Synthesis of an Optically Active, Bicyclic 2-Pyridone Dipeptide Mimetic

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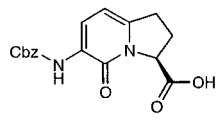
The eleven-step preparation of the bicyclic 2-pyridone dipeptide mimetic **1** [(3*S*)-6-(benzyloxycarbonylamino)-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylic acid] in optically active form (60% ee) is described. Key steps in the synthesis of **1** include the osmium-catalyzed asymmetric dihydroxylation of olefin **13** [(6-but-3-enyl-2-methoxypyridin-3-yl)carbamic acid benzyl ester] and the intramolecular cyclization of protected diol **19** [(3′*R*)-{6-[4′-(*tert*-butyldimethylsilanyloxy)-3′-hydroxybutyl]-2-methoxypyridin-3-yl}carbamic acid benzyl ester] to afford the pyridinium salt **20** [(3*S*)-[3-(*tert*-butyldimethylsilanyloxymethyl)-5-methoxy-2,3-dihydro-1*H*-indolizin-6-yl]carbamic acid benzyl ester trifuoromethanesulfonic acid salt]. Several alternate methods to prepare olefin **13** are also discussed.

Introduction

The synthesis of rigid, non-peptidic chemical entities intended to mimic portions of biologically important peptides has been an area of increasing research in recent years.[1] Many examples of such peptide mimetics have been prepared by a number of research groups and evaluated for both their ability to duplicate a given peptidic structure[2] (e.g., β-turn) and to function as an effector of some targeted biological activity[3] (e.g., enzyme inhibition). Despite the considerable research conducted in this area to date, there is still a need to prepare additional novel chemical structures which can position peptide-related functional groups in spatially restricted locations. Such structures would allow for additional mimicry of certain peptide conformations and may possess uniquely beneficial physical properties which differ from those of existing peptide mimetics. Accordingly, we recently desired to synthesize the bicyclic 2-pyridone **1** for incorporation into potential peptide-based inhibitors of the human rhinovirus 3C protease. To the best of our knowledge, no synthesis of **1** has been reported to date, although preparations of the structurally related bicyclic pyrimidinones **2**[4] and **3**,[5] and the indolizidinone **4**[6] have been detailed. In this report, we describe an efficient synthesis of **1** which affords this peptide mimetic in optically active form (60% ee).



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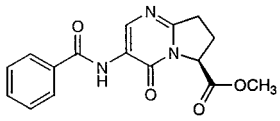

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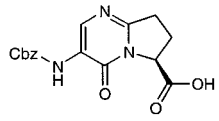

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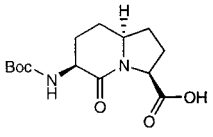

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Results and Discussion

Retrosynthetic analysis (Scheme 1) of **1** suggested that the bicyclic 2-pyridone structure could be arrived at via an intramolecular cyclization event effected on optically active, monoprotected diol **5**. Intermediate **5**, in turn, was envisioned to arise from the asymmetric dihydroxylation of pyridine **6** with subsequent selective protection of the

(1) For recent reviews of peptide mimics, see: (a) Ripka, A. S.; Rich, D. H. *Curr. Opin. Chem. Biol.* **1998**, *2*, 441. (b) Gante, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699. (c) Liskamp, R. M. J. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 1. (d) Adang, A. E. P.; Hermkens, P. H. H.; Linders, J. T. M.; Ottenheijm, H. C. J.; van Staveren, C. J. *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 63. (e) Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bös, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E. *J. Med. Chem.* **1993**, *36*, 3039. (f) Giannis, A.; Kolter, T. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1244. (g) Kahn, M. *Synlett* **1993**, 821.

(2) For some recent examples, see: (a) Johannesson, P.; Lindeberg, G.; Tong, W.; Gogoll, A.; Karlén, A.; Hallberg, A. *J. Med. Chem.* **1999**, *42*, 601. (b) Gosselin, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 7463. (c) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 5937. (d) Reference 6. (e) Siddiqui, M. A.; Préville, P.; Tarazi, M.; Warder, S. E.; Eby, P.; Gorseth, E.; Puumala, K.; DiMaio, J. *Tetrahedron Lett.* **1997**, *38*, 8807. (f) Slomczynska, U.; Chalmers, D. K.; Cornille, F.; Smythe, M. L.; Beusen, D. D.; Moeller, K. D.; Marshall, G. R. *J. Org. Chem.* **1996**, *61*, 1198. (g) Li, W.; Hanau, C. E.; d'Avignon, A.; Moeller, K. D. *J. Org. Chem.* **1995**, *60*, 8155.

