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Synthesis of Functionalized Piperidinones

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A versatile, stereoselective synthesis of 5-hydroxypiperidinones with substituents at N1, C3, and C6 has been developed. The sequence involves ring-closing metathesis of a diene amide and epoxidation of the resulting alkene, followed by base-mediated elimination, and finally hydrogenation.

Introduction

5-Hydroxypiperidinones of the general type **1** are reported to be inhibitors of HIV proteases.[1] Their design is based on the well-studied C2 symmetric cyclic ureas (e.g., **2** and ring-contracted derivatives of type **3**) developed in the laboratories of Dupont-Merck.[2,3] Heterocycles of this type take advantage of the C2 symmetry of HIV protease and can be viewed as being mimics of extended protease inhibitors[4] in which the ring substituents act as the P1, P1′, P2, and P2′ binding groups (see Figure 1).[5] As might be expected, the most potent inhibitors of this type have aryl groups at all available positions.[1,2]

Compounds of type **1** offer some possible advantages over **2** and **3**. For example, the lack of C2-symmetry in these compounds is likely to impart physical and chemical properties such as improved solubility relative to the cyclic ureas. These compounds also offer greater flexibility and ease of incorporation of substituents to allow optimization of interactions with the enzyme. Despite this potential, little work has been reported on the synthesis of 5-hydroxypiperidinones of type **1**.[1,6] Here we report of a general synthetic method for accessing functionalized 5-hydroxypiperidinones with stereochemical control at C5 and C6 (anti as in **23** and **24**). Existing methods rely on the construction of a suitable linear precursor followed by cyclization,[1] or alternatively, an extended sequence using a vinylogous Mannich reaction as a key step.[6]

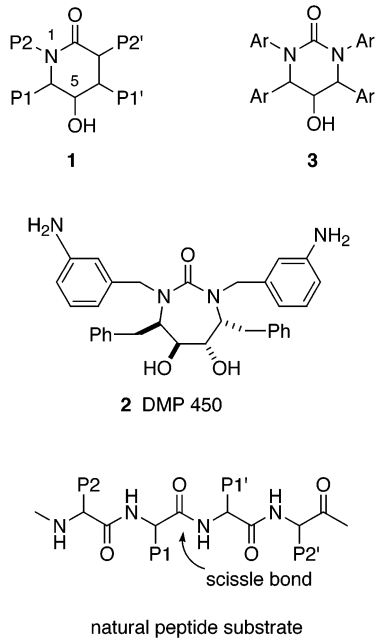

FIGURE 1. Comparison of cyclic HIV protease inhibitors and a natural peptide substrate depicting the P1−P*n* and P1′−P*n*′ (Schechter−Berger) nomenclature.[5]

Results and Discussion

Our synthetic strategy to this class of compound is centered on ring-closing metathesis (RCM) of a suitably substituted diene (see **7** and **17**) to give a piperidenone (see **8** and **18** and **19**), followed by introduction of the hydroxyl group at C5 in two steps. In the first instance we chose to establish this approach by the construction of the basic 5-hydroxypiperidinone skeleton (Scheme 1). The racemic diene **7**, derived as a complex mixture (by ^{1}H and ^{13}C NMR) of rotamers from the condensation of (±)-2-benzylbut-3-enoyl chloride **6**[7] with *N*-benzylprop-2-enylamine **4**,[8] was treated with Grubbs' ruthenium

(1) De Lucca, G. V. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 501.

(2) (a) Lam, P. Y. S.; Ru, Y.; Jadhav, P. K.; Aldrich, P. E.; De Lucca, G. V.; Eyermann, C. J.; Chang, C.-H.; Emmett, G.; Holler, E. R.; Daneker, W. F.; Li, L.; Confalone, P. N.; McHugh, R. J.; Han, Q.; Markwalder, J. A.; Seitz, S. P.; Sharpe, T. R.; Bacheler, L. T.; Rayner, M. M.; Klabe, R. M.; Shum, L.; Winslow, D. L.; Kornhauser, D. M.; Jackson, D. A.; Erickson-Viitanen, S.; Hodge, C. N. *J. Med. Chem.* **1996**, *39*, 3514. (b) Hodge, C. N.; Aldrich, P. E.; Bacheler, L. T.; Chang, C.-H.; Eyermann, C. J.; Garber, S.; Grubb, M.; Jackson, D. A.; Jadhav, P. K.; Korant, B.; Lam, P. Y. S.; Maurin, M. B.; Meek, J. L.; Otto, M. J.; Rayner, M. M.; Reid, C.; Sharpe, T. R.; Shum, L.; Winslow, D. L.; Erickson-Viitanen, S. *Chem. Biol.* **1996**, *3*, 301.

(3) De Lucca, G. V.; Liang, J.; De Lucca, I. *J. Med. Chem.* **1999**, *42*, 135.

(4) Cohen, J. *Science* **1996**, *272*, 1880.

(5) Note the use of Schechter−Berger nomenclature [Schechter, I.; Berger, A. *Biochem. Biophys. Res. Commun.* **1967**, *27*, 157]. The residues on the N-terminal side of the peptide bond that is cleaved are denoted (in order) P1−P*n*, and those on the C-terminus are denoted P1′−P*n*′. In turn, the corresponding subsites on the enzyme are denoted S*n*−S*n*′

(6) Battistini, L.; Rassu, G.; Pinna, L.; Zanardi F.; Casiraghi, G. *Tetrahedron: Asymmetry* **1999**, *10*, 765.

