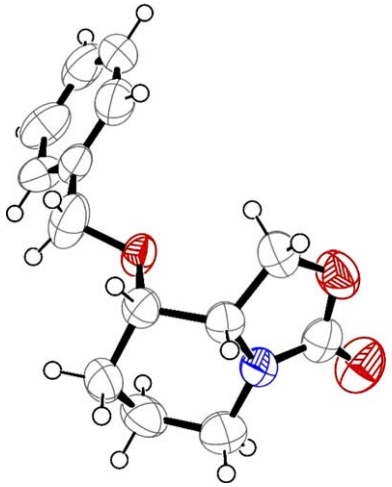
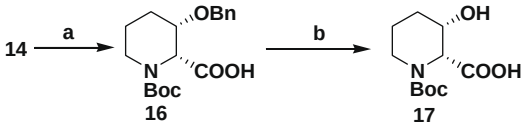


Figure 1. ORTEP diagram of cyclic carbamate **15**.



Scheme 5. Synthesis of *N*-Boc-protected *cis*-(2*R*,3*S*)-3-hydroxy pipecolic acid **17**. Reagents and conditions: (a) $RuCl_3$, $NaIO_4$, CH_3CN:CCl_4:H_2O, rt, 64%; (b) H_2, $Pd(OH)_2$, EtOH, rt, 48 h, 70%.

In conclusion, a simple and reliable method has been developed for the synthesis of *N*-Boc-protected *cis*-(2*R*,3*S*)-3-hydroxy pipecolic acid starting from D-glucose via regioselective reductive cleavage of benzylidene acetal.[26] We are confident that the functionalized chiral intermediate **14** will find wide application in the synthesis of piperidine alkaloids with diverse biological activities. The synthetic potential of the regioselective reductive cleavage of benzylidene acetal is being explored in our group.

Acknowledgments

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23. *Experimental procedure for the regioselective reductive cleavage of benzylidene acetal 13:* To a solution of compound **13** (200 mg, 0.62 mmol) at −78 °C in dry DCM (30 mL) was added Et_3SiH (120 μL, 0.75 mmol) followed by $EtAlCl_2$ (417 μL, 0.75 mmol) and the resultant mixture was stirred for additional 1 h. The reaction mixture was slowly warmed to 0 °C and then quenched with saturated $NaHCO_3$ solution. The reaction mixture was extracted with ethyl acetate and the combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product on purification by column chromatography over silica gel (gradient elution with 10–35% EtOAc in hexane) yielded the unreacted starting material (28 mg, 14%) and the pure alcohol **14** (171 mg, 85%) as a viscous liquid. $[\alpha]_D^{25}$ +66.7 (*c* 1, $CHCl_3$); IR (Neat): 3448, 2934, 1667, 1454, 1416, 1363, 1319, 1248, 1178, 1154, 1096, 1044, 979, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H), 4.58–4.55 (br s, 2H), 4.06–4.02 (m, 4H), 3.67–3.61 (m, 1H), 2.8 (br s, 1H), 2.2 (br s, 1H), 1.92 (br s, 1H), 1.72–1.70 (m, 2H), 1.60–1.56 (m, 2H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 138.0, 128.5, 128.3, 127.8, 127.5, 80.0, 76.0, 73.1, 70.8, 66.1, 58.7, 128.3, 25.8, 23.9; HRMS (ESI) calcd for $C_{18}H_{27}NO_4Na$ $(M+Na)^+$: 344.1838; found: 344.1844.
24. *X-ray crystallographic analysis for compound* **15**: $C_{14}H_{17}NO_3$, MW = 247.29, orthorhombic, $P2_12_12_1$, a = 8.8214(3), b = 10.9036(3), c = 13.3824(4) Å, V = 1287.19(7) Å^3, Z = 4, D_{calcd} = 1.276 Mg/m^3, $F(000)$ = 528, T = 298 K, colorless needles, 0.39 × 0.35 × 0.32 mm, 16,670 reflections collected (R_{int} = 0.0267), 3193 unique. All measurements were carried out on a Bruker axs (Kappa Apex2) equipped with graphite monochromatic Mo Ka radiation. Structure refinements by full-matrix least-squares methods on F^2. Programs: SHELXS and SHELXL [Bruker axs (Kappa Apex2)]. Crystallographic details have been deposited at the Cambridge Crystallographic Data Centre (deposition number CCDC 684130).
25. During the oxidation of alcohol **14** to acid **16** using $RuCl_3$–$NaIO_4$ reagent system, a small amount of 3-benzoyloxy pipecolic acid derivative was also isolated in 10–12% yield.
26. *Spectral data for selected compounds*: Compound **9**: $[\alpha]_D^{25}$ −23.4 (*c* 1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.48–7.45 (m, 2H), 7.38–7.33 (m, 3H), 5.47 (s, 1H), 4.27–4.26 (m, 1H), 4.12 (dd, *J* = 14.4, 7.2 Hz, 2H), 3.61–3.55 (m, 3H), 2.65–2.59 (m, 1H), 2.52–2.46 (m, 1H), 2.22–2.20 (m, 1H), 2.00–1.98 (m, 1H), 1.25 (t,