(3) For some recent examples, see: (a) Bachand, B.; DiMaio, J.; Siddiqui, M. A. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 913. (b) Boatman, P. D.; Ogbu, C. O.; Eguchi, M.; Kim, H.-O.; Nakanishi, H.; Cao, B.; Shea, J. P.; Kahn, M. *J. Med. Chem.* **1999**, *42*, 1367. (c) Liu, R.; Dong, D. L.-Y.; Sherlock, R.; Nestler, H. P. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 847. (d) Karanewsky, D. S.; Bai, X.; Linton, S. D.; Krebs, J. F.; Wu, J.; Pham, B.; Tomaselli, K. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2757. (e) Wagner, J.; Kallen, J.; Ehrhardt, C.; Evenou, J.-P.; Wagner, D. *J. Med. Chem.* **1998**, *41*, 3664. (f) Dolle, R. E.; Prasad, C. V. C.; Prouty, C. P.; Salvino, J. M.; Awad, M. A. M.; Schmidt, S. J.; Hoyer, D.; Ross, T. M.; Graybill, T. L.; Speier, G. J.; Uhl, J.; Miller, B. E.; Helaszek, C. T.; Ator, M. A. *J. Med. Chem.* **1997**, *40*, 1941.

(4) Bemis, G.; Golec, J. M. C.; Lauffer, D. J.; Mullican, M. D.; Murcko, M. A.; Livingston, D. J. International patent application: WO 95/35308, 1995.

(5) Webber, S. E.; Dragovich, P. S.; Prins, T. J.; Littlefield, E. S.; Marakovits, J. T.; Babine, R. E. U.S. Pat. 5,962,487.

(6) (a) Lombart, H.-G.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 9437. (b) Lombart, H.-G.; Lubell, W. D. *J. Org. Chem.* **1994**, *59*, 6147. (c) Mueller, R.; Revesz, L. *Tetrahedron Lett.* **1994**, *35*, 4091.

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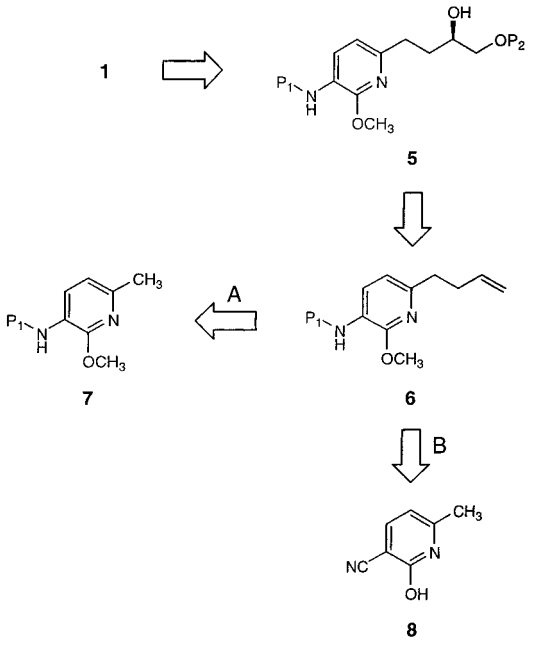
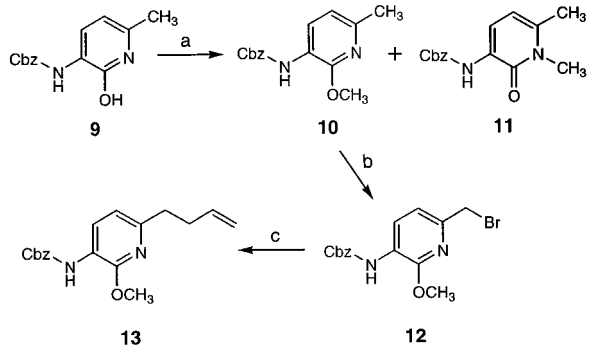
Scheme 1. Retrosynthetic Analysis of Bicyclic 2-Pyridone 1



primary alcohol present in the resulting diol. To complete the retrosynthetic analysis, two approaches were considered for the preparation of pyridine **6**. The first (A) anticipated obtaining **6** from intermediate **7** by either dianion formation and electrophilic allylation or by benzylic halogenation and nucleophilic allylic displacement. The second (B) relied on the known benzylic derivatization of the dianion of 2-hydroxy-6-methylnicotinonitrile (**8**)[7,8] with subsequent transformation of the nitrile functional group. At the outset of our synthetic efforts, it was not known which (if any) of the above approaches would successfully afford the desired peptide mimetic products.