(7) Rajendra, G.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 4471.

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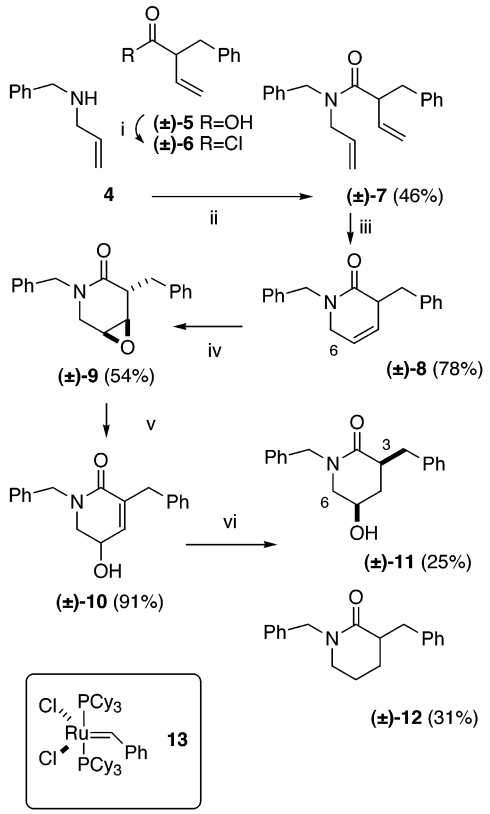
SCHEME 1[a]

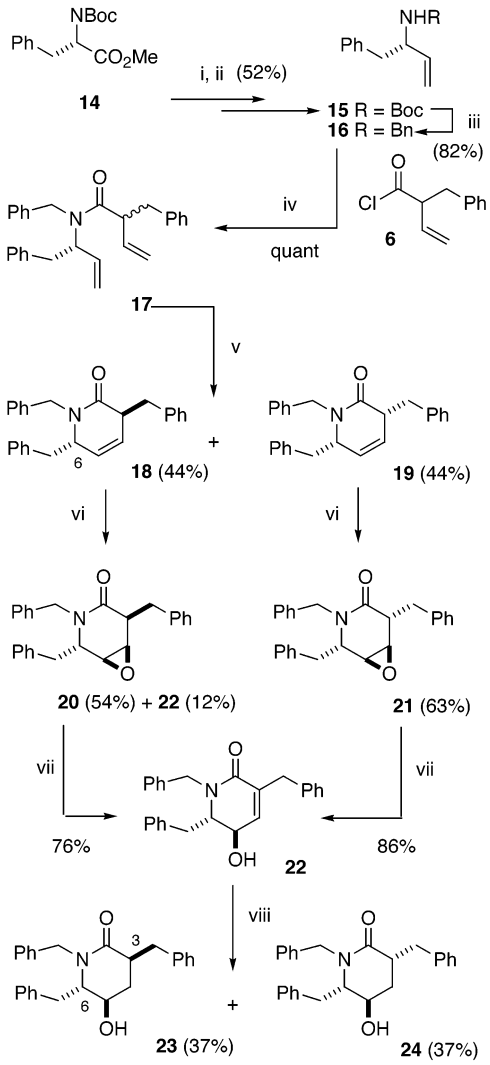


[a] Reagents and conditions: (i) $(COCl)_2$, DMF (cat.), ether, 0 °C (ref 7); (ii) DCM, rt; (iii) **13**, DCM, reflux; (iv) Oxone, $NaHCO_3$, Me_2CO, H_2O; (v) LDA, THF, −78 °C; (vi) Pd/C, H_2, EtOAc.

catalyst **13**[9] to give (±)-**8** in 78%. Introduction of the hydroxy group at C5 was then achieved by an epoxidation/elimination sequence (see steps iv and v). To this end, (±)-**8** were treated with dimethyl dioxirane generated in situ from Oxone,[10] to give (±)-**9** and the corresponding racemic syn diastereoisomer (9:1 by ^{1}H NMR, 77%). Recrystallization of this mixture gave pure (±)-**9** in 54%, the relative configuration of which was confirmed by X-ray crystallography (see Supplementary Information). Opening the epoxide of (±)-**9** on treatment with LDA at −78 °C gave the allylic alcohols (±)-**10**, the structures of which were also corroborated by X-ray crystallography (see Supplementary Information). In the final step the allylic alcohols **10** were reduced with hydrogen and Pd on C to give the desired 5-hydroxypiperidinones (±)-**11**[11] and a derivative [(±)-**12**] in which the C5 hydroxyl group had been removed. With this sequence in hand we next turned our attention to the synthesis of 5-hydroxypiperidin-2-ones with C5 and C6 substituents (Scheme 2).

