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Synthetic studies on tetrazomine: lipase PS resolution of racemic *cis*-β-hydroxypipecolic acid

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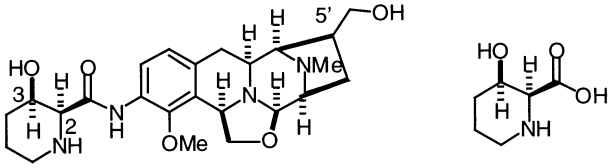
Abstract

An efficient enzymatic resolution of racemic *cis*-β-hydroxypipecolic acid is described affording both the (2*S*,3*R*) and (2*R*,3*S*) protected amino acids in good yield and high enantiomeric ratios.

Tetrazomine (**1**, Fig. 1) is an antitumor antibiotic that was isolated from *Saccharothrix mutabilis* and reported by the Yamanouchi Pharmaceutical Co. in Japan.[1] Preliminary antitumor/antimicrobial assays of this substance indicate that tetrazomine displays potent antitumor activity against P388 leukemia in vivo and displays good antimicrobial activity against both Gram-negative and Gram-positive organisms. Tetrazomine is structurally related to the quinocarcin and bioxalomycin classes of antitumor antibiotics, but is distinct from these agents by virtue of containing the unusual amino acid β-hydroxypipecolic acid. The absolute stereochemistry of the β-hydroxypipecolic acid stereoisomer present in tetrazomine has been determined in these laboratories to be (*2*S,3*R*), (–)-**2**.[2]



1 Tetrazomine (-)-**2**, (*2S, 3R*)

Figure 1.

As part of a program directed at tackling the total synthesis of tetrazomine, we required a practical synthesis of (–)-**2**. The previous synthesis[3] of (–)-**2** was accomplished recently by Corey

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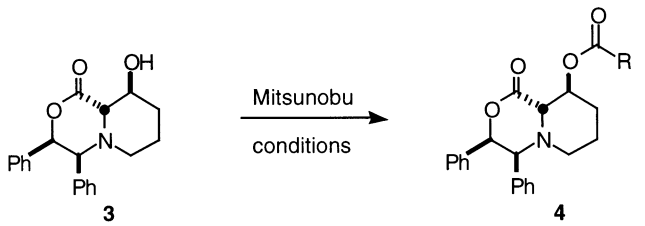
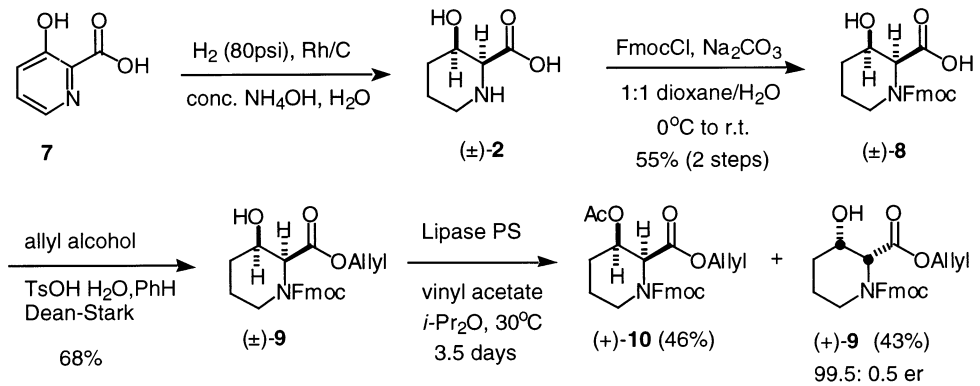
et al. This synthesis entailed an aldol condensation using an ammonium salt catalyst, yielding a 1:1 mixture of *syn*/*anti* aldol products. Initially, we attempted a Mitsunobu[4] inversion of the secondary alcohol of previously reported **3**[2] (Scheme 1). Unfortunately, under various conditions the only product that was obtained was acylation with retention of configuration (**4**). The mechanism of this acylation was not investigated and an alternative route was explored.



Scheme 1.

