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An Asymmetric Synthesis of (2*S*,5*S*)-5-Substituted Azepane-2-Carboxylate Derivatives

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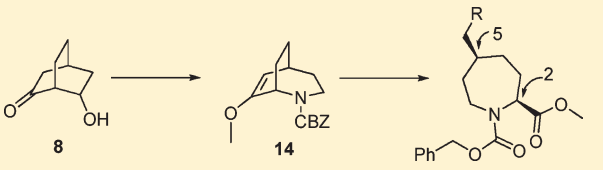
Supporting Information

ABSTRACT: To facilitate a drug discovery project, we needed to develop a robust asymmetric synthesis of (2*S*,5*S*)-5-substituted-azepane-2-carboxylate derivatives. Two key requirements for the synthesis were flexibility for elaboration at C5 and suitability for large scale preparation. To this end we have successfully developed a scalable asymmetric synthesis of these derivatives that starts with known hydroxy-ketone **8**. The key step features an oxidative cleavage of aza-bicyclo[3.2.2]nonene **14**, which simultaneously generates the C2 and C5 substituents in a stereoselective manner.



Cyclic amino acid derivatives are important components of biologically active substances, including proteins, because of their conformational rigidity and specific orientation of substituents.[1] For these exact reasons cyclic amino acid derivatives are ideally suited to serve as chiral building blocks in organic synthesis and as core structures in effective catalysts for asymmetric bond forming reactions.[2] Additionally, the rich functionality of substituted cyclic amino acids makes them attractive intermediates for natural product synthesis.[3] Therefore, strategies for the efficient asymmetric synthesis of substituted cyclic amino acid derivatives are of intense interest to the pharmaceutical industry. While many good methods exist for the preparation of substituted proline and pipecolic acid derivatives, relatively few approaches to the stereospecific preparation of substituted azepine carboxylic acids have been presented in the literature.[4]

To facilitate a drug discovery project, we needed to develop a robust asymmetric synthesis of (2*S*,5*S*)-5-substituted-azepane-2-carboxylate derivatives **1** (Figure 1). Two key requirements for the proposed synthesis were flexibility for elaboration at C-5 and suitability for large scale preparation.

Our initial approach for the preparation of C5 substituted azepine 2-carboxylic acids started from (*S*)-allylglycine (**2**), which is an article of commerce or can be readily prepared[5,6] (Scheme 1). Subsequent amine protection, followed by *N*-alkylation with the appropriately substituted homoallyl group and ring closing metathesis provides the C-5 substituted dehydroazepine-2-carboxylate **5** in good overall yield.[7] However, attempts to reduce the olefin stereoselectively resulted predominantly in the *trans*-disubstituted amino ester **6**. Conversion of methyl ester **5** to the corresponding bulky ester (R = adamantyl)

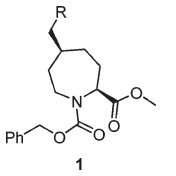


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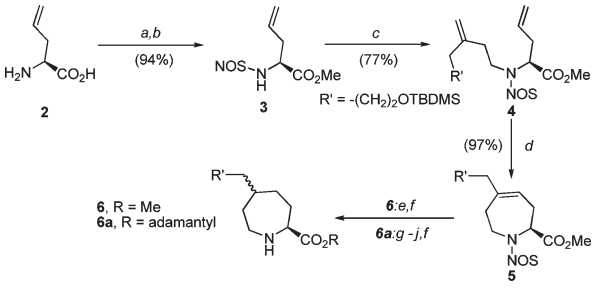
Figure 1. Target compounds.

Scheme 1. Initial Approach[a]



[a] Reagents and conditions: (a) MeOH, $SOCl_2$, 60 °C; (b) NOS-Cl, $NaHCO_3$, Et_2O, water; (c) Ph_3P, DIAD, THF, rt, 77% yield; (d) 4% Hoveyda−Grubbs second generation (301224-40-8), CH_2Cl_2, reflux; (e) PhSH, K_2CO_3, DMF; (f) MeOH, 5% $Rh/Al_2O_3/H_2$, 30 bar, 30 °C; (g) PhSH, K_2CO_3, DMF, BOC_2O; (h) LiOH, THF, water; (i) 1-adamantyl bromide, Ag_2O, Et_2O; (j) 2 M HCl/Et_2O.