The key starting allylamine **16** required for this series of reactions was conveniently derived from the *N*-Boc-protected L-phenylalanine methyl ester in three steps. Reduction of **14** with DIBAL to the aldehyde, followed by immediate Wittig olefination[12] with $Ph_3P^+CH_3Br^-$ and KHDMS gave allyl carbamate **15**. Alkylation of carbamate **15** with benzyl bromide and sodium hydride followed by treatment with TFA provided the allyl amine **16** (steps i−iii, Scheme 2). Acylation of the amine **16** with acid chloride **6**[7] afforded the key diene **17** as a mixture of epimers. Cyclization of **17**, on treatment with Grubbs' ruthenium catalyst **13**, afforded the key intermediates **18** and **19** in a ratio of 1:1 by ^{1}H NMR.[13] The diastereoisomers were readily separated by silica gel flash column chromatography, and the stereochemistry of compound **19** was confirmed as shown by X-ray crystallography (see Supplementary Information).

SCHEME 2[a]



[a] Reagents and conditions: (i) DIBAL, toluene, −78 °C; (ii) Ph_3PMeBr, KHMDS, THF, −78 °C; (iii) NaH, BnBr, DMF/THF, 0 °C followed by TFA, DCM; (iv) DCM, rt; (v) **13**, DCM reflux; (vi) Oxone, $NaHCO_3$, Me_2CO, H_2O; (vii) LDA, THF, −78 °C; (viii) Pd/C, H_2, EtOAc.

(8) Kaafarani, M.; Crozet, M. P.; Surzur, J.-M. *Bull. Chim. Fr.* **1981**, *2*, 449.

(9) Nguyen, S. T.; Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974. For a related cyclization, see: Sauriat-Dorizon, H.; and Guibé, F. *Tetrahedron. Lett.* **1998**, *39*, 6711.

(10) Adam, W.; Bialas. J.; Hadjiarapoglou, L. *Chem. Ber.* **1991,** *124*, 2377.

(11) Reduction is assumed to occur from the face opposite the hydroxyl group. Compare compound **23**.

(12) Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487.

(13) Both **18** and **19** gave readily assignable ^{1}H NMR spectra; however, the precursor acyclic amide **17** was observed as a complex mixture of epimers and rotamers.

Introduction of the hydroxy group at C5 was achieved as before by epoxidation followed by ring opening to give the allylic alcohol **22**. To minimize eclipsing interactions, compound **18** is likely to exist as a somewhat flattened boat. Epoxidation of this was expected to proceed anti to the pseudoaxial C6 benzyl group.[14] A similar outcome was also predicted for **19**, which would be expected to have an even stronger facial selectivity. The result from both series would be epoxides with the same relative stereochemistry at C5 and C6 (see **20** and **21**) whereby the configuration at C6 is defined by the starting amino acid **14**. Base-mediated ring opening of each of these epoxides would then be expected to give the same allylic alcohol **22**.

Thus, separate treatment of the diastereoisomers **18** and **19** with dimethyl dioxirane generated in situ from Oxone[10] gave epoxides **20** and **21**, respectively. It should be noted that **21** has the same C3, C4, and C5 relative configuration as the epoxide **9** from the earlier series (see Scheme 1). As expected, treatment of **20** and **21** with LDA gave a single allylic alcohol, assigned as **22**. This result also served to confirm our prediction of the facial selectivities for the epoxidation of **18** and **19** and underscores the role of minimization of eclipsing interaction between the C6 substituent and the substituent on the amide nitrogen in determining the conformation of compounds **18** and **19**. It should be noted that no other epoxide isomers were detected in the crude ^{1}H NMR spectra of the products from the epoxidation reactions of **18** and **19**. However, 12% of **22** was isolated from reaction of **18**, which accounts for lower yield of epoxide in this sequence as compared to the reaction of **19** (see Scheme 2). The final conversion to the desired 5-hydroxypiperidinone skeleton was achieved by catalytic hydrogenation. To this end, **22** was treated with hydrogen and Pd on C to give **23** (37%) and **24** (37%) without competing catalytic hydrogenolysis as was observed in the analogous reaction of (±)-**10** (see Scheme 1). The assignment of these structures was based on an observed NOE between H3 and H5 for **23** but not **24**.

In conclusion, a versatile synthesis for the preparation of 5-hydroxypiperidinones with functionality at N1, C3 and C6 has been developed beginning with readily available amino acid derivative **16**. A range of optically active amino esters and acid derivatives of general type **6** is available[7] such that the method should provide access to a variety of 5-hydroxypiperidinones with differing substituents at C6 and C3. Ongoing work in this area is focused on the introduction of substituents at C4 and biological testing of these compounds.

Experimental Section

General Methods. Melting points were taken on an electrothermal apparatus and are uncorrected. NMR experiments were performed at either 300 or 500 MHz for ^{1}H NMR and either 75 or 126 MHz for ^{13}C NMR with internal standard TMS (^{1}H NMR) and the solvent signal (^{13}C NMR). Elemental analyses were performed by an elemental analyzer. Optical rotations were obtained on a digital polarimeter and data are reported as $[\alpha]^{20}_D$ (concentration g/100 mL, solvent). All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware, and all solvents were dried and freshly distilled prior to use.

