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Efficient Asymmetric Synthesis of the Vasopeptidase Inhibitor BMS-189921

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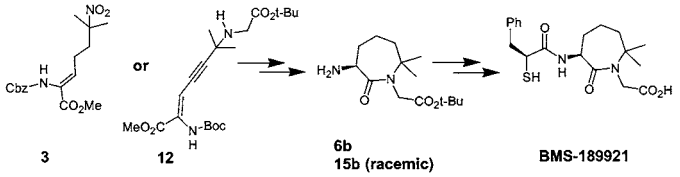
ABSTRACT



An efficient asymmetric synthesis of the vasopeptidase inhibitor BMS-189921 was accomplished. Two short enantioselective syntheses of the common key intermediate (*S*)-α-aminoazepinone 6b were developed. Olefin 3 was converted to 6b via asymmetric hydrogenation. Alternatively, enyne 12 was converted to racemic α-aminoazepinone 15b, which was transformed to 6b by a practical dynamic resolution.

Vasopeptidase inhibitors, compounds which inhibit both angiotensin converting enzyme (ACE) and neutral endopeptidase (NEP), represent potential new modalities for the treatment of hypertension and congestive heart failure. α-Amidoazepinones have been investigated intensively as conformationally restricted dipeptidomimetic surrogates capable of dual inhibition of both enzymes.[1−3] In this regard, Robl et al.[1] reported the design and properties of a potent vasopeptidase inhibitor, BMS-189921, which was selected for clinical development. In this letter, we describe two new short and efficient routes to the key intermediate (*S*)-α-aminoazepinone **6b** and its efficient conversion to BMS-189921.

In the first approach, the stereocenter in **6b** was established by asymmetric hydrogenation of olefin **3** (Scheme 1). Addition of excess 2-nitropropane to acrolein formed crystal-

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§ Solid State Chemistry.

(1) Robl, J. A.; Sulsky, R.; Sieber-McMaster, E.; Ryono, D. E.; Cimarusti, M. P.; Simpkins, L. M.; Karanewski, D. S.; Chao, S.; Asaad, M. M.; Seymour, A. A.; Fox, M.; Smith, P. L.; Trippodo, N. C. *J. Med. Chem.* **1999**, *42*, 305 and references therein.

(2) Delaney, N. G.; Barrish, J. C.; Neubeck, R.; Natarajan, S.; Cohen, M.; Rovnyak, G. C.; Huber, G.; Murugesan, N.; Girotra, R.; Sieber-McMaster, E.; Robl, J. A.; Asaad, M. M.; Cheung, H. S.; Bird, J. E.; Waldron, T.; Petrillo, E. W. *Bio. Med. Chem. Lett.* **1994**, *4*, 1783.

(3) Freidinger, R. M.; Perlow, D. S.; Veber, D. F. *J. Org. Chem.* **1982**, *47*, 104.

(4) (a) Rosini, G.; Marotta, E.; Ballini, R.; Petrini, M. *Synthesis* **1986**, 237. (b) Shechter, H.; Ley, D. E.; Zeldin, L. *J. Am. Chem. Soc.* **1952**, *74*, 3664.

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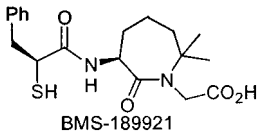
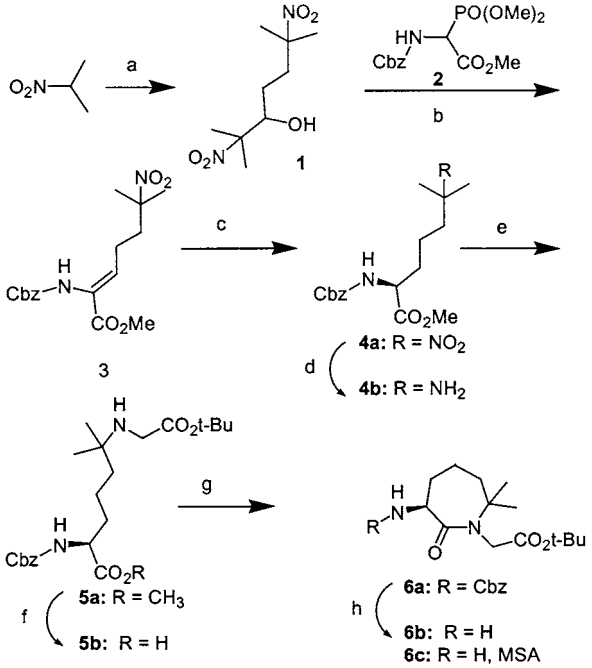
line alcohol **1** (70% yield)[4] via conjugate addition followed by a Henry reaction.