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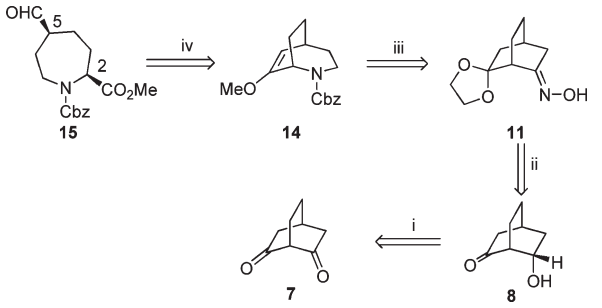
Scheme 2. New Approach, Retrosynthesis



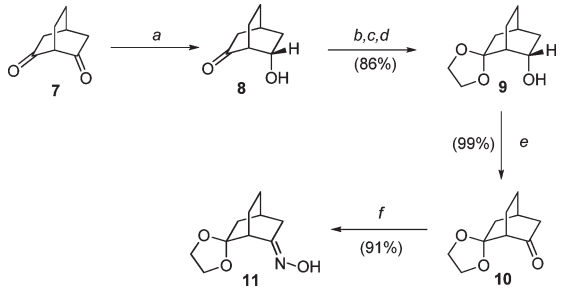
greatly improved the stereoselectivity of the olefin reduction (H_2/Rh/Al_2O_3, MeOH, 30 bar, 30 °C) to give a preponderance of the *cis*-disubstituted amino ester **6a**. However, this approach suffered from other limitations. Most notably, the C5 substituent had to be introduced relatively early in the synthesis, greatly reducing flexibility for producing alternative substituents at this position.

In considering an alternate strategy, we envisioned solving the stereoselectivity problem by liberating the C2 and C5 substituents simultaneously from the oxidative cleavage of an azabicyclo[3.2.2]nonene derivative **14** (Scheme 2). In addition, this approach enabled oxidative differentiation of the C2 and C5 substituents, leaving a versatile aldehyde substituent at C5 for further elaboration. Finally, the required azabicyclononene was envisioned to be derived from Beckmann rearrangement of bicyclo[2.2.2]oxime **11**. This compound is ultimately derived from the known 6-keto-bicyclo[2.2.2]octanol **8**. Compound **8** is obtained from baker's yeast reduction of bicyclo[2.2.2]-octanedione **7**.[8d,9]

The principal advantage to starting the synthesis with bicyclo-[2.2.2]octanedione (**7**) was its known desymmetrization, which sets all of the stereocenters of the final compound[9d] (Scheme 3). Since this is a reductive desymmetrization, theoretically either enantiomer of **1** could be produced by manipulating the oxidation state of the alcohol or ketone functionality of **8**. Because baker's yeast selectively reduces the pro-*R* carbonyl group, which ultimately must participate in the Beckmann rearrangement to produce the desired enantiomer of **1**, our synthesis required protection of the remaining ketone and reoxidation of the secondary alcohol. Attempts to directly ketalize **8** with ethylene glycol and catalytic *p*-toluenesulfonic acid ($PhCH_3$, reflux) resulted in extensive retro-aldol reaction with subsequent ketal/acetal formation and very little formation of the desired ketal. This side reaction was circumvented by benzoylating the alcohol before ketalization under these conditions. Removal of the benzoyl group provided **9** in good overall yield from **8**. Oxidation to the ketone with NMO and catalytic TPAP[10] produced **10** in quantitative yield.

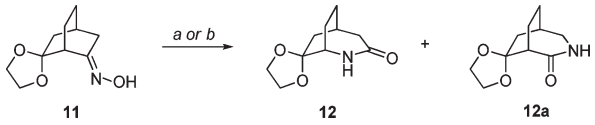
Formation of the oxime and subsequent Beckmann rearrangement required some optimization to ensure reproducibly high yields and regioselectivity in the production of the bicyclo [3.2.2] azepinone **12** (Scheme 4). Refluxing a solution of **10**, hydroxylamine hydrochloride, and sodium acetate in methanol led exclusively to the desired *trans* oxime **11** as a viscous oil. However, it was discovered that this isomer slowly equilibrates to a 2:1 mixture of the *trans* and *cis* oximes over several days at room temperature. Heating this mixture in refluxing ethanol for 30 min afforded the *trans* oxime **11** in quantitative yield.

Scheme 3. Conversion to Oxime[a]



[a] Reagents and conditions: (a) baker's yeast;[9d] (b) BzCl, DMAP, CH_2Cl_2; (c) ethylene glycol, cat. pTsOH, $PhCH_3$, reflux; (d) LiOH, water, THF; (e) TPAP, NMO, 4 Å sieves, MeCN; (f) hydroxylamine HCl, NaOAc, MeOH.