(2*S)-*N*-Allyl-*N*-benzyl-2-benzylbut-3-enamide (7).** Oxalyl chloride (9.91 mL, 113.59 mmol) was added to an ice-cooled solution of **5**[7] (9.92 g, 75.72 mmol) in anhydrous ether (100 mL). After 5 min of stirring at this temperature one drop of DMF was added and the reaction mixture was stirred for a further 3 h at 0 °C. The mixture was allowed to warm to room temperature, and stirring was continued for 16 h. The ether was removed in vacuo to give an orange oil that was distilled in vacuo to give **6** as a pale yellow liquid (7.507 g, 47%). A sample of **6** (3.48 g, 17.96 mmol) was then added to **4**[8] (2.20 g, 14.97 mmol) in anhydrous dichloromethane (25 mL) at 0 °C. The solution was allowed to warm to room temperature and then stirred at this temperature for 16 h. The mixture was diluted with water (30 mL) and dichloromethane (30 mL) and then vigorously stirred for a further 30 min. The organic fraction was separated, and the aqueous phase was back-extracted with dichloromethane (3 × 30 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated in vacuo to give a yellow oil that was purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate (9:1) to give **7** as straw colored oil (2.10 g, 46%): ν_{max} cm^{-1} 1651 and 1634; ^{1}H NMR mixture of rotamers (300 MHz, $CDCl_3$) δ 2.84 (1H, m), 3.26 (1H, dd, J = 8.8 and 13.2 Hz), 3.57 (1H, m), 3.70 (1H, dd, J = 6.3 and 15.1 Hz), 3.78 (1H rotamer A, dd, J = 6.3 and 15.1 Hz), 4.15 (1H rotamer B, dd, J = 5.4, 15.1 Hz), 4.23 and 4.44 (2H rotamer B, ABq, J = 17.1 Hz), 4.51 and 4.61 (2H rotamer A, ABq, J = 14.6 Hz), 4.82−5.18 (4H, m), 5.54−5.80 (1H, m), 5.98 (1H, m), 6.91−7.32 (10H, m); ^{13}C NMR mixture of rotamers (126 MHz, $CDCl_3$) δ 39.65, 39.68, 48.55, 48.64, 48.93, 49.47, 49.82, 49.96, 116.94, 116.99, 117.06, 117.60, 126.48, 126.49, 126.52, 127.42, 127.62, 128.29, 128.50, 128.54, 128.69, 129.01, 129.62, 132.97, 133.10, 137.03, 137.39, 137.53, 137.66, 139.64, 139.66, 173.16, 173.44; HRMS calcd for $C_{21}H_{23}NO$ 305.1779, found 305.1771.

(3*S)-1,3-Dibenzyl-3,6-dihydro-1*H*-pyridin-2-one (8).** A solution of **7** (1.00 g, 3.27 mmol) and bis(tricyclohexylphophine)benzylidene ruthenium(IV) dichloride (0.134 g, 0.163 mmol) in anhydrous degassed dichloromethane (150 mL) was heated under reflux for 16 h. The solution was cooled to room temperature, and water (100 mL) was added, followed by vigorous stirring for 30 min. The organic layer was separated, and the aqueous phase was back-extracted with dichloromethane (3 × 50 mL). The combined organic fractions were dried ($MgSO_4$), filtered. and concentrated in vacuo to give a black oil. Spent catalyst was removed by passing the oil through a pad of silica eluting with petroleum ether/ethyl acetate (6:4). The thus obtained residue was purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate (8:2) to give **8** as a straw colored oil (0.704 g, 78%): ν_{max} cm^{-1} 1641; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.08 (1H, dd, J = 8.3 and 13.2 Hz), 3.17 (1H, dd, J = 3.9 and 13.2 Hz), 3.34 (1H, m), 3.34−3.64 (2H, m), 4.52 (1H, d, J = 14.65 Hz), 4.67 (1H, d, J = 14.65 Hz), 5.64 (2H, m), 7.12−7.32 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 38.73 (CH), 42.66, 47.45, 49.31, 120.69, 125.79, 125.84, 126.91, 127.56, 127.61, 128.09, 129.25, 136.10, 137.71, 169.05; HRMS calcd for $C_{19}H_{19}NO$ 277.1468, found 277.1471.

(5*S,6*R**,7*S**)-3,5-Dibenzyl-7-oxa-3-aza-bicyclo[4.1.0]-heptan-4-one (9).** To a solution of **8** (1.50 g, 5.42 mmol) in acetone (50 mL) and water (65 mL) was added sodium hydrogen carbonate (15.50 g, 184.5 mmol). The mixture was stirred vigorously for 10 min at room temperature and then cooled to 0 °C. Oxone (33.3 g, 54.15 mmol) was added portionwise to the reaction mixture, and stirring was continued at 0 °C for 2 h and then at room temperature for 16 h. The mixture was diluted with ethyl acetate (75 mL) and water (50 mL). The organic layer was separated, and the aqueous phase was back-extracted with ethyl acetate (4 × 75 mL). The combined

(14) This premise is supported by molecular modeling. A conformational search using Spartan 5.0, for compound **18** (MMF Force Field, Monte Carlo) indicated that all conformers within 5 kcal/mol of the global minimum had the C6 group in a pseudoaxial position and the C3 group pseudoequatorial.

organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to give a light brown oil. This was purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate (7:3) to give the a 9:1 mixture of the *anti* expoxide **9** and the corresponding *syn* diastereoisomer as cream solid (1.25 g, 77%). This mixture was recrystallized from ethyl acetate/petroleum ether to give **9** as colorless bricks (0.870 g, 54%): ν_{max} cm^{-1} 1645; ^1H NMR (300 MHz, $CDCl_3$) δ 2.47 (1H, d, J = 14.2 Hz), 3.11 (2H, m), 3.13 (1H, m), 3.30 (1H, d J = 14.2 Hz), 3.34−3.38 (2H, m), 4.37 (1H, d, J = 14.6 Hz), 4.54 (1H, d, J = 14.6 Hz), 7.12−7.32 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.52, 44.17, 44.84, 49.64, 49.91, 54.29, 126.89, 127.42, 128.15, 128.35, 128.55, 129.36, 135.99, 136.93, 168.30; HRMS calcd for $C_{19}H_{19}NO_2$ 293.1416, found 293.1423.