Initially, we chose to examine the synthetic pathway suggested by retrosynthetic analysis A. Accordingly, the known 2-hydroxypyridine **9** was prepared from 2-hydroxy-6-methylpyridine-3-carboxylic acid via Curtius rearrangement followed by condensation of the resulting isocyanate (not shown) with benzyl alcohol (Scheme 2).[9] Selective transformation of **9** to the *O*-methylation product **10** proved to be somewhat challenging. In accordance with literature precedent, derivatization of the sodium salt of **9** with iodomethane afforded the corresponding *N*-alkylation adduct **11** nearly exclusively in 91% yield.[10] Employment of silver-mediated alkylation conditions[11]

Scheme 2[a]



[a] Reagents and conditions: (a) 1.05 equiv of $(CH_3)_3O{\cdot}BF_4$, CH_2Cl_2, 23 °C, 36 h, 92%; (b) 1.4 equiv of NBS, 0.02 equiv of benzoyl peroxide, CCl_4, reflux, 18 h, 12%; (c) 1.0 equiv of $CH_2{=}CHCH_2MgBr$, THF, 0 °C, 10 min, then 2.0 equiv of $CH_2{=}CHCH_2MgBr$, THF, 50 °C, 30 min, 37%.

afforded roughly a 1:1 mixture of the desired **10** and the undesired **11** as qualitatively determined by thin-layer chromatographic analysis. The desired transformation was eventually effected in good yield (92%) by exposure of **9** to trimethyloxonium tetrafluoroborate for 1.5 days at room temperature. The identical reaction conditions were previously employed for the selective *O*-methylation of related 2-hydroxypyridines.[12]

Attempted formation of the dianion of **10** and subsequent benzylic allylation under a variety of conditions were unsuccessful at producing the key olefin intermediate **13**. These failures presumably resulted from the inability of the deprotonated Cbz NH moiety to function as an appropriate activator for benzylic deprotonation.[7] Alternatively, **10** was converted to bromide **12** through a radical halogenation process, and the latter intermediate was transformed into **13** by displacement with allylmagnesium bromide (Scheme 2). Although this sequence successfully provided olefin **13**, it suffered from several drawbacks. First, the radical bromination of **10** to give **12** was a highly variable, often low-yielding reaction that did not transfer well to large scale.[13] Similar difficulties in effecting the radical halogenation of related pyridines have been described in the literature.[11a,b] In addition, the desired bromide **12** was difficult to purify from both the starting material **10** and several reaction side products. Second, the conversion of **12** to **13** also proceeded in low yield, required a somewhat tedious purification process, and was not easily amenable to scale-up. These factors combined to severely limit the throughput of material from the readily available **10** to the desired olefin **13** and prompted us to develop an alternate synthesis of the latter intermediate.

An improved preparation of olefin **13** which eventually provided the bicyclic 2-pyridone **1** was realized by pursuit of the synthesis illustrated in retrosynthetic analysis pathway B (Scheme 1). As depicted in Scheme 3, slow

(7) DeJohn, D.; Domagala, J. M.; Kaltenbronn, J. S.; Krolls, U. *J. Heterocyclic Chem.* **1983**, *20*, 1295, and references therein.

(8) For clarity purposes, several chemical entities are described and depicted as 2-hydroxypyridines rather than the corresponding 2-pyridone tautomers. Single isomers of such compounds were always observed in their ^{1}H NMR spectra, but no attempt was made to rigorously determine the precise structure of these isomers.