Scheme 4. Beckmann Rearrangement[a]



[a] Reagents and conditions: (a) TsCl, Pyr, 0−55 °C, 9 M H_2SO_4; (b) TsCl, Et_3N, CH_2Cl_2, −10 to 0 °C, SiO_2, MeOH, Pyr. Condition (a) produces both lactam **12** and lactam **12a** (12/12a = 8/1 to 2/1, 62−78% yield). Condition (b) produces exclusively lactam **12**, in 62% yield.

Initially the Beckmann rearrangement was effected with TsCl in pyridine at 0 °C followed by warming to 55 °C for 1 h (Scheme 4). Acid-catalyzed hydrolysis (9 M H_2SO_4, water) of the intermediate pyridinium imine gave rise to lactam **12** (62−78%). On scales of up to 1 g of oxime **11**, this method produced a favorable 8:1 ratio of the desired 3-oxo-lactam **12** to the undesired 2-oxo-lactam **12a**. However, scaling this procedure to 3−5 g resulted in severe erosion of this ratio to 2:1. We hypothesized that the longer heating times necessitated by larger reaction volumes enabled the intermediate anti tosyloxime to undergo an acid-catalyzed, nucleophilic oxime isomerization, producing the undesired lactam isomer **12a**.[11] Consistent with this hypothesis, conducting the Beckmann rearrangement at room temperature over extended periods of time (48 h) produced the desired lactam **12** as the sole product.

Capitalizing on these observations, we developed conditions more amenable to large scale reactions. Treating oxime **11** with Et_3N in CH_2Cl_2 at −10 to 0 °C to form the intermediate tosyloxime, followed by treatment with SiO_2, MeOH, and finally 1.1 equiv of pyridine at room temperature consistently produced the desired 3-oxo-lactam **12** in 62% yield, as the exclusive lactam product. The absolute configuration of lactam **12** was verified by single crystal X-ray diffraction studies of its thioamide derivative, produced by treating **12** with Lawesson's reagent in dioxane.[12]

Conversion of lactam **12** to CBZ protected amine **13** was achieved in 86% overall yield through amide reduction followed by protection of the intermediate secondary amine (Scheme 5). Direct manipulation of the spiroketal to produce the methyl enol ether failed to give the desired product; therefore, a three-step process was developed. Cleavage of the dioxolane with 80% formic acid at room temperature afforded the corresponding

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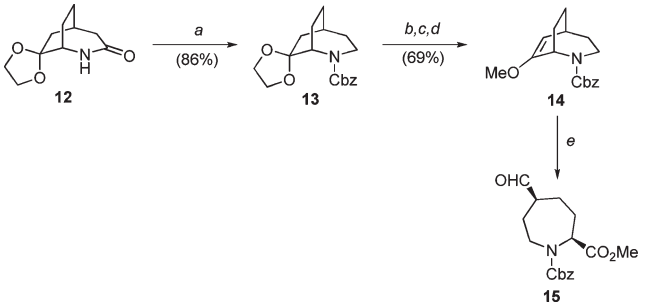
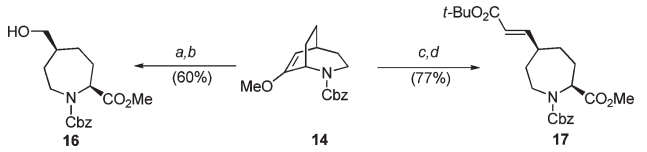
Scheme 5. Formation of Enol Ether and Ozonolysis[a]



[a] Reagents and conditions; (a) $LiAlH_4$, THF, 50 °C, then CbzCl, K_2CO_3 in MeOH; (b) 80% HCO_2H, water; (c) p-TsOH, $HC(OMe)_3$, anhyd. MeOH; (d) Ac_2O, $FeCl_3$, 0 °C; (e) O_3, 1 equiv of MeOH in CH_2Cl_2, −78 °C, Ph_3P or Me_2S.

Scheme 6. In Situ Aldehyde Conversion[a]



[a] Reagents and conditions: (a) O_3, 1 equiv of MeOH in CH_2Cl_2, −78 °C, Ph_3P; (b) $NaBH_4$, MeOH; (c) O_3, 1 equiv of MeOH in CH_2Cl_2, −78 °C, Me_2S; (d) Ph_3PCHCO_2t-Bu, THF, rt.

ketone in 80% yield. Initial attempts to directly convert this ketone to the enol-ether **14** (*p*-TsOH, MeOH, or TMSOTf with trimethyl orthoformate) were unsuccessful, resulting in mixtures of ketone and dimethyl ketal. However, intentional conversion of the ketone to its dimethyl ketal could be achieved with methanol, *p*-toluene sulfonic acid, and trimethyl orthoformate in 94% yield. Subsequent treatment of the dimethyl ketal with anhydrous ferric chloride in acetic anhydride smoothly afforded the desired enol-ether **14** in 92% isolated yield.[13,14]