(5*R)-1,3-Dibenzyl-5-hydroxy-5,6-dihydro-1*H*-pyridin-2-one (10).** LDA (1.02 mL of a 2 M solution in heptane/THF/ethyl benzene, 2.04 mmol) was added dropwise, over 30 min, to a −78 °C solution of **9** (0.500 g, 1.71 mmol) in anhydrous THF (15 mL) under an atmosphere of argon. The reaction mixture was stirred at −78 °C for 1 h and then warmed to room temperature over 1 h. Water (5 mL) and 10% aqueous HCl (15 mL) and ethyl acetate (15 mL) were added, and the mixture was vigorously stirred for 1 h. The organic phase was separated, and the aqueous phase was back-extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo to a yellow oil that was purified by silica gel column chromatography eluting with petroleum ether/ ethyl acetate (6:4). The resulting white solid (0.460 g, 91%) was recrystallized from ethyl acetate/ether to give **10** as colorless bricks (320 mg, 64%): mp = 99−101 °C; ν_{max} cm^{-1} 3385, 1664, 1612; ^1H NMR (500 MHz, $CDCl_3$) δ 1.98 (1H, brs), 3.34 (1H, dd, J = 4.4 and 13.2 Hz), 3.46 (1H, dd, J = 4.4 and 13.2 Hz), 3.65 (1H, d, J = 15.6 Hz), 3.71 (1H, d, J = 15.6 Hz), 4.20 (1H, m), 4.58 (1H, d, J = 14.6 Hz), 4.69 (1H, d, J = 14.6 Hz), 6.13 (1H, d, J = 4.4 Hz), 7.21−7.33 (10H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 36.91, 50.60, 52.51, 62.41, 126.61, 127.83, 128.36, 128.75, 128.94, 129.63, 135.89. 137.09, 137.70, 138.88, 164.10; HRMS calcd for $C_{19}H_{19}NO_2$ 293.1416, found 293.1417.

(3*S,5*R**)-1,3-Dibenzyl-5-hydroxy-piperidin-2-one (11) and (3*R**)-1,3-Dibenzylpiperidinone (12).** A solution of **10** (0.072 g, 0.25 mmol) in ethyl acetate (10 mL) was vigorously stirred at room temperature with 10% palladium on carbon (0.010 g) under an atmosphere of hydrogen for 16 h. The reaction mixture was filtered through a pad of Celite and concentrated in vacuo to give a yellow oil. The oil was purified by silica gel column chromatography eluting with petroleum ether/ ethyl acetate (7:3) to give two products. Compound **12** was obtained as a cream solid (33 mg, 31%): ν_{max} cm^{-1} 1635; ^1H NMR (500 MHz, $CDCl_3$) δ 1.42−1.80 (4H, m), 2.65 (1H, br), 2.75 (1H, m), 3.18 (2H, m), 3.45 (1H, m), 4.62 (2H, m), 7.14−7.33 (10H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.82, 26.00, 38.17, 43.75, 47.77, 50.70, 126.35, 127.51, 128.23, 128.56, 128.795, 129.615, 137.61, 140.315, 172.14; HRMS calcd for $C_{19}H_{19}NO$ 279.1638, found 279.1631.

Compound **11** was isolated as a light yellow gum (27 mg, 25%): ν_{max} cm^{-1} 3358, 1616; ^1H NMR (500 MHz, $CDCl_3$) δ 1.44 (1H, m), 1.88 (1H, m), 2.55 (1H, m), 2.72 (1H, dd J = 9.8 and 13.7 Hz), 2.93 (1H, dd J = 8.8 and 11.7 Hz), 3.25 (1H, m), 3.35 (1H, dd J = 3.9 and 13.7 Hz), 3.88 (1H, m), 4.47 (1H, d, J = 14.6 Hz), 4.53 (1H, d, J = 14.6 Hz), 7.11−7.39 (10H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 35.52, 38.05, 41.64, 50.81, 53.71, 65.08, 126.54, 127.77, 128.33, 128.65, 128.90, 129.64, 137.64, 139.74, 171.205; HRMS calcd for $C_{19}H_{21}NO_2$ 295.1572, found 295.1578.

