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Asymmetric synthesis of a potent azepanone-based inhibitor of the cysteine protease cathepsin K

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Abstract—In this account we detail the asymmetric synthesis of **1**, a potent azepanone-based inhibitor of cathepsin K (K_i = 0.16 nM), which has been shown to inhibit the production of biomarkers of bone resorption in monkeys. The key steps in the synthesis sequence were the utility of the Evans aldol reaction coupled with the ring closing olefin metatheses to assemble the azepanone core contained within **1**.

The papain superfamily of cysteine proteases is a highly homologous class of enzymes whose members mediate a diverse array of biological processes in both normal cell homeostasis and the pathophysiology of disease.[1] We have described recently the design, synthesis, and pharmacological characterization of **1** (Fig. 1), a potent azepanone-based inhibitor of the osteoclast-specific cysteine protease cathepsin K.[2] The racemic synthesis of this azepanone inhibitor template relied on a final stage HPLC separation of the C-4 diastereomers to provide analogs **1** and **2**. Azepanone **1**, which contains the C4-*S* stereochemistry, is a 0.16 nM inhibitor of cathepsin K while the corresponding C4-*R* diastereomer **1** was 1/6000th as potent ($K_{i,app}$ = 980 nM).

Having established the importance of the C4 stereocenter of azepanone **1** in determining inhibitor potency several asymmetric synthesis routes in which this chiral center would be controlled throughout were investigated. From a retrosynthesis perspective, it was desirable to also control the regiochemistry of the amino alcohol installation, a feature only partially reduced to practice in the original synthesis of **1**. As shown in Scheme 1, inhibitor **1** is readily derived from (3*R*,4*S*)-4-amino-1-(pyridine-2-sulfonyl)-azepan-3-ol (**3**). In racemic form we have utilized this intermediate as a linchpin building block for the synthesis of a variety of cysteine protease inhibitors, thereby making an asymmetric synthesis of this template all the more desirable. Amino alcohol **3** was envisioned to derive from the cyclic aldol adduct **4** via Curtius rearrangement. The acyclic diene **5** would serve as a precursor to formation of the azepine **4** via ring closing olefin metatheses[3] and would be assembled via aldol condensation of aldehyde **7** with the chiral

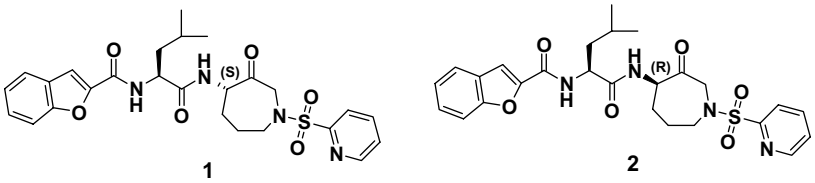

Figure 1. Azepanone-based inhibitors of cathepsin K.

