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Synthesis of Novel Enantiopure 4-Hydroxypipecolic Acid Derivatives with a Bicyclic β-Lactam Structure from a Common 3-Azido-4-oxoazetidine-2-carbaldehyde Precursor

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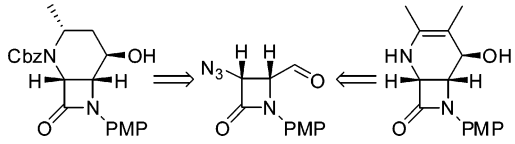

Two different stereocontrolled accesses to new 4-hydroxypipecolic acid analogues with a bicyclic β-lactam structure have been developed by using intramolecular reductive amination or allenic hydroamination reactions in 2-azetidinone-tethered azides. The access to the cyclization precursors was achieved from 3-azido-4-oxoazetidine-2-carbaldehyde via metal-mediated carbonyl−allenylation in aqueous environment or by organocatalytic direct aldol reaction. The tin hydride-promoted cyclization of the 2-azetidinone-tethered azidoallene is totally regioselective for the central allenic carbon providing a fused piperidine.

4-Hydroxypipecolic acids are naturally occurring nonproteinogenic amino acids which have been isolated from the leaves of *Calliandra pittieri*, *Strophantus scandeus*, and *Acacia oswaldii*,[1] and are constituents of many biologically active natural and synthetic products such as depsipeptide antibiotics,[2] *N*-methyl-D-aspartic acid (NMDA) receptor antagonists,[3] and HIV protease inhibitors such as palinavir (Figure 1).[4] Due to the great interest in these derivatives much effort has been devoted to their preparation.[5]

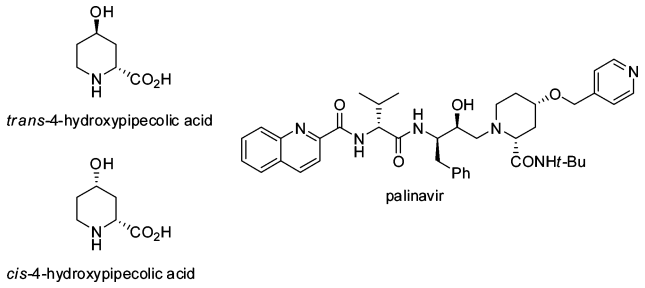

FIGURE 1. Representative biologically relevant 4-hydroxypipecolic acids.

In addition to the important medicinal properties of the β-lactam nucleus,[6] the 2-azetidinone skeleton has been extensively used as a template on which to build cyclic structures fused to the four-membered ring, using the chirality and functionalization of the β-lactam nucleus as a stereocontrolling element.[7] On the other hand, when designing peptide-based drugs, the use of conformationally constrained amino acids is

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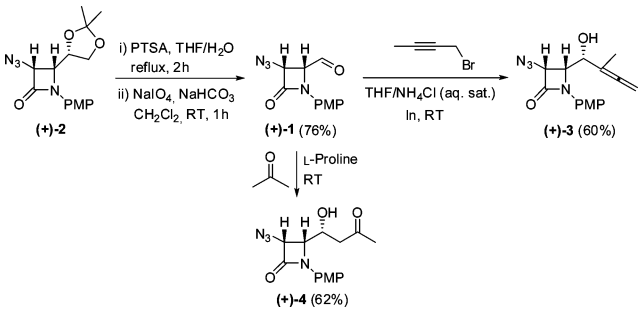
SCHEME 1. Preparation of Azidoallenol 3 and Azidoaldol 4

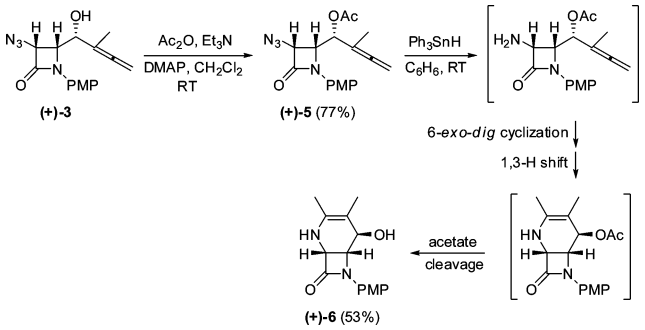


a major strategy.[8] Following our ongoing project in β-lactam chemistry,[9] we became interested in the introduction of structural constraints on the 4-hydroxypipecolic acid nucleus. We report herein two different stereocontrolled accesses to new 4-hydroxypipecolic acid analogues with a bicyclic β-lactam structure, which rely on heterocyclization reactions in both a 2-azetidinone-tethered azidoallene as well as a 2-azetidinone-tethered azidoaldol.