Scheme 1. Synthesis of α-Aminoazepinone **6b** via Enantioselective Reduction of Nitroenamide **3**[a]



[a] Reaction conditions: (a) Acrolein, Et_3N. (b) DBU, CH_2Cl_2. (c) [(COD)Rh-(*S*,*S*)-Et-DUPHOS]OTf, H_2, MeOH, 40 psi. (d) Zn, HCl. (e) $BrCH_2CO_2$-*t*-Bu, DIPEA, CH_3CN. (f) LiOH (aq), THF. (g) EDC, HOBT, DIPEA, CH_2Cl_2. (h) H_2, $Pd(OH)_2$, MeOH; MSA.

This product, which was considerably easier to isolate and handle than the initially formed Michael adduct and readily amenable to base-catalyzed retro-Henry reaction, was condensed (DBU, CH_2Cl_2) with commercially available phosphonate **2** to produce **3** (90% yield, 92% (*Z*)-selectivity).[5] The assignment of (*Z*)-geometry to the predominant isomer was based on literature precedent and later confirmed by single-crystal X-ray analysis.[6a] Enantioselective hydrogenation of the mixture of olefins [(COD)Rh-S,S-EtDuPHOS]-OTf[7] (MeOH, 40 psi) provided **4a** (90% yield, 99% ee). As expected with this catalyst system,[7a] the presence of the corresponding (*E*)-isomer (8%) did not adversely affect the enantioselectivity of hydrogenation.

Initial efforts to reduce the nitro group in **4a** to the corresponding amine under catalytic hydrogenation conditions (Pt, Pd, or Rh catalysts) resulted in partial hydrogenolysis of the Cbz moiety as well as saturation of the phenyl ring in the protecting group. On the other hand, reduction using Zn in methanolic HCl smoothly provided amine **4b**.[8] N-Alkylation of this compound with *tert*-butyl bromoacetate furnished amino diester **5a** (90% yield), which was selectively saponified (LiOH, aq THF) to **5b** (98% yield) with no detectable racemization at the stereogenic center. Lactamization of the amino acid was effected using EDC in the presence of HOBT (DIPEA, CH_3CN), providing the protected azepinone **6a** (90% yield). Under these conditions, epimerization was less than 2% as determined by chiral HPLC. In the absence of HOBT, epimerization increased to 4%. Removal of the Cbz protecting group [H_2, $Pd(OH)_2$, MeOH] was facile and gave amine **6b** in 92% yield and 97% ee. The optical purity of this material was further enhanced by crystallization of the corresponding MSA salt **6c** followed by regeneration of the free base with NaOH (92% yield, 99.9% ee).

While this eight-step synthesis of α-aminoazepinone **6b** was reasonably efficient, it proved to be difficult to maintain a reasonable substrate/catalyst ratio as the asymmetric hydrogenation of **3** was scaled up. The DuPHOS catalyst proved to be sensitive to the presence of impurities carried over from the Wadsworth−Emmons reaction used to prepare the hydrogenation substrate. Multiple charges of catalyst were required, especially on >100 g inputs of olefin, to drive the hydrogenation to completion. Passing the olefin through a silica gel pad prior to hydrogenation was helpful but did not provide a complete remedy. This issue, as well as concerns around the toxicity of 2-nitropropane and the introduction of the azepinone nitrogen in the incorrect oxidation state, made this path unattractive when envisioning a multikilogram scale synthesis.

As a result, we developed an alternative synthesis of **6b** involving a conceptually different approach (Scheme 2) in which enyne **12**, constructed via Heck−Sonogashira-type coupling[9] of alkyne **8** with vinyl bromide **11**, was converted to racemic aminoazepinone **15b**. An efficient crystallization-driven dynamic resolution was then developed for conversion