Keywords: Asymmetric synthesis; Aldol; Ring closing olefin metatheses.
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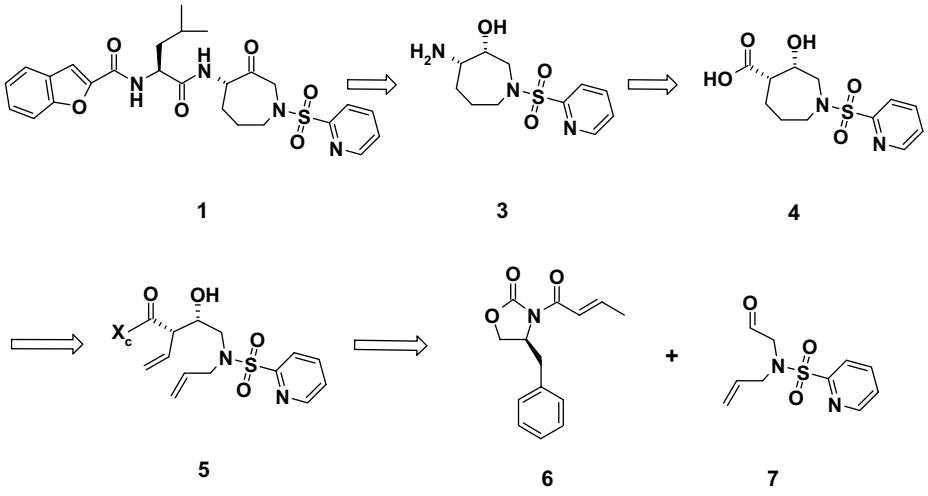
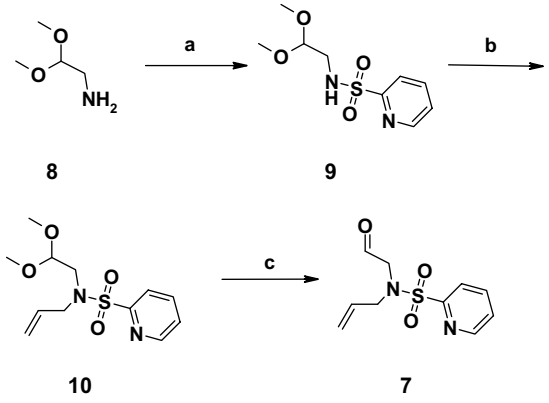


Scheme 1. Retrosynthesis of azepanone **1**.

crotonate imide **6**.[4] The high level of stereocontrol imparted by Evans aldol reaction would be utilized to install the C4-*S* stereocenter requisite in **1**.

The preparation of aldehyde **7** is described in Scheme 2. Treatment of aminoacetaldehyde dimethyl acetal (**8**) with freshly prepared 2-pyridinesulfonyl chloride provided sulfonamide **9** in 88% yield. Deprotonation of **9** with sodium *tert*-pentoxide in DMF followed by quenching this mixture with allyl bromide provided **10** in 51% yield. Removal of the dimethylacetal protecting group under acidic conditions then provided aldehyde **7** in 51% yield.

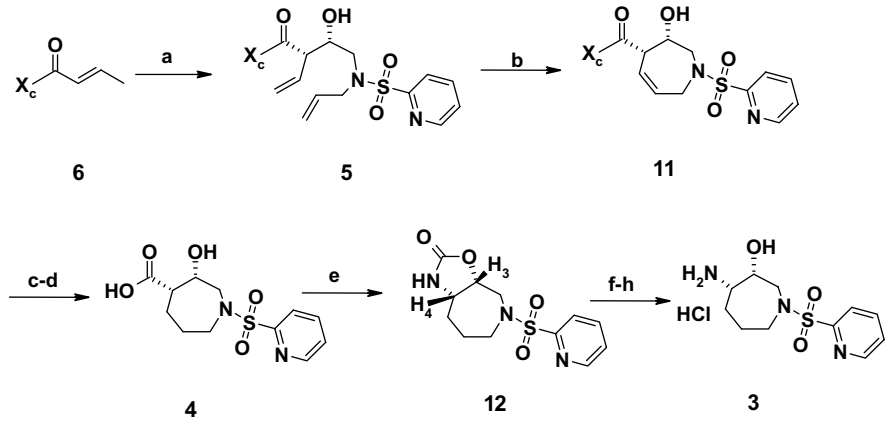
As detailed in Scheme 3 assembly of the azepine ring system began with the aldol condensation of aldehyde **7** with acrylate **6** utilizing the procedure developed by Evans and co-workers to provide the diene **5** in 68% yield.[4,5] Based upon the amply precedented nature of this transformation we have, at this point, assumed that the product **5** possesses the 3*S*,4*S* absolute stereochemistry. Treatment of **5** with the Grubbs bis(tricyclohexylphosphine)benzylidineruthenium(IV) dichloride ring closing olefin metatheses catalyst cleanly effected azepene formation to provide **11** in 75% yield.[6] Hydrogenation of **11** under standard conditions (10% Pd–C, CH_3OH, H_2) followed by hydrolysis of the chiral auxiliary gave azepanol **4**. Treatment of **4** with diphenylphosphoryl azide effected the Curtius rearrangement,[7] a process known to proceed with retention of configuration,[8] to provide the cyclic urethane **12** in 61% yield.[9] The 8.55 Hz coupling constant between H_3 and H_4 in the ^1H NMR of **12** is consistent with the desired *cis* ring fusion and suggests that the fidelity of the critical C4 stereocenter was maintained during the Curtius rearrangement. Differential NOE experiments further confirmed the *cis* relationship of H_3 and H_4. Initial attempts to saponify the cyclic urethane of **12** to produce directly amino alcohol **3** were low yielding. The vagaries of this transformation were rectified upon treatment of **12** with di-*tert*-butyl dicarbonate to form the intermediate *N*-Boc cyclic urethane, which was saponified with cesium carbonate in methanol and water to give the *N*-Boc protected amino alcohol (not shown).[10] Removal of the *N*-Boc carbamate under acidic conditions provided (3*R*,4*S*)-4-amino-1-(pyridine-2-sulfonyl)-azepan-3-ol (**3**) as the hydrochloride salt.