(3*S)-3-Benzylamino-4-phenyl-1-butene (16).** To an ice-cooled solution of methyltriphenylphosphonium bromide (5.119 g, 14.34 mmol) in anhydrous THF (30 mL) was added KHDMS (30.11 mL, 0.5 M solution in toluene, 15.06 mmol). The mixture was cooled to −78 °C over 30 min and *N*-(*tert*-butoxycarbonyl)-L-phenylalaninal[15] in anhydrous THF (30 mL) was added dropwise. Stirring was continued at −78 ° for 2 h and then at room temperature for 16 h. The mixture was diluted with ethyl acetate (150 mL) and water (150 mL), and the organic layer was separated. The aqueous layer was back-extracted with ethyl acetate (3 × 100 mL), and the combined organic fractions were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate (20:3) to give the **15** as a white solid[16] (0.923 g, 52%): $[\alpha]^{20}_D$ = +15.0 (*c* 0.6, $CHCl_3$).

A solution of **15** (900 mg, 3.64 mmol) in anhydrous dichloromethane (15 mL) was added to a suspension of sodium hydride (88 mg, 3.64 mmol) in anhydrous DMF (15 mL) at 0 °C. After 30 min of stirring at 0 °C, benzyl bromide (0.520 mL, 4.37 mmol) was added, the mixture was warmed to room temperature, and stirring was continued at this temperature for 16 h. The mixture was diluted with dichloromethane (50 mL) and saturated aqueous ammonium chloride (80 mL). The organic layer was separated, and the aqueous fraction was back-extracted with dichloromethane (2 × 40 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and evaporated to a cream solid that was purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate (9:1). This material was dissolved in dichloromethane (10 mL), the solution was cooled to 0 °C, and trifluoroacetic acid (8 mL) was added. The mixture was allowed to warm to room temperature with stirring over 24 h. The resulting mixture was diluted with dichloromethane (20 mL), and 2 M aqueous sodium hydroxide was added to give pH 7 (aqueous phase). The organic layer was separated, and the aqueous phase was back-extracted with dichloromethane (3 × 30 mL). The combined organic fraction was dried ($MgSO_4$), filtered, concentrated and then purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate (8:2) to give **16** (550 mg, 82%) $[\alpha]^{20}_D$ = −17.0 (*c* 2, $CHCl_3$); ν_{max} cm^{-1} 3319, 3063, 3026, 2918; ^1H NMR (500 MHz, $CDCl_3$) δ 2.75 (1H, dd J = 8.8 and 13.2 Hz), 2.79 (1H, dd J = 5.9 and 13.2 Hz), 3.30 (1H, m), 3.59 (1H, d J = 13.2 Hz), 3.81 (1H, d J = 13.2 Hz), 5.11 (2H, m), 5.71 (1H, m), 7.14−7.34 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.43, 51.09, 61.85, 116.30, 126.32, 126.735, 127.95, 128.30, 128.35, 129.39, 138.47, 140.41, 140.64; HRMS calcd for $C_{17}H_{19}N$ 238.1596, found 238.1593.

(3*S*,6*S*)-(1,3,6)-Tribenzyl-3,6-dihydro-1*H*-pyridin-2-one (18) and (3*R*,6*S*)-Tribenzyl-3,6-dihydro-1*H*-pyridin-2-one (19). A solution of **16** (0.940 g, 3.97 mmol) in anhydrous dichloromethane (10 mL) was added to an ice-cooled and stirred solution of **6** (0.835 g, 3.97 mmol) in anhydrous dichloromethane (20 mL). The mixture was allowed to warm to room temperature, and stirring was continued for 16 h. Saturated aqueous sodium hydrogen carbonate (100 mL) and dichloromethane (50 mL) were added, and the resulting mixture was vigorously stirred for 30 min. The organic layer was separated and the aqueous phase was back-extracted with dichloromethane (3 × 100 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate (20:3) to give **17** as a colorless oil (1.560 g, quant): ν_{max} cm^{-1} 1649, 1631; ^1H NMR (500 MHz; $CDCl_3$) complex mixture that was unable to be assigned; HRMS calcd for $C_{28}H_{31}NO$ 395.2249, found 395.2237. To a solution of **17** (1.40 g, 3.54 mmol) in anhydrous dichloromethane (30 mL) was added bis(tricyclohexylphosphine) benzylidine ruthenium(IV) dichloride (Grubb's catalyst) (146 mg, 1.77 mmol), and the mixture was heated to reflux for 16 h. Additional catalyst was added and refluxing was continued for a further 24 h. The mixture was diluted with dichloromethane (50 mL) and water (150 mL), and the organic fraction was separated. The aqueous phase was back-extracted with dichloromethane (3 × 70 mL), and the combined organic

