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Asymmetric synthesis of (2*S*,4*R*)-4-hydroxypipecolic acid

Clinton A. Brooks and Daniel L. Comins *

Department of Chemistry, North Carolina State University, Raleigh, NC 27695-8204, USA

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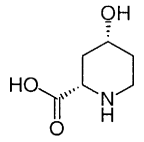
Abstract

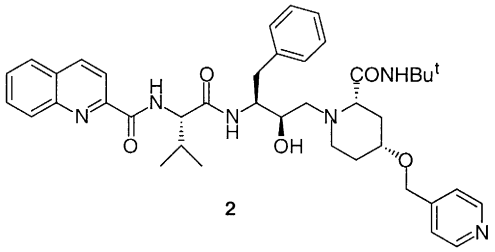
An asymmetric synthesis of (2*S*,4*R*)-4-hydroxypipecolic acid was accomplished in eight steps and 31% overall yield.

Keywords: asymmetric synthesis; pyridinium salts; dihydropyridones; amino acids.

Pipecolic acid derivatives are useful synthetic intermediates for the preparation of medicinally important compounds such as peptides,[1] immunosuppressants,[2] enzyme inhibitors[3,4] or NMDA antagonists.[5] The naturally occurring (2*S*,4*R*)-4-hydroxypipecolic acid (**1**) is found as a constituent of certain cyclopeptide antibiotics[6] and has been used as a building block in a synthesis of palinavir (**2**), a potent HIV protease inhibitor.[7] Several racemic and a few enantioselective preparations of **1** have been reported.[8] Syntheses of enantiopure (2*S*,4*R*)-**1** have been carried out by resolution or by using starting materials from the chiral pool. Herein we report the first chiral auxiliary mediated asymmetric synthesis of **1**.



1



2

Addition of vinylmagnesium bromide to chiral 1-acylpyridinium salt **3**, formed in situ from 4-methoxy-3-(triisopropylsilyl)pyridine[9] and the chloroformate of (−)-TCC,[10] provided the crude dihydropyridone **4** in high yield and 85% de (Scheme 1). Recrystallization of the crude product from methanol, and purification of the concentrated mother liquor by radial PLC (SiO_2, EtOAc/hexanes), gave a 78% yield of diastereomerically pure **4** as a white solid, mp 133–134°C. Reaction with sodium methoxide followed by aqueous acid provided dihydropyridone **5** in 89% yield with 94% recovery of the chiral auxiliary, (−)-TCC. *N*-Acylation of **5** with *n*-BuLi and benzyl chloroformate gave a near quantitative

* Corresponding author.

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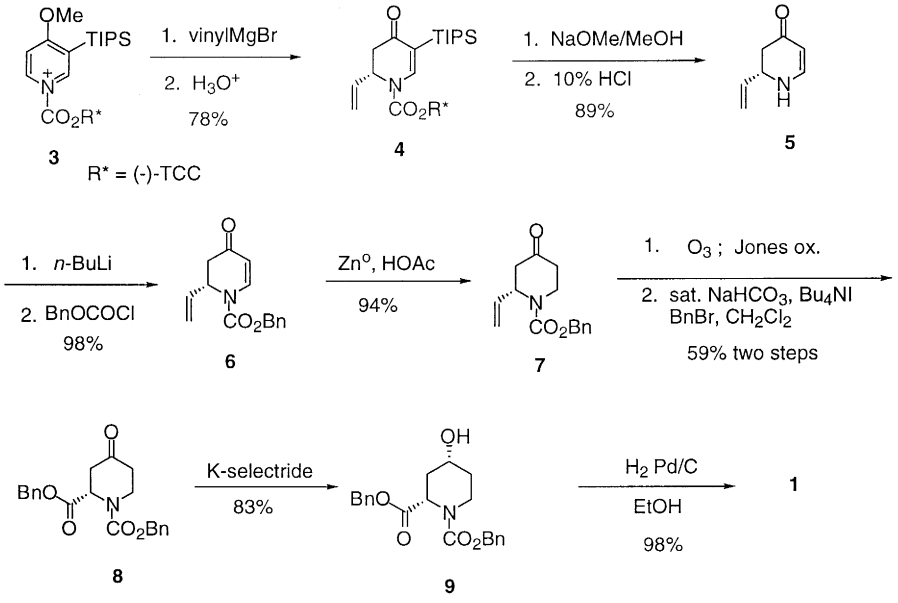
yield of enantiopure carbamate **6**. Although conjugate reduction of dihydropyridone **6** could be carried out with L-Selectride,[11] the use of zinc and acetic acid was found to be more convenient and provided the piperidone **7** $[\alpha]_D^{25}$ −30.8 (*c* 1.67, $CHCl_3$), in higher yield. Oxidative cleavage of the vinyl group with ozone and subsequent esterification of the crude acid gave ester **8** $[\alpha]_D^{23}$ −17.9 (*c* 0.24, $CHCl_3$), in 59% yield for the two steps. Stereoselective reduction of the C-4 keto group with K-Selectride afforded the piperidinol **9**[12] $[\alpha]_D^{23}$ +81 (*c* 0.105, $CHCl_3$). Catalytic hydrogenation of **9** gave the desired (2*S*,4*R*)-4-hydroxypipecolic acid (**1**) in 98% yield as a white solid. An analytically pure sample was obtained by recrystallization from hot methanol: mp 273–274°C [lit.[8] mp 273–275°C], $[\alpha]_D^{23}$ −20.7 (*c* 0.30, H_2O) [lit.[8] $[\alpha]_D^{25}$ −21.0 (*c* 1.03, H_2O)]. The spectral properties of our (−)-**1** are in agreement with reported data. The naturally occurring **1** was constructed enantioselectivity in eight steps and 31% overall yield.[13,14] The general approach should be amenable to the preparation of other substituted pipecolic acids as either antipode.



Scheme 1.

Acknowledgements

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13. The structure assigned to each new compound is in accord with its IR and ^{1}H and ^{13}C NMR spectra and elemental analysis or high-resolution mass spectra.
14. NMR data: Compound **6**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J*=8.2, 1H), 7.38 (m, 5H), 5.79 (m, 1H), 5.36–5.06 (m, 6H), 2.89 (dd, *J*=16.4 and 6.8 Hz, 1H), 2.53 (d, *J*=16.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.2, 152.5, 141.5, 135.0, 132.8, 128.8, 128.4, 117.5, 107.6, 69.2, 54.8, 39.9. Compound **7**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.77 (m, 1H), 5.19 (m, 5H), 4.21 (m, 1H), 3.38 (m, 1H), 2.78–2.26 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 155.3, 136.4, 136.1, 128.6, 128.3, 128.0, 117.9, 67.7, 53.4, 43.4, 40.4, 39.2. Compound **8**, ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.15 (m, 10H), 5.30–4.90 (m, 5H), 4.12 (m, 1H), 3.68 (m, 1H), 3.00–2.65 (m, 2H), 2.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.2, 170.8, 155.8, 136.2, 135.2, 128.9, 128.8, 128.5, 128.4, 128.2, 68.2, 67.7, 54.8, 41.3, 40.5, 39.8.