The starting substrate, 3-azido-4-oxoazetidine-2-carbaldehyde **1** (PMP = 4-$MeOC_6H_4$), was prepared in optically pure form using standard methodology. Enantiopure 2-azetidinone **2** was obtained following a literature method from the *p*-anisidine-derived imine of (*R*)-2,3-*O*-isopropylideneglyceraldehyde, through Staudinger reaction with azidoacetyl chloride in the presence of Et_3N as a single cis-enantiomer.[10] Acetonide hydrolysis to provide the corresponding diol, followed by oxidative cleavage, smoothly formed 3-azido-4-oxoazetidine-2-carbaldehyde **1** in excellent yield (Scheme 1). 2-Azetidinone-tethered azidoallenol **3** was regio- and diastereoselectively achieved via indium-mediated Barbier-type carbonyl−allenylation reaction of β-lactam aldehyde **1** in aqueous media (Scheme 1). The L-proline-catalyzed direct aldol reaction between carbaldehyde **1** and acetone afforded adduct **4** as the exclusive isomer (Scheme 1).

Having obtained the monocyclic precursors **3** and **4**, the next stage was set to carry out the key cyclization step. Straightforward reduction to amines is one of the most attractive synthetic applications of azides, because they serve as one of the most reliable ways to introduce an amino substituent onto a carbon atom. The conversion of azides to amines can be achieved by a large variety of reported methods.[11] It occurred to us that exposure of the azide moiety of 2-azetidinone-tethered azides **3** and **4** to chemoselective reductive conditions might serve as a straightforward procedure for the preparation of new bicyclic 4-hydroxypipecolic acid analogues, because under the reaction conditions the resulting amino group would attack the allene or aldol functionalities. The allene moiety represents a versatile and useful building block in organic synthesis, specially in the area of transition metal-assisted reactions.[12] Instead of an alkene or an alkyne, an allene component is a fascinating substrate in an aminocyclization reaction because of its unique reactivity and the synthetic use of the final products.[13] However, regioselectivity problems are significant (*endo-trig* versus *exo-dig* versus *exo-trig* cyclization). Our initial experiments on cyclization reactions of azidoallenol **3** with Ph_3P-H_2O or Ph_3SnH led to complications. To circumvent this problem, we decided to protect the alcohol group of the allenic alcohol as acetate before subjecting it to the aminocyclization reaction. On this basis, we first used the Staudinger protocol for the construction of the fused azacycle. However, when we tried to reduce azide **5** using the triphenylphosphine method,[14] a complex reaction mixture was observed. Fortunately, we found that 2-azetidinone-tethered azidoallenic acetate **5** when treated at room temperature with triphenyltin hydride in benzene solution gave in a totally regioselective fashion the bicyclic 4-hydroxypipecolic acid analogue **6** through a 6-*exo-dig* aminocyclization with concomitant acetate cleavage (Scheme 2).[15]

SCHEME 2. Synthesis of Enantiopure Fused Bicycle 6



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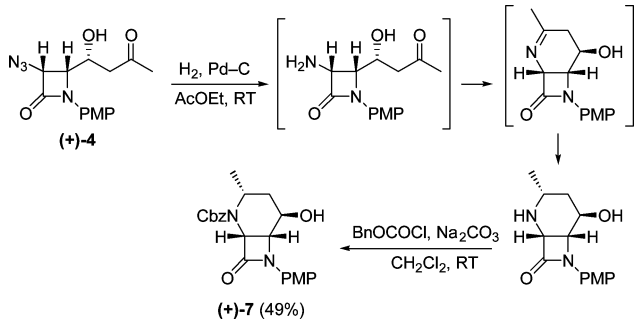
SCHEME 3. Synthesis of Enantiopure Fused Bicycle 7