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fractions were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate (20:3) to give **18** (573 mg, 44%): $[\alpha]^{20}_D = +1.6$ (*c* 1, $CHCl_3$); ν_{max} cm^{-1} 1641; ^1H NMR (500 MHz, $CDCl_3$) δ 2.49 (1H, m), 2.81 (1H, dd, $J = 3.4$ and 13.7 Hz), 2.90 (2H, m), 3.17 (1H, dd, $J = 4.4$ and 14.2 Hz), 3.93 (1H, m), 3.98 (1H, d, $J = 15.1$ Hz), 5.57 (2H, m), 5.67(1H, d, $J = 15.1$ Hz), 7.00−7.28 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.23, 39.04, 41.52, 46.59, 57.47, 125.06, 126.09, 126.68, 127.21, 127.40, 127.57, 128.09, 128.17, 128.55, 129.60, 129.91, 135.88, 136.81, 138.93, 170.525; *m*/*z* (ES+) MH^+, 368.2 (100%). Further elution gave **19** as a colorless solid (568 mg, 44%), which was recrystallized from ethyl acetate/ petroleum ether to give colorless bricks: $[\alpha]^{20}_D = -109.0$ (*c* 1, $CHCl_3$); mp = 155 °C; ν_{max} cm^{-1} 1639; ^1H NMR (500 MHz, $CDCl_3$) δ 2.15 (2H, m), 2.71 (1H, dd, $J = 3.4$ and 13.2 Hz), 2.96 (1H, dd, $J = 3.9$ and 12.7 Hz), 3.21 (1H, m), 3.93 (1H, m), 4.00 (1H, d, $J = 15.1$ Hz), 5.46 (1H, dd, $J = 3.4$ and 10.7 Hz), 5.51 (1H, dd, $J = 3.4$ and 10.7 Hz), 5.67 (1H, d, $J = 15.1$ Hz), 6.97−7.34 (15H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 39.57, 39.82, 43.77, 46.68, 57.72, 124.89, 126.09, 126.37, 126.74, 127.41, 128.00, 128.15, 128.31, 128.63, 129.60, 129.81, 136.32, 136.90, 138.51, 170.37; *m*/*z* (ES+) MH^+, 368.2 (100%).

(1*S*,2*S*,5*S*,6*R*)-(2,3,5)-Tribenzyl-7-oxa-3-aza-bicyclo[4.1.0]-heptan-4-one (20). To a solution of **18** (333 mg, 0.94 mmol) in acetone (12 mL) and water (10 mL) was added sodium hydrogen carbonate (2.694 g, 32.07 mmol). The mixture was cooled in an ice bath, and Oxone (5.801 g, 9.43 mmol) was added portion-wise over 5 min. The resulting mixture was vigorously stirred at this temperature for 2 h and then at room temperature for 16 h. The majority of acetone was removed under reduced pressure before ethyl acetate (50 mL) and water were added (50 mL). The organic layer was separated, and the aqueous layer was back-extracted with ethyl acetate (4 × 30 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated, and the resulting residue was purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate (10:2) to give **20** as a white solid (189 mg, 54%). $[\alpha]^{20}_D = +68.5$ (*c* 3.3, $CHCl_3$); ν_{max} cm^{-1} 1645; ^1H NMR (500 MHz, $CDCl_3$) δ 1.79 (1H, dd, $J = 3.9$ and 11.2 Hz), 2.73 (1H, dd, $J = 11.2$ and 14.2 Hz), 2.86 (1H, dd, $J = 3.9$ and 14.2 Hz), 2.91 (1H, m), 3.01 (1H, dd, $J = 6.3$ and 14.2 Hz), 3.25 (1H, m), 3.54 (1H, dd, $J = 3.9$ and 13.7 Hz), 3.86 (1H, d, $J = 15.1$ Hz), 3.98 (1H, m), 5.46 (1H, d, $J = 15.1$ Hz), 7.05−7.35 (15H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 34.52, 37.09, 42.54, 48.08, 52.54, 53.09, 55.66, 126.20, 127.21, 127.29, 127.51, 128.39, 128.64, 128.67, 129.20, 129.76, 135.56, 136.41, 139.22, 168.69; HRMS calcd for $C_{26}H_{25}NO_2$ 383.1885, found 383.1881. Compound **22** (12%) was also isolated (data as reported below).

(1*S*,2*S*,5*R*,6*R*)-(2,3,5)-Tribenzyl-7-oxa-3-aza-bicyclo[4.1.0]-heptan-4-one (21). Alkene **18** (228 mg, 0.65 mmol) in acetone (8 mL) and water (7 mL) was treated with sodium hydrogen carbonate (1.845 g, 21.96 mmol) and Oxone (3.972 g, 6.46 mmol) as described for the preparation of **20**. The crude product was purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate (20:3) to give **21** as a white solid (150 mg, 60%): $[\alpha]^{20}_D = -49.3$ (*c* 1, $CHCl_3$); mp = 123−125 °C; ν_{max} cm^{-1} 1643; ^1H NMR (500 MHz, $CDCl_3$) δ 2.30 (2H, m), 2.82 (1H, dd, $J = 3.9$ and 14.2 Hz), 3.08 (1H, dd, $J = 3.9$ and 13.7 Hz), 3.16 (2H, br), 3.29 (1H, m), 3.86 (1H, d, $J = 15.6$ Hz), 3.90 (1H, br), 5.51 (1H, d, $J = 15.6$ Hz), 7.03−7.35 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.19, 37.59, 44.19, 47.72, 52.37, 53.71, 56.14, 126.87, 127.18, 127.39, 127.66, 128.67, 128.75, 128.92, 129.18, 129.38, 136.21, 136.29, 138.24, 168.73; HRMS calcd for $C_{26}H_{25}NO_2$ 383.1885, found 383.1889.