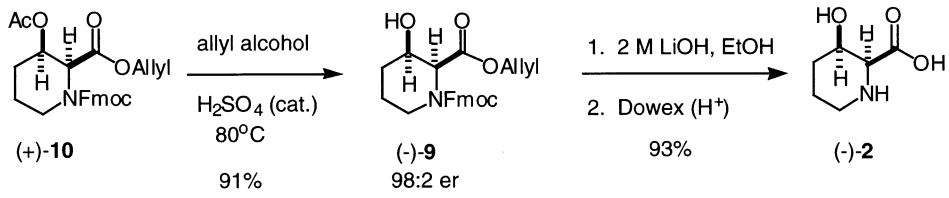
The literature revealed that the racemic *cis*-β-hydroxypipecolic acid [(±)-**2**] was available in one-step from picolinic acid (**7**) via reduction using Rh/C.[5] Since (±)-**2** is thus readily available, we endeavored to resolve the enantiomeric pair of amino acids. The use of Lipase PS has been reported by Toyooka et al.[6] for the resolution of a structurally related pipecolic acid derivative and this method was examined in the present context.

As shown in Scheme 2, picolinic acid was reduced as previously described[5] and the amine protected as the corresponding Fmoc derivative (±)-**8**[7] in 55% yield for the two steps. Esterification of the acid to the allyl ester afforded (±)-**9**[8] in 68% yield. Enzymatic resolution of this protected amino acid racemate[9] using Lipase PS (Amano) proceeded smoothly forming the acetate of the (2*S*,3*R*) isomer, providing (+)-**10**[10] in 46% yield. The (2*R*,3*S*) amino acid (+)-**9** was recovered in 43% yield and an enantiomeric ratio (er) of 99.5:0.5 was determined by chiral HPLC analysis.[11]



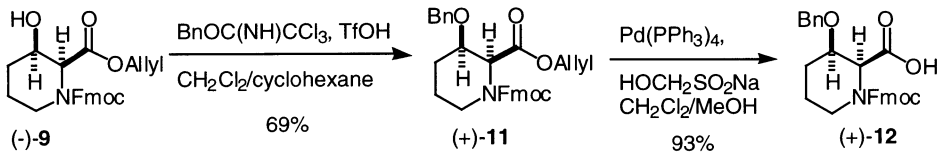
Scheme 2.

The acetate (+)-**10** was easily cleaved to form (−)-**9** in 91% yield (Scheme 3). The er of (−)-**9** was found to be 98:2 by chiral HPLC analysis.[11] To confirm the absolute stereochemistry, (−)-**9** was converted to the free amino acid (−)-**2** via treatment with lithium hydroxide. The optical rotation matched that of the literature value.[2] With these amino acids in hand, we next investigated the conversion of (−)-**9** to a suitably protected form that would be compatible with peptide coupling strategies.



Scheme 3.

The hydroxyl group on the amino acid (–)-**9** was protected as the benzyl ether using benzyl trichloroacetimidate and triflic acid[12] to afford (+)-**11**[13] in 69% yield (Scheme 4). Finally, the allyl ester was cleaved in 93% yield using palladium tetrakistriphenylphosphine and the sodium salt of hydroxymethanesulfinic acid[14] to afford the amino acid (+)-**12**.[15] This substance should be a useful protected form of (–)-**2** suitable for incorporation into peptides as well as synthetic strategies directed toward tetrazomine. This route to (–)-**2** compares favorably to the previous synthesis due to higher er (98:2 versus 91:9).



Scheme 4.

Acknowledgements

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7. (±)-**8**: ^{1}H NMR (300 MHz) (d_6-DMSO, 120°C) δ 1.35–1.80 (4H, m); 1.93 (1H, s); 3.07 (1H, ddd, J=12.9, 12.9, 3.3 Hz); 3.66 (1H, m); 3.76 (1H, m); 4.26 (1H, d, J=6.3 Hz); 4.37 (2H, d, J=5.7 Hz); 4.68 (1H, d, J=5.7 Hz); 7.32 (2H, t, J=7.5 Hz); 7.40 (2H, t, J=7.5 Hz); 7.63 (2H, t, J=7.5 Hz); 7.84 (2H, d, J=7.5 Hz). HRMS (FAB) calcd for $C_{21}H_{22}NO_5$ (MH^+) 368.1498; found 368.1502.
8. (±)-**9**. ^{1}H NMR (300 MHz) (d_6-DMSO, 120°C) δ 1.44 (1H, m); 1.71 (3H, m); 3.20 (1H, ddd, J=12.3, 12.3, 3.3 Hz); 3.78 (2H, m); 4.27 (1H, dd, J=6.0 Hz); 4.42 (2H, d, J=6.6 Hz); 4.54 (1H, s, broad); 4.62 (2H, m); 4.82 (1H, d, J=7.2 Hz); 5.21 (1H, dd, J=10.2, 1.2 Hz); 5.35 (1H, dd, J=17.1, 1.8 Hz); 5.91 (1H, m); 7.33 (2H, t, J=7.5 Hz); 7.41 (2H, t, J=7.5 Hz); 7.62 (2H, d, J=7.5 Hz); 7.84 (2H, d, J=7.5 Hz). HRMS (FAB) calcd for

$C_{24}H_{26}NO_5$ (MH^+) 408.1811; found 408.1820. (−)-**9**. $[\alpha]_D^{20} = -33.6$ ($c = 1.5$ CH_2Cl_2). (+)-**9**. $[\alpha]_D^{20} = +36.8$ ($c = 1.2$ CH_2Cl_2).