Exposure of aldol adduct **4** to the Ph_3P-H_2O reductive system did afford a mixture of highly polar compounds, which could not be characterized. The hydrogenation reaction of azidoaldol **4** performed in the presence of Boc_2O revealed through ^1H NMR monitoring the formation of little cyclization product, while the major components in the mixture were side products. Then it was decided to carry out reduction of the azide and in situ cyclization and protection of the resultant secondary amine as the benzylcarbamate. Interestingly, exposure of compound **4** to H_2 (1 atm) in ethyl acetate at room temperature in the presence of a catalytic amount of Pd (10% on C) followed by the addition of benzyl chloroformate provided the 4-hydroxypipecolic acid analogue **7** with a bicyclic β-lactam structure (Scheme 3).

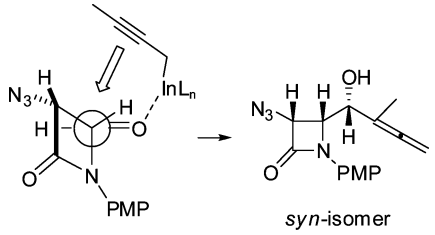


FIGURE 2. Model to explain the observed 4,1′-*syn* stereochemistry for the allenylation reaction of 3-azido-4-oxoazetidine-2-carbaldehyde **1**.

The structure and stereochemistry of compounds **6** and **7** were assigned by NMR studies. The cis-stereochemistry of the four-membered ring was set during the cyclization step to form the 2-azetidinone ring, and it was transferred unaltered during further synthetic steps. The bicyclic structures (by DEPT, HMQC, HMBC, and COSY) and the stereochemistry (by vicinal proton couplings and qualitative homonuclear NOE difference spectra) of fused β-lactams **6** and **7** were established by NMR one- and two-dimensional techniques. Taking into account that azidoallenol **3** and azidoaldol **4** could be obtained and cyclized to bicyclic 4-hydroxypipecolic acid derivatives **6** and **7**, the stereochemistry at the carbinolic stereogenic center for compounds **3** and **4** was immediately deduced by comparison with the NOE results of the bicyclic β-lactams **6** and **7**. The high diastereoselectivity of the allenylation reaction of 3-azido-4-oxoazetidine-2-carbaldehyde **1** can be explained by addition of the organometallic reagent from the less hindered *re* face of the carbonyl group following a nonchelated Felkin−Anh model, as depicted in Figure 2.[16] The configuration at the carbinolic chiral center of the aldol product **4** is consistent with a Zimmerman−Traxler six-membered-ring chairlike model for the aldolization step,[17] as depicted in Figure 3. Stereoselective formation of bicycle **7** can be understood on the basis of cis addition of hydrogen atoms to the less hindered face of the unsaturated center, since the more accessible side of the intermediate imine is the face that is not blocked by the β-lactam ring.

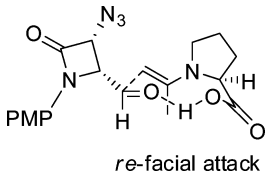


FIGURE 3. Transition state model for the L-proline-catalyzed aldol addition reaction of acetone to β-lactam aldehyde **1**.

In conclusion, we have described here two different stereocontrolled routes to new 4-hydroxypipecolic acid analogues with a bicyclic β-lactam structure. We have shown that combination of intramolecular reductive amination or allenic hydroamination reactions in 2-azetidinone-tethered azides may lead to a useful preparation of the piperidine-fused β-lactam core. The tin hydride-mediated cyclization of the 2-azetidinone-tethered azidoallene is totally regioselective for the central carbon in the allenic motif. Applications to different heterocycles employing these aminocyclizations are underway.

Experimental Section

General. Melting points were taken using a Gallenkamp apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-300, Varian VRX-300S, or Bruker AC-200. NMR spectra were recorded in $CDCl_3$ solutions, except where otherwise stated. Chemical shifts are given in ppm relative to TMS (^1H, 0.0 ppm) or $CDCl_3$ (^{13}C, 76.9 ppm). Low- and high-resolution mass spectra were taken on a HP5989A spectrometer, using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. Specific rotation $[\alpha]_D$ is given in 10^{-1} deg cm^2 g^{-1} at 20 °C, and the concentration (*c*) is expressed in g per 100 mL. All commercially available compounds were used without further purification. THF was distilled from Na-benzophenone. Benzene, dichloromethane, and triethylamine were distilled from CaH_2. Flame-dried glassware and standard Schlenk techniques were used for moisture-sensitive reactions. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh). Identification of products was made by TLC (Kiesegel 60F-254). UV light (λ = 254 nm), and a vanillin solution in sulfuric acid and 95% EtOH (1 g of vanillin, 5 mL of H_2SO_4, 150 mL of EtOH) was used to develop the plates.