(5*R*,6*S*)-(1,3,6)-Tribenzyl-5-hydroxy-5,6-dihydro-1*H*-pyridin-2-one (22). Route A. A solution of LDA (0.248 mL, 2 M solution in THF/benzene, 0.50 mmol) was added dropwise to a −78 °C stirred solution of **20** (190 mg, 0.50 mmol) in anhydrous THF (10 mL). The mixture was stirred for 2 h at −78 °C and then allowed to warm to room temperature over 16 h. Water (5 mL), ethyl acetate (20 mL), and 10% aqueous HCl (20 mL) were added, and the mixture was vigorously stirred for 20 min. The organic layer was separated, and the aqueous phase was back-extracted with ethyl acetate (4 × 20 mL). The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated to give a residue that was purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate.(7:3) to give **22** as a light yellow oil that crystallized on standing (144 mg, 76%): $[\alpha]^{20}_D = -90.4$ (*c* 1, $CHCl_3$); mp = 130−133 °C; ν_{max} cm^{-1} 3382, 1646, 1608; ^1H NMR (500 MHz, $CDCl_3$) δ 1.80 (1H, br), 2.60 (1H, dd, $J = 8.3$ and 13.7 Hz), 2.80 (1H, dd, $J = 6.3$ and 13.7 Hz), 3.58 (1H, d, $J = 14.6$ Hz), 3.65 (2H, m), 3.76 (1H, d, $J = 15.6$ Hz), 3.88 (1H, m), 5.27 (1H, d, $J = 14.6$ Hz), 6.10 (1H, m), 6.98−7.34 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.78, 38.03, 48.92, 63.57, 63.72, 126.40, 126.93, 127.69, 128.39, 128.54, 128.75, 128.81, 129.10, 129.34, 131.52, 137.02, 137.11, 138.54, 139.05, 162.69; HRMS calcd for $C_{26}H_{25}O_2N$ 383.1885, found 383.1879.

Route B. Epoxide **21** (150 mg, 0.41 mmol) in anhydrous THF (10 mL) was similarly treated with a 2 M solution of lithium diisopropylamide in THF/benzene (0.203 mL, 0.41 mmol) to give **22** as a light yellow oil (81 mg, 54%). Spectroscopic data as above.

(3*S*,5*R*,6*S*)-(1,3,6)-Tribenzyl-5-hydroxy-piperidin-2-one (23) and (3*R*,5*R*,6*S*)-(1,3,6)-Tribenzyl-5-hydroxy-piperidin-2-one (24). A solution of **22** (67 mg, 0.17 mmol) in ethyl acetate (10 mL) was vigorously stirred with 10% palladium on carbon (10 mg) under a atmosphere of hydrogen for 72 h at room temperature. The mixture was filtered through a pad of Celite and concentrated to give a residue that was purified by silica gel column chromatography eluting with petroleum ether/ethyl acetate (7:3) to give two products. Compound **23** was obtained as a colorless oil (25 mg, 37%): $[\alpha]^{20}_D = -62.5$ (*c* 2, $CHCl_3$); ν_{max} cm^{-1} 3351, 1611; ^1H NMR (500 MHz, $CDCl_3$) δ 1.71 (1H, s), 1.78 (2H, m), 2.14 (1H, dd, $J = 9.3$ and 14.2 Hz), 2.71 (1H, dd, $J = 5.4$ and 14.2 Hz), 3.00 (2H, m), 3.21 (1H, dd, $J = 3.4$ and 12.2 Hz), 3.39 (1H, m), 3.73 (2H, m), 5.45 (1H, d, $J = 15.1$ Hz), 6.93−7.33 (15H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.17, 37.65, 37.72, 39.24, 48.51, 63.80, 64.76, 126.38, 126.82, 127.37, 128.03, 128.34, 128.59, 128.73, 128.81, 129.67, 137.24, 137.31, 138.28, 171.42; HRMS calcd for $C_{25}H_{27}NO_2$ 385.2042, found 385.2031**.** Compound **24** was obtained as a white gum (25 mg, 37%). $[\alpha]^{20}_D = +10.9$ (*c* 2, $CHCl_3$); ν_{max} cm^{-1} 3393, 1602; ^1H NMR (500 MHz, $CDCl_3$) δ 1.25 (1H, br), 1.62 (1H, m), 2.01 (1H, ddd $J = 4.4$, 7.8 and 14.65 Hz), 2.57 (1H, m), 2.71 (1H, dd, $J = 8.3$ and 13.7 Hz,), 2.85 (1H, dd, $J = 10.2$ and 13.7 Hz), 2.97 (1H, dd, $J = 4.9$ and 13.7 Hz), 3.45 (1H, dd, $J = 4.4$ and 7.8 Hz), 3.48 (1H, dd, $J = 4.4$ and 13.7 Hz), 3.80 (1H, m), 3.81 (1H, d, $J = 14.6$ Hz), 5.46 (1H, d, $J = 14.6$ Hz), 7.05−7.34 (15H, m); ^{13}C NMR (126 MHz, $CDCl_3$) δ 29.95, 38.41, 38.57, 39.37, 48.31, 64.09, 66.75, 126.19, 126.95, 127.51, 128.19, 128.39, 128.69, 128.82, 129.06, 129.49, 137.04, 137.15, 140.06, 172.28; HRMS calcd for $C_{26}H_{27}NO_2$ 385.2042, found 385.2045.

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Supporting Information Available: Details of the crystal structure analyses of **9**, **10**, and **19**. NMR spectra of compounds **7**−**12**, **16**, and **18**−**24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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