Ozonolysis of **14**, followed by reduction of the ozonide with either triphenylphosphine or dimethyl sulfide afforded (2*S*,5*S*)-carboxaldehyde **15** in >75% crude yield. However, due to instability upon purification, aldehyde **15** was immediately converted to more stable functionalized derivatives as outlined in Scheme 6. For example, **15** was immediately reduced ($NaBH_4$, MeOH) to provide alcohol **16** in 60% overall yield from **14**. Alternatively, aldehyde **15** could be homologated in situ with *tert*-butyloxycarbonyl-triphenylphosphorane to give diester **17** in 77% overall yield from **14**.

In summary, we have devised a robust asymmetric synthesis of (2*S*,5*S*)-5-substituted-azepane-2-carboxylate derivatives that proceeds in 12 steps and in 17−22% overall yield from known hydroxy-ketone **8**. This synthesis has been successfully scaled to prepare multigram quantities of the key intermediate enol-ether **14** and represents a practical alternative to other methods for preparing these complex cyclic amino acids. Furthermore, access to aldehyde **15** enabled late stage elaboration at C5 to facilitate SAR development.

EXPERIMENTAL SECTION

The full experimental details and characterization data for the conversion of compound **8** to compound **14** are found in the Supporting Information.

1-Benzyl-2-methyl-(2*S*,5*S*)-5-(hydroxymethyl)azepane 1,2-Dicarboxylate (16). Compound **14** (220 mg, 0.766 mmol) was dissolved in 5 mL of CH_2Cl_2 containing 32 μL of MeOH in a round-bottomed flask. The solution was cooled to −78 °C (reaction becomes slightly turbid) and ozone was bubbled into the reaction mixture until a pale blue color was sustained. The mixture was stirred for 15 min at −78 °C, then the excess ozone was discharged by using a stream of nitrogen until the blue color was completely dissipated. The mixture was treated with Ph_3P (393 mg, 1.5 mmol), stirred for 5 min at −78 °C, and warmed to room temperature. After the solution was stirred for 3 h at rt, the CH_2Cl_2 was removed under a stream of nitrogen and the residue was dissolved in 4 mL of MeOH. The mixture was treated with $NaBH_4$ (56.7 mg, 1.96 mmol) in a single portion. The mixture was stirred for 2 h at room temperature, the volatiles were removed in vacuo, and the residue was partitioned between saturated $NaHCO_3$ and ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to a colorless oil. The crude material was purified over silica gel eluting with ethyl acetate/hexane to give 153 mg (60%) of **16** as a colorless oil: $[\alpha]_D$ −30.8 (*c* 1.22, $CHCl_3$); IR (film) 1740, 1686, 1416, 1248, 1198, 1176, 1022, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.28 (m, 5 H), 5.25−5.03 (m, 2 H), 4.76 (dd, *J* = 5.4, 8.3 Hz, 1 H), 4.59 (dd, *J* = 5.0, 8.3 Hz, 1 H), 3.82−3.69 (m, 3 H), 3.65−3.45 (m, 4 H), 2.20−2.03 (m, 1 H), 2.04−1.67 (m, 4 H), 1.59−1.35 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) (observed) δ 173.0, 172.9, 156.6, 156.0, 136.8, 136.7, 128.7, 128.6, 128.2, 128.0, 127.9, 67.6, 67.6, 66.4, 66.3, 59.4, 59.0, 52.3, 52.2, 43.0, 42.7, 40.0, 39.7, 30.6, 27.6, 27.2, 26.5; HRMS calcd for $C_{17}H_{24}NO_5$ [M + H] 322.1654, found 322.1644.