Procedure for the Intramolecular Allenic Hydroamination of 2-Azetidinone-Tethered Azide (+)-5. Synthesis of Bicycle (+)-6. A solution of the 2-azetidinone-tethered azidoallene (+)-**5** (75 mg, 0.22 mmol) and triphenyltin hydride (386 mg, 1.10 mmol) in benzene (1 mL) was stirred at room temperature until complete disappearance (TLC) of starting material. The solvent was removed under reduced pressure and 32 mg (53%) of fused adduct (+)-**6** was obtained after purification by flash chromatography on silica

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gel using dichloromethane/ethyl acetate (9:1 containing 2% of triethylamine) as eluent.

Bicycle (+)-6. Colorless oil; $[\alpha]_D$ +70.7 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.74 (br s, 1H), 7.41 and 6.92 (d, each 2H, $J = 9.0$ Hz), 6.12 (dd, 1H, $J = 3.9$, 1.7 Hz), 5.99 (d, 1H, $J = 6.3$ Hz), 5.22 (m, 1H), 3.82 (s, 3H), 2.16 (s, 3H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.9, 157.1, 127.7, 122.0, 119.0, 118.1, 114.7, 96.9, 87.1, 76.9, 55.5, 29.7, 22.7; IR ($CHCl_3$, cm^{-1}) ν 3350, 3320, 1744; MS (ES) *m*/*z* 275 ($M^+ + 1$, 100), 274 (M^+, 5). Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.55; H, 6.57; N, 10.28.

Procedure for the Intramolecular Reductive Amination of 2-Azetidinone-Tethered Azide (+)-4. Synthesis of Bicycle (+)-7. To a solution of the aldol (+)-**4** (90 mg, 0.30 mmol) in ethyl acetate (16 mL) was added 10% Pd/C (15 mg). The suspension was stirred under H_2 (1 atm) over 4 h at room temperature. After this time, the reaction mixture was filtered through Celite, and the solvent was evaporated affording the corresponding aminoalcohol. Benzyl chloroformate (49 μL, 0.36 mmol) was added to a solution of the above crude aminoalcohol (0.30 mmol) and Na_2CO_3 (38 mg, 0.36 mmol) in dry dichloromethane (2 mL), and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was treated with water and extracted with dichloromethane, and the organic layer was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford a crude product, which was purified by silica gel column chromatography (eluent: ethyl acetate/hexanes, 1:2) to afford bicycle (+)-**7** (58 mg, 49% yield).

Bicycle (+)-7: colorless solid; mp 170−171 °C (hexanes/ethyl acetate); $[\alpha]_D$ +44.2 (*c* 0.8, $CHCl_3$); ^1H NMR δ 7.34 (m, 7H), 6.87 (d, 2H, $J = 9.0$ Hz), 6.14 (d, 1H, $J = 10.1$ Hz), 5.35 (dd, 1H, $J = 10.1$, 5.1 Hz), 5.12 (s, 2H), 4.28 (m, 2H), 3.78 (s, 3H), 3.53 (br s, 1H), 2.64 (m, 2H), 2.08 (s, 3H); ^{13}C NMR δ 165.0, 156.8, 155.9, 135.8, 130.5, 128.5, 128.2, 128.1, 120.6, 118.2, 114.5, 114.3, 67.4, 66.0, 59.9, 58.4, 55.4, 47.3, 30.5; IR ($CHCl_3$, cm^{-1}) ν 3330, 1742, 1720; MS (EI) *m*/*z* 396 (M^+, 9), 149 (100). Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.77; H, 6.05; N, 7.01.

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Supporting Information Available: Compound characterization data and experimental procedures for compounds **1** and **3**−**5**, as well as ^1H NMR and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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