J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 136.5, 127.6, 126.9, 124.8, 99.7, 79.7, 69.8, 63.8, 59.4, 28.0, 25.1, 12.9; HRMS (ESI) calcd for $C_{15}H_{20}O_5Na$ $(M+Na)^+$: 303.1208; found: 303.1210. *Compound* **10**: $[\alpha]_D^{25}$ +42.4 (c 1, $CHCl_3$); IR (neat): 2965, 2103, 1727, 1403, 1179, 1085, 977, 754, 697, 659 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.41 (m, 2H), 7.31–7.28 (m, 3H), 5.51 (s, 1H), 4.45 (dd, J = 12.4, 1.2 Hz, 1H), 4.16 (dd, J = 12.4, 2 Hz, 1H), 4.07–4.02 (m, 3H), 2.8 (d, J = 1.6, 1H), 2.42 (t, J = 7.2, 2 Hz, 2H), 2.13–2.09, (m, 1H), 1.90–1.89 (m, 1H), 1.16 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 137.5, 129.2, 128.3, 126.3, 102.3, 78.6, 70.9, 60.5, 55.6, 29.6, 27.5, 14.2; HRMS (ESI) calcd for $C_{15}H_{19}N_3O_4Na$ $(M+Na)^+$: 328.1273; found: 328.1272. *Compound* **11**: $[\alpha]_D^{25}$ +64.8 (c 1, $CHCl_3$); IR (neat) 2933, 2855, 1720, 1454, 1396, 1105, 964, 750, 696, 496 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.46 (m, 2H), 7.34–7.33 (m, 3H), 7.06 (br s, 1H), 5.54 (s, 1H), 4.23 (s, 1H), 4.10 (d, J = 12.4 Hz, 1H), 4.02 (d, J = 12.4 Hz, 1H), 3.35 (s, 1H), 2.73–2.59 (m, 1H), 2.34–2.33 (m, 1H), 2.28–2.19 (m, 1H), 1.99–1.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 137.8, 129.5, 128.5, 126.4, 101.2, 70.2, 69.7, 49.7, 26.1, 26.0; HRMS (ESI) calcd for $C_{13}H_{16}NO_3$ $(M+H)^+$: 234.1130; found: 234.1132. *Compound* **12**: $[\alpha]_D^{25}$ +56.3 (c 1, $CHCl_3$); IR (neat): 2933, 2855, 1454, 1396, 1105, 964, 750, 696, 496 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.38 (m, 2H), 7.27–7.23 (m, 3H), 5.41 (s,1H), 3.9 (dd, J = 24.8, 11.6 Hz, 2H), 3.85 (s, 1H), 3.08 (d, J = 13.4 Hz, 1H), 2.58 (t, J = 13.4 Hz, 1H), 2.44 (s, 1H), 2.02 (d, J = 12.7 Hz, 1H), 1.68–1.59 (m, 2H), 1.28–12.6 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 128.9, 128.2, 126.1, 101.4, 72.7, 72.2, 51.8, 45.9, 29.9, 20.9; HRMS (ESI) calcd for $C_{13}H_{18}NO_2$ $(M+H)^+$: 220.1338; found: 220.1333. *Compound* **13**: $[\alpha]_D^{25}$ +141.7 (c 1, $CHCl_3$); IR (neat): 2933, 2855, 1659, 1446, 1110, 970, 750, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.47 (m, 2H), 7.39–7.34 (m, 3H), 5.52 (s, 1H), 4.44 (d, J = 12.4 Hz, 1H), 4.27 (dd, J = 6.4, 3.6 Hz, 1H), 4.04–4.0 (m, 1H), 3.98 (dd, J = 12.4, 2.4 Hz, 1H), 3.64 (ddd, J = 18, 12, 6 Hz, 1H), 3.52 (s, 1H), 2.06–2.05 (m, 1H), 1.81–1.73 (m, 2H), 1.69–1.61 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 138.4, 129.1, 128.4, 126.2, 101.2, 79.7, 72.1, 71.3, 49.3, 38.26, 28.5, 24.2, 18.7: HRMS (ESI) calcd for $C_{18}H_{25}NO_4Na$ $(M+Na)^+$: 342.1681; found: 342.1691. *Compound* **15**: $[\alpha]_D^{25}$ +63.7 (c 1, $CHCl_3$), IR (neat): 2944, 2861, 1735, 1449, 1420, 1237, 1196, 1095, 1028, 976, 740, 635 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.19 (m, 5H), 4.62 (d, J = 12 Hz, 1H), 4.30 (d, J = 12.2 Hz, 1H), 4.20 (d, J = 5.2 Hz, 1H), 4.14 (d, J = 8.4 Hz, 1H), 3.88 (m, 1H), 3.68 (m, 1H), 3.39 (br s, 1H), 2.89 (m, 1H) 1.89 (m, 1H), 1.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 137.6, 128.5, 127.8, 127.4, 70.3, 70.1, 63.3, 57.5, 40.9, 25.2, 17.9; HRMS (ESI) calcd for $C_{14}H_{17}NO_3Na$ $(M+Na)^+$: 270.1106; found: 270.1112. *Compound* **16**: $[\alpha]_D^{25}$ +13.9 (c = 0.6, $CHCl_3$); IR (neat): 2955, 1736, 1636, 1544, 1439, 1226 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.19 (m, 5H), 5.15 (br s, 1H), 4.69–4.66 (m, 2H), 3.67–3.59 (m, 2H), 2.85 (m, 1H), 2.30–1.97 (m, 2H), 1.88–1.76 (m, 2H), 1.38 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 135.9, 128.9, 128.7, 128.0, 80.8, 75.5, 71.9, 55.6, 40.7, 28.3, 27.4, 23.5; HRMS (ESI) calcd for $C_{18}H_{25}NO_5Na$ $(M+Na)^+$: 358.1630; found: 358.1620.