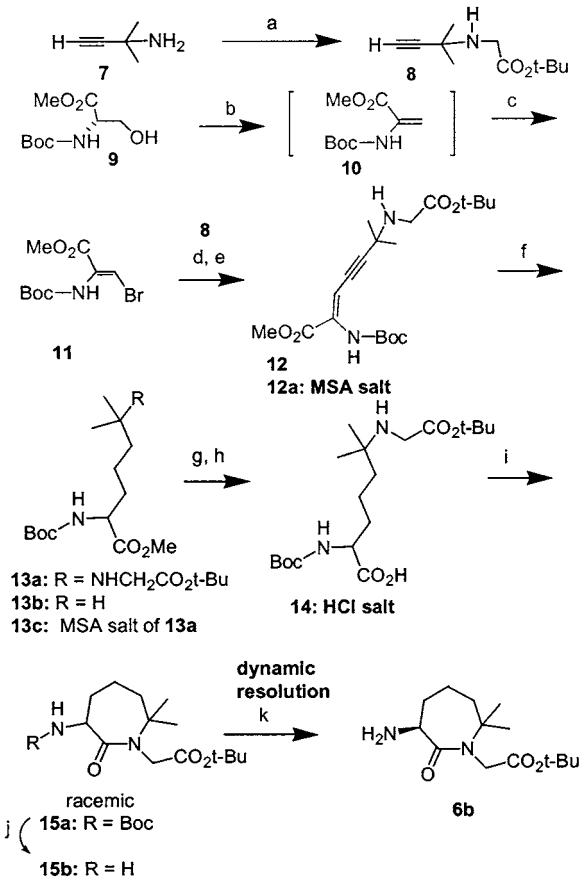
(5) (a) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53. (b) Kazmaier, U. *Tetrahedron Lett.* **1996**, *37*, 5351. (c) Treatment of **1** with $NaBH_4$ resulted in retro-Henry reaction and produced the corresponding alcohol in high yield. Similarly, treatment of **1** with the enolate of *tert*-butyl dichloroacetate provided the corresponding glycidic ester. We are currently investigating the scope and applications of this process.

(6) (a) Crystallographic Data for **3**: $C_{17}H_{22}O_6N_2$; colorless rods from neat oil; cell parameters (T = 22 °C) a = 16.539(2) Å, b = 6.287(1) Å, c = 17.498(2) Å, β = 100.69(1)°, V = 787.9(8) Å^3; space group $P2_1/n$, Z = 4; R = 0.062, R_w = 0.081 for refinement based on 2059 observed [$I \gtrsim 3\sigma(I)$] reflections. (b) For **18**: $C_{21}H_{28}N_2O_5S$; colorless prisms from CH_2Cl_2/hexanes; cell parameters (T = −31 °C) a = 12.542(1) Å, b = 15.434(1) Å, c = 11.167(1) Å, V = 2161.5(5) Å^3; space group $P2_12_12_1$, Z = 4; R = 0.061, R_w = 0.086 for refinement based on 2203 observed [$I \gtrsim 3\sigma(I)$] reflections. Coordinates from the X-ray determinations have been deposited in the Cambridge Crystallographic Database and can be obtained upon request to the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.

(7) (a) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 101125. (b) Stammers, T. A.; Burk, M. J. *Tetrahedron Lett.* **1999**, *40*, 3325. (c) Xiao, D.; Zhang, Z.; Zhang, X. *Org. Lett.* **1999**, *1*, 1679. (d) Zhou, Y. G.; Tang, W.; Wang, W. B.; Li, W.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 4952. (e) Reetz, M. T.; Mehler, G.; Meiswinkel, A.; Sell, T. *Tetrahedron Lett.* **2002**, *43*, 7941.

(8) (a) Hoover, F. W.; Hass, H. B. *J. Org. Chem.* **1947**, *12*, 506. (b) Bryce, M. R.; Gardiner, J. M.; Hursthouse, M. B.; Short, R. L. *Tetrahedron Lett.* **1987**, *28*, 577. (c) Adams, J. P.; Box, D. S. *J. Chem. Soc., Perkin. Trans. 1* **1999**, 749.

Scheme 2. Synthesis of Racemic α-Aminoazepinone **15b** via Enyne **12** and Its Dynamic Resolution to **6b**[a]



[a] Reaction conditions: (a) $BrCH_2CO_2$-*t*-Bu, THF. (b) MsCl, Et_3N, CH_2Cl_2. (c) NBS, Et_3N. (d) $Pd(PPh_3)_4$, CuI, Et_3N. (e) MSA. (f) H_2, 5% Rh/C, MeOH. (g) LiOH, THF (aq). (h) HCl (aq). (i) EDC, HOBT, DIPEA. (j) MSA, EtOH (aq); NaOH (aq), EtOAc. (k) (*R*)-CSA, 2-hydrozy-5-nitro-benzaldehyde, toluene, 70 °C; NaOH (aq), EtOAc.

of **15b** to (*S*)-α-aminoazepinone **6b**. In this approach, the azepinone ring nitrogen is introduced at the correct oxidation state.