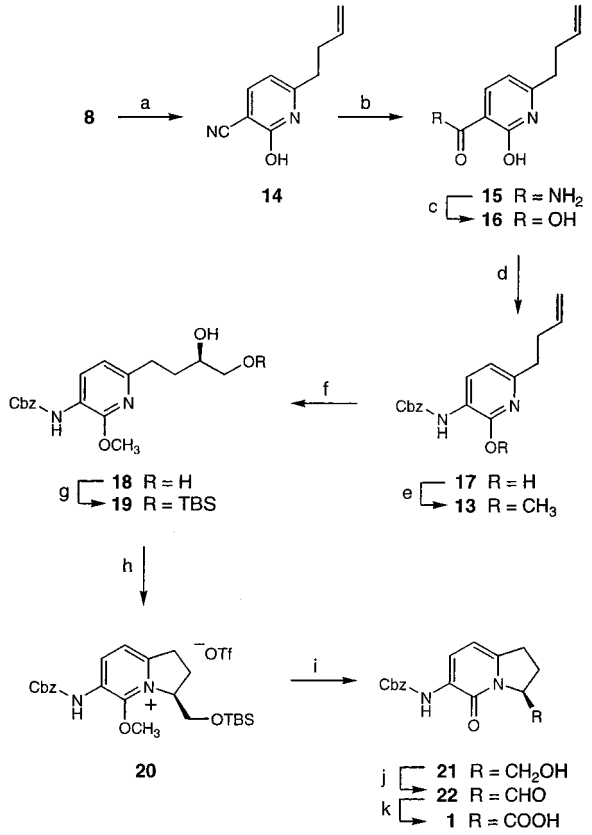
(9) Sanderson, P. E. J.; Lyle, T. A.; Cutrona, K. J.; Dyer, D. L.; Dorsey, B. D.; McDonough, C. M.; Naylor-Olsen, A. M.; Chen, I.-W.; Chen, Z.; Cook, J. J.; Cooper, C. M.; Gardell, S. J.; Hare, T. R.; Krueger, J. A.; Lewis, S. D.; Lin, J. H.; Lucas, B. J., Jr.; Lyle, E. A.; Lynch, J. J., Jr.; Stranieri, M. T.; Vastag, K.; Yan, Y.; Shafer, J. A.; Vacca, J. P. *J. Med. Chem.* **1998**, *41*, 4466. A slightly modified workup procedure was employed in the present work.

(10) For general references on the alkylation of 2-hydroxypyridines, see: (a) Scriven, E. F. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, U.K., 1984; Vol. 2, pp 165−314. (b) Tieckelmann, H. In *Pyridine and Its Derivatives*; Abramovitch, R. A., Ed.; Wiley-Interscience: New York, 1974; Vol. 14, Supplement 3, Chapter 12, pp 597−1180.

(11) For examples of *O*-alkylation of 2-hydroxypyridines effected by silver salts, see: (a) Pomel, V.; Rovera, J. C.; Godard, A.; Marsais, F.; Quéguiner, G. *J. Heterocyclic Chem.* **1996**, *33*, 1995. (b) Gray, M. A.; Konopski, L.; Langlois, Y. *Synth. Commun.* **1994**, *24*, 1367. (c) Carabateas, P. M.; Brundage, R. P.; Gelotte, K. O.; Gruett, M. D.; Lorenz, R. R.; Opalka, C. J., Jr.; Singh, B.; Thielking, W. H.; Williams, G. L.; Lesher, G. Y. *J. Heterocyclic Chem.* **1984**, *21*, 1857. (d) Honma, Y.; Sekine, Y.; Hashiyama, T.; Takeda, M.; Ono, Y.; Tsuzurahara, K. *Chem. Pharm. Bull.* **1982**, *30*, 4314.

(12) Beak, P. B.; Covington, J. B.; Smith, S. G.; White, J. M.; Zeigler, J. M. *J. Org. Chem.* **1980**, *45*, 1354.