9. Procedure for lipase PS resolution: to a solution of (±)-**9** (380 mg, 0.93 mmol) in 20 mL iPr_2O at 30°C was added 1.52 g lipase PS. The reaction progress was monitored by HPLC until 50% completion (Waters novapak HR silica, isocratic 70/30 hexanes/EtOAc, 2 mL/min, UV 254 nm). When complete, the mixture was filtered through Celite and the solvent was removed in vacuo. The crude product was purified via flash chromatography (gradient 25–50% EtOAc/hex) to afford 191 mg (+)-**10** (43%) and 165 mg (+)-**9** (46%).
10. (+)-**10**: ^{1}H NMR (300 MHz) (d_6-DMSO, 120°C) δ 1.53 (1H, m); 1.78 (3H, m); 2.10 (3H, s); 3.22 (1H, ddd, $J = 12.9$, 12.9, 3.6 Hz); 3.82 (1H, dd, $J = 12.9$, 5.1 Hz); 4.27 (1H, t, $J = 6.3$ Hz); 4.42 (2H, d, $J = 6.6$ Hz); 4.63 (2H, m); 4.84 (1H, m); 5.04 (1H, d, $J = 6.3$ Hz); 5.24 (1H, dd, $J = 11.7$, 1.5 Hz); 5.33 (1H, dd, $J = 17.3$, 1.5 Hz); 5.91 (1H, m); 7.32 (2H, t, $J = 7.5$ Hz); 7.41 (2H, t, $J = 7.5$ Hz); 7.61 (2H, d, $J = 7.5$ Hz); 7.84 (2H, d, $J = 7.5$ Hz). HRMS (FAB) calcd for $C_{26}H_{28}NO_6$ (MH^+) 450.1917; found 450.1916. $[\alpha]_D^{20} = +12.8$ ($c = 1.1$ CH_2Cl_2).
11. Chiral HPLC conditions: Pirkle Whelk-O 2 (*R*,*R*), isocratic 85/15 hex/*i*PrOH, 1 mL/min, UV 254 nm.
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13. (+)-**11**: ^{1}H NMR (300 MHz) (d_6-DMSO, 120°C) δ 1.39(1H, m); 1.73 (3H, m); 2.89 (1H, s); 3.22 (1H, m); 3.70 (2H, m); 4.03 (2H, m); 4.26 (1H, ddd, $J = 12.9$, 12.9, 5.7 Hz); 4.46 (2H, m); 4.55 (1H, d, $J = 6.3$ Hz); 4.90 (1H, d, $J = 6.3$ Hz); 5.15 (1H, m); 5.31 (1H, m); 5.84 (1H, m); 7.14–7.49 (10H, m); 7.60 (1H, d, $J = 7.5$ Hz); 7.78 (2H, m). HRMS (FAB) calcd for $C_{31}H_{32}NO_5$ (MH^+) 498.2280; found 428.2280. $[\alpha]_D^{20} = +15.0$ ($c = 1.4$ CH_2Cl_2).
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15. (+)-**12**: ^{1}H NMR (300 MHz) (d_6-DMSO, 120°C) δ 1.41 (1H, m); 1.72 (3H, m); 3.26 (1H, ddd, $J = 12.6$, 12.6, 3.9 Hz); 3.65 (1H, m); 3.76 (1H, m); 4.05 (1H, s); 4.28 (1H, t, $J = 6.3$ Hz); 4.42 (1H, m); 4.55 (1H, 1/2ABq, $J = 11.7$ Hz); 4.67 (1H, 1/2ABq, $J = 11.7$ Hz); 4.87 (1H, d, $J = 6.3$ Hz); 7.18–7.43 (8H, m); 7.50–7.86 (5H, m). HRMS (FAB) calcd for $C_{28}H_{28}NO_5$ (MH^+) 458.1967; found 458.1959. $[\alpha]_D^{20} = +12.2$ ($c = 0.9$ CH_2Cl_2).