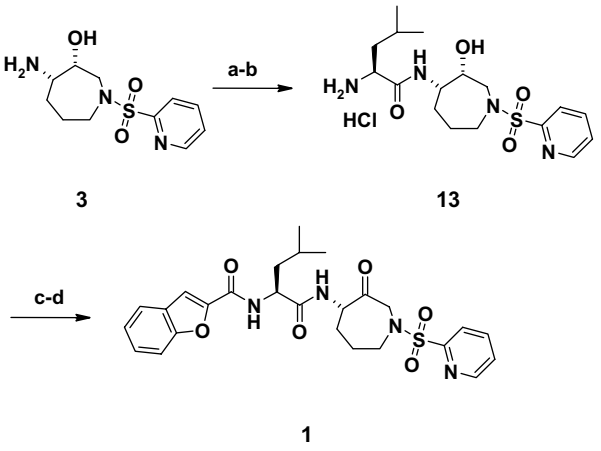
Scheme 2. Reagents and conditions: (a) 2-pyridinesulfonyl chloride, aqueous satd $NaHCO_3$, CH_2Cl_2, 88%; (b) Na-*t*-pentoxide, DMF, allyl bromide, 51%; (c) 3 M HCl/dioxane, THF, 51%.

Conversion of amino alcohol **3** to azepanone **1** was straightforward and is shown in Scheme 4. Acylation of **3** with *N*-Boc-leucine in the presence of HOBt and EDC followed by removal of the *N*-Boc carbamate provided the amine hydrochloride **13**. Acylation of **13** with benzofuran-2-carboxylic acid followed by Dess–Martin periodinane oxidation gave the chiral azepanone **1** in 95% yield.[11]

In this communication the asymmetric synthesis of the potent azepanone-based cathepsin K inhibitor **1** has been detailed. The stereocontrol imparted by the Evans aldol reaction combined with ring closing olefin metatheses for the construction of the 7-membered ring azepane were critical transformations in the synthesis. A key intermediate of this synthesis sequence is (3*R*,4*S*)-4-amino-1-(pyridine-2-sulfonyl)-azepan-3-ol (**3**). The utility of **3** in the asymmetric construction of inhibitors



Scheme 3. Reagents and conditions: (a) *n*-Bu_2BOTf, TEA, CH_2Cl_2, **7**, 68%; (b) bis(tricyclohexylphosphine)benzylidineruthenium(IV) dichloride, CH_2Cl_2, reflux, 75%; (c) 10% Pd–C, CH_3OH, H_2, 100%; (d) LiOH, 30% H_2O_2, THF, H_2O, −10 °C, 89%; (e) $(PhO)_2P(O)N_3$, TEA, toluene, reflux, 61%; (f) Boc_2O, TEA, DMAP, THF, 92%; (g) Cs_2CO_3, CH_3OH, 66%; (h) 4 N HCl/dioxane, CH_3OH, 100%.