1-Benzyl-2-methyl-(2*S*,5*S*)-5-[(1*E*)-3-*tert*-butoxy-3-oxo-prop-1-en-1-yl]azepane 1,2-Dicarboxylate (17). Compound **14** (0.400 g, 1.39 mmol) was dissolved in 5 mL of CH_2Cl_2 containing 56 μL of MeOH in a round-bottomed flask. The mixture was treated with ozone as described above. Following the ozonolysis, the mixture was treated with Me_2S (0.501 mL, 6.96 mmol). After being stirred for 5 min at −78 °C, the mixture was warmed to room temperature and stirred for 2 h. The volatiles were removed under a stream of nitrogen. The residue was placed under high vacuum for 10 min and was dissolved in 4 mL of dry THF. The mixture was treated with *tert*-butyl triphenylphosphoranylidene-acetate (576 mg, 1.53 mmol) at room temperature then stirred for 22 h, and the volatiles were removed in vacuo. The crude material was purified over silica eluting with ethyl acetate/hexane to give 449 mg (77%) of **17** as a colorless oil: $[\alpha]_D$ −12.4 (*c* 1.43, $CHCl_3$); IR (film) 1746, 1699, 1414, 1150, 981, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5 H), 6.81 (ddd, *J* = 3.7, 5.8, 15.9 Hz, 1 H), 5.71 (ddd, *J* = 1.7, 11.0, 15.9 Hz, 1 H), 5.21−5.05 (m, 2 H), 4.70 (dd, *J* = 5.6, 10.3 Hz, 0.5 H), 4.55 (dd, *J* = 5.1, 10.0 Hz, 0.5 H), 3.80−3.73 (m, 1 H), 3.72 (s, 2 H), 3.60 (s, 1 H), 3.49 (ddd, *J* = 3.4, 8.5, 14.9 Hz, 0.5 H), 3.38−3.31 (m, 0.5 H), 2.56−2.49 (m, 1 H), 2.13−2.01 (m, 1 H), 1.97−1.89 (m, 1 H), 1.88−1.70 (m, 4 H), 1.48 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) (observed) δ 173.1, 173.0, 166.2, 166.1, 156.6, 156.0, 150.4, 136.8, 136.7, 128.7, 128.6, 128.2, 128.1, 127.9, 127.8, 122.9, 122.8, 80.6, 67.6, 67.6, 59.3, 58.9, 52.4, 52.2, 41.7, 41.4, 38.7, 38.3, 33.1, 33.0, 30.1, 29.7, 28.3, 26.2, 25.9; ^1H NMR (600 MHz, DMSO-d_6 at 110 °C) (rotamers resolved) δ 7.41−7.27 (m, 5 H), 6.76 (dd, *J* = 6.1, 15.9 Hz, 1 H), 5.72 (dd, *J* = 1.5, 15.9 Hz, 1 H), 5.17−5.04 (m, 2 H), 4.59 (dd, *J* = 5.1, 8.7 Hz, 1 H), 3.67−3.56 (m, 4 H), 3.55−3.43 (m, 1 H), 2.91 (s, 1 H), 2.08−1.92 (m, 2 H), 1.86−1.77 (m, 1 H), 1.76−1.58 (m, 3 H), 1.46 (s, 9 H); ^{13}C NMR (151 MHz, DMSO-d_6 at 110 °C) (rotamers resolved) δ 171.4, 164.5, 154.8, 150.2, 136.3, 127.6, 127.1, 126.7, 121.4, 79.1, 66.0, 58.1, 51.0, 41.2, 37.5, 32.0, 28.9, 27.3, 25.3; HRMS calcd for $C_{23}H_{31}NO_6Na$ [M + Na] 440.2043, found 440.2041.

ASSOCIATED CONTENT

Supporting Information. A Complete description of experimental details, product characterization data, copies of

proton and carbon NMR spectra, and single crystal X-ray data are included. This material is available free of charge via the Internet at http://pubs.acs.org."

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(12) For a single crystal (0.32 × 0.18 × 0.14 mm^3) of (1*S*,5*S*)-3*H*-spiro[4-azabicyclo[3.2.2]nonane-6,2′-[1,3]dioxolane]-3-thione, X-ray intensity data were collected at 299 K on a Bruker-AXS APEX2 diffractometer. A total of 1919 independent reflections were observed. Laue symmetry revealed an orthorhombic crystal system with the following unit cell dimensions: a = 6.9899(2) Å, b = 22.4792(7) Å, c =6.8185(3) Å; volume = 1071.37(7) $Å^3$; Z = 4; D_{calc} = 1.322 Mg/m^3. The space group was assigned as $P2_12_12$. The structure was solved by direct methods, using the SHELXTL suite. All non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atom located on N2 was found from the Fourier difference map and refined freely. All remaining hydrogen atoms were fixed in idealized positions. The final model refined to a goodness fit of 1.148 with R1 = 0.0778 ($I > 2\sigma$) and wR2 = 0.1614. Absolute configuration was assigned based on a Flack parameter of 0.01(3).

(13) We gratefully acknowledge Professor E .J. Corey for the extremely useful and timely suggestion of these reaction conditions.

(14) Failure to deactivate the silica gel (0.5−1.0% Et_3N) used in the final purification of **14** results in significant disproportionation on the column to give mixtures of compound **14**, dimethyl ketal, and ketone.