Thus, N-alkylation of commercially available 1,1-dimethylpropargylamine **7** with *tert*-butyl bromoacetate formed ester **8** in 93% yield. Vinyl bromide **11** was prepared from *N*-(*t*-butoxycarbonyl)-L-serine methyl ester **9** by dehydration (MsCl, Et_3N, CH_2Cl_2) followed by bromination and isomerization (NBS, Et_3N).[9f,10] Under the literature[9f] conditions, which employed excess reagents for similar conversions, colored product was produced in low yield. We found that a stoichiometric amount of NBS in the bromination and catalytic Et_3N for the isomerization produced much cleaner product in acceptable yield. The (*Z*)-olefin geometry was based on literature precedents for similar compounds.[10] Cross-coupling[9] of **11** with alkyne **8** [0.002 equiv of $Pd(Ph_3P)_4$, 0.02 equiv of CuI, Et_3N) furnished enyne **12** in 90% yield, which was purified by crystallization of the corresponding MSA salt **12a**. The geometry of the olefin was preserved during the coupling and purification operations.[9]

Saturation of **12** via catalytic hydrogenation was initially problematic due to competing hydrogenolysis of the glycine subunit (to produce **13b**) as well as general catalyst poisoning.[11] Employment of the MSA salt **12a** effectively neutralized the issue of catalyst poisoning; however, the hydrogenolysis side reaction remained significant (10−30%) when using Rh−Al_2O_3 or Pt−C catalysts. After considerable experimentation, we found that reduction of **12a** over 5% Rh−C at 0 °C effectively minimized hydrogenolysis to ∼2%. Crystallization of the resulting salt **13c** efficiently purged low levels of **13b**. Saponification of this material (2.1 equiv of LiOH, aq THF) formed the amino acid, which was isolated as the hydrochloride salt **14** and then cyclized (EDC, HOBT, DIPEA) to azepinone **15a**. Selective removal of the Boc protecting group in the presence of the *tert*-butyl ester was unsuccessful using formic acid, TFA, or HCl under a variety of conditions.[12] However, reaction with MSA (aq EtOH) produced racemic α-aminoazepinone **15b** with high selectivity in 75% overall yield from **13c**.

Dynamic resolution comprises the preferential crystallization of an enantiomer (or diastereomeric salt) with concomitant racemization of the undesired enantiomer in solution, and, in principle, can reach 100% efficiency.[13] Armstrong[13e] and Wetter[13f] have reported dynamic resolutions of phenyl-ring fused α-aminoazepinones. In these examples, racemization of the unwanted enantiomer was brought about via enolization of the azomethine formed with 2-hydroxy-5-nitro benzaldehyde (HNB) used in catalytic amounts.

Following these leads, a dynamic resolution of **15b** was developed by systematically screening the relative solubilities of diastereomeric salts derived from a variety of acids.[14,15]

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(11) Misiti, D.; Zappia, G.; Monache, G. D. *Synthesis* **1999**, 873 and references therein.

(12) Gibson, F. S.; Bergmeier, S. C.; Rappoport, H. *J. Org. Chem.* **1994**, *59*, 3216 and references therein.

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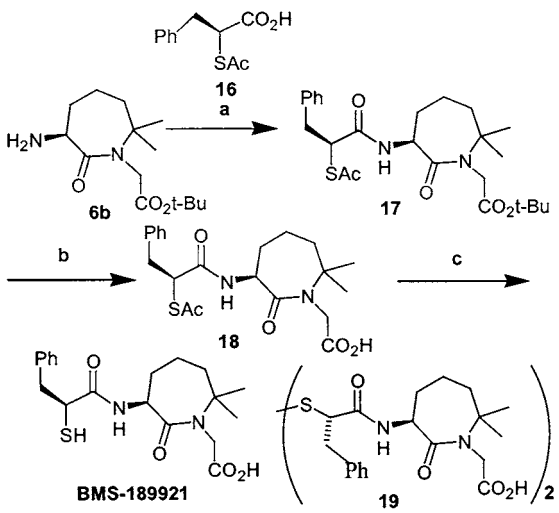
(14) (a) Classical resolution[14b] of racemic **15b** with D-tartaric acid and (*R*)-CSA gave the corresponding salts in 30% (99% ee) and 44% (99.8% ee) yields (50% theoretical maximum), respectively. (b) Brenner, M.; Rickenbacher, H. R. *Helv. Chim. Acta* **1958**, *21*, 181.