Scheme 4. Reagents and conditions: (a) *N*-Boc-leucine, EDC, HOBt, TEA, CH_2Cl_2, 72%; (b) 4 N HCl/dioxane, CH_3OH; (c) benzofuran-2-carboxylic acid, EDC, HOBt, TEA, CH_2Cl_2 61% for two steps; (d) Dess–Martin periodinane, CH_2Cl_2, 95%.

of other cysteine proteases of the papain superfamily will be detailed in subsequent publications.

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9. Characterization data for cyclic urethane **12**: $[\alpha]_D^{23}$ −7.2 (*c* 0.68, $CHCl_3$); IR ($CHCl_3$) 3430, 1770 (s), 1360 (m), 1210 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 4.71 Hz, 1H), 7.97 (m, 1H), 7.92 (dd, J = 7.89, 1.65 Hz, 1H), 7.52 (ddd, J = 7.12, 4.90, 1.67 Hz, 1H), 6.08 (s, 1H), 4.99 (ddd, J = 10.6, 8.49, 5.30 Hz, 1H), 4.18 (dd, J = 14.8, 5.11 Hz, 1H), 4.06 (td, J = 9.40, 2.70 Hz, 1H), 3.97 (d, J = 13.6 Hz, 1H), 3.18 (dd, J = 14.8, 10.6 Hz, 1H), 2.97 (t, J = 12.4 Hz, 1H), 1.87 (m, 3H), 1.68 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 157.2, 150.1, 138.1, 126.8, 122.5, 77.0, 55.7, 52.3, 49.7, 30.4, 26.9; MS (ESI) *m/z* 298.0 $(M+H)^+$.
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11. Characterization data for azepanone **1**: Mp 179–181 °C (amorphous solid); $[\alpha]_D^{23}$ +49 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3410 (m), 1720 (m), 1660 (s), 1650 (s), 1500 (s), 1340 (s), 1210 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, J = 4.74 Hz, 1H), 8.00 (d, J = 7.81 Hz, 1H), 7.95 (td, J = 7.59, 1.71 Hz, 1H), 7.68 (d, J = 7.25 Hz, 1H), 7.54 (m, 2H), 7.49 (d, J = 0.93 Hz, 1H), 7.44 (ddd, J = 8.42, 7.20, 1.23 Hz, 1H), 7.31 (td, J = 7.54, 0.90 Hz, 1H), 7.11 (d, J = 8.49 Hz, 1H), 6.99 (d, J = 6.67 Hz, 1H), 5.18 (ddd, J = 11.3, 6.55, 2.84 Hz, 1H), 4.81 (dd, J = 19.1, 1.75 Hz, 1H), 4.73 (m, 1H), 4.13 (m, 1H), 3.87 (d, J = 18.9 Hz, 1H), 2.71 (ddd, J = 14.3, 12.1, 2.30 Hz, 1H), 2.26 (m, 1H), 2.16 (m, 1H), 1.85 (m, 1H), 1.75 (m, 2H), 1.65 (br s, 1H), 1.46 (m, 1H), 1.03 (d, J = 1.63 Hz, 3H), 1.01 (d, J = 1.71 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.7, 170.6, 158.6, 157.2, 154.8, 150.2, 148.1, 138.2, 127.5, 127.1, 127.0, 123.7, 122.7, 122.5, 111.9, 110.9, 58.7, 57.9, 51.5, 51.4, 41.9, 31.7, 28.3, 24.8, 22.9, 22.1; MS (ESI) *m/z* 527.4 $(M+H)^+$.