Scheme 3. Conversion of α-Amino Azepinone **6b** to BMS-189921[a]



[a] Reaction conditions: (a) EDC, CH_2Cl_2, −20 to 0 °C. (b) TFA, CH_2Cl_2, 25 °C, 5 h; NaH_2PO_4, NaOH (aq). NaOH (aq), DTT, CH_3OH.

We found that employment of 0.95 equiv of (*R*)-CSA (Scheme 2) in the presence of HNB in toluene solvent gave the (*R*)-CSA salt of **6b** in 79% yield (99.8% ee) on a multikilogram scale. Careful removal of the HNB from the resolved salt prior to neutralization to the free base was essential in order to avoid erosion of the enantiopurity resulting from racemization of the corresponding Schiff base. The coupling of α-aminoazepinone **6b** with (*S*)-2-(acetylthio)benzenepropanoic acid **16**[16] (EDC, CH_2Cl_2, −30 to 0 °C) furnished amide **17** (96% yield, Scheme 3). Up to ∼1% epimerization of the stereocenter adjacent to the thioester was observed during this reaction. In addition, during coupling reactions at ambient temperature, >5% acetyl transfer from the sulfur to the amine nitrogen was observed. This side reaction, as well as the epimerization, was almost completely suppressed when couplings were performed below −20 °C. Selective deprotection of the *tert*-butyl ester in **17** required careful control of conditions due to the labile thioester and the instability of the product **18** to strongly acidic conditions.[17] Reaction of **17** with TFA (15 mol equiv, CH_2Cl_2, 25 °C, 5 h) followed by workup with pH 5 buffer (NaH_2PO_4, aq NaOH) resulted in formation of crystalline acid **18** (93% yield). The absolute configurations of the two chiral centers in **18** were confirmed by single-crystal X-ray analysis.[6b] Deprotection of **18** required rigorous attention to detail in order to minimize formation of disulfide **19**, which was very prone to epimerization under the basic reaction conditions.[18] Control experiments in similar systems established that **19** is a significant source of diastereomer found in BMS-189921 resulting from cleavage of the epimerized disulfide by free thiol in solution. After experimenting with different additives capable of acting as reducing agents, we found that conducting the saponification in the presence of 5 mol % dithiothreitol[19] with rigorous exclusion of oxygen minimized disulfide formation and the resulting epimerization. Ultimately, deacetylation of **18** (aq NaOH, DTT, deoxygenated MeOH) provided BMS-189921 in 95% yield.[20] Material from this process was typically >99.5% pure by HPLC. To fuel advanced toxicology and clinical studies, the synthesis of BMS-189921 proceeding through the dynamic resolution of **15b** was chosen for further development. Details of this work will be reported soon.[21]

Acknowledgment. We thank Analytical R & D for their valuable support and the Science Information Department, Bristol-Myers Squibb, for helpful literature searches during the course of this work.

Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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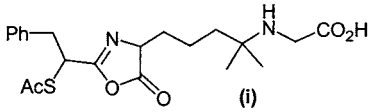
(15) We also investigated the suitability of other esters in the dynamic resolution. For example, it was not possible to resolve the corresponding methyl ester. This work will be published as part of a full paper.

(16) (a) Commercially available from Davos Chemical Corporation. (b) Allegrini, P.; Soriato, G. Patent WO 9942438, Jan. 26, 1999; *Chem. Abstr.* **1999**, *131*, 157650.

(17) On extended exposure to TFA, azepinone **18** was converted to azalactone (**i**).



(18) Marked sensitivity of chiral α-mercaptoacyl amides to epimerization during deacylation procedures has been reported. Strijtveen, B.; Kellog, R. M. *J. Org. Chem.* **1986**, *51*, 3664.

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(20) Kronenthal, D. R.; Deshpande, R. P. U.S. Patent 6444810, Sept. 3, 2002.

(21) All new compounds were characterized by spectroscopic methods and gave satisfactory elemental analyses.