Scheme 3[a]



[a] Reagents and conditions: (a) 2.5 equiv of LDA, 1.5 equiv of $CH_2{=}CHCH_2Br$, THF, 0→23 °C, 30 min, 58%; (b) H_2O_2, 1:2 EtOH: 10% NaOH, 50 °C, 18 h, 100%; (c) 10% KOH, reflux, 20 h, 92%; (d) 2.0 equiv of Et_3N, 1.5 equiv of $(PhO)_2P(O)N_3$, 1,4-dioxane, reflux, 7.5 h, then 2.0 equiv of BnOH, reflux, 16 h, 49%; (e) 1.2 equiv of $(CH_3)_3O{\cdot}BF_4$, 0.6 equiv of 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 23 °C, 65 h, 91%; (f) 0.01 equiv of $(DHQD)_2$-AQN, 3.0 equiv of $K_3Fe(CN)_6$, 3.0 equiv of K_2CO_3, 0.004 equiv of $K_2OsO_4{\cdot}2H_2O$, 1:1 *tert*-BuOH:H_2O, 0 °C, 20 h, 98%; (g) 2.5 equiv of Et_3N, 1.6 equiv of (TBS)Cl, 0.045 equiv of DMAP, CH_2Cl_2, 23 °C, 19 h, 82%; (h) 4.0 equiv of 2,6-lutidine, 1.5 equiv of Tf_2O, CH_2Cl_2, −78→+23 °C, 1 h; (i) 3.0 equiv of TBAF, THF, 23 °C, 1 h, 58% from **19**; (j) 2.6 equiv of DMSO, 1.3 equiv of oxalyl chloride, 5.0 equiv of Et_3N, 5.5 equiv of AcOH, CH_2Cl_2, −78 °C, 2 h; (k) 5% $KMnO_4$, 2:3 5% NaH_2PO_4:*tert*-BuOH, 23 °C, 5 min, 30% from **21**.

addition of solid **8** to 2.5 equiv of lithium diisopropylamide in cold tetrahydrofuran (THF) provided a solution of the corresponding dilithium salt in accordance with the reported literature method.[7] The dilithio intermediate thus obtained was quenched with allyl bromide to give the allylated pyridine **14** in good yield. Hydrolysis of the nitrile moiety present in **14** was accomplished by a two-step procedure which involved initial peroxide-mediated conversion to the primary amide **15**.[14] Extended exposure of **15** to refluxing aqueous KOH then provided the carboxylic acid **16** in good yield. Curtius rearrangement of **16** was effected in a manner analogous to that described for the preparation of **9** above (Scheme 2), and trapping of the resulting isocyanate (not shown) with benzyl alcohol afforded the desired carbamate **17** in moderate yield. Treatment of **17** with trimethyloxonium tetrafluoroborate in the presence of 2,6-di-*tert*-butylpyridine provided olefin **13** in excellent yield following purification by flash column chromatography. The employment of 2,6-di-*tert*-butylpyridine in the conversion of **17** to **13** dramatically reduced the appearance of side products which presumably resulted from acid-effected olefin decomposition. It should be noted that the synthetic operations which convert **8** to **17** were performed without silica gel purification of the reaction products and were readily amenable to multigram scale operations.

Table 1. Osmium-Catalyzed Asymmetric Dihydroxylation of Olefin 13 Employing Various Chiral Cinchona Alkaloid Ligands

entry	ligand	yield of **18**[a] (%)	ee[b] (%)	ref
1	$(DHQD)_2$-PHAL	96	55.5	16a
2	$(DHQD)_2$-PYR	91	75.1	16b
3	$(DHQD)_2$-AQN	98	83.4	16c
4	$(DHQ)_2$-AQN	96[c]	78.0	16c

[a] Isolated yield after purification by silica gel chromatography. [b] Determined by chiral HPLC analysis (see Supporting Information for additional details). [c] Enantiomer of **18**.

Having developed a synthesis which reliably afforded relatively large quantities of olefin **13**, we then examined the asymmetric dihydroxylation of this intermediate.[15] A variety of cinchona alkaloid ligands have been employed for the osmium-catalyzed, asymmetric dihydroxylation of monosubstituted terminal olefins such as **13**, although none have been indicated to give optimal results for every such substrate.[16] Accordingly, we examined all such commercially available cinchona alkaloid ligands for their ability to assist in the transformation of olefin **13** to optically active diol **18**. As seen in Table 1, osmium-catalyzed dihydroxylation of **13** employing any of the above ligands provided the desired diol **18** in excellent yields. The $(DHQD)_2$-AQN ligand, however, afforded **18** with the highest levels of enantioselectivity and was therefore selected for the large-scale preparation of this intermediate.[17] Utilization of the related $(DHQ)_2$-AQN ligand for the dihydroxylation of **13** provided the enantiomer of **18** (not shown) in good yield and nearly equally high ee (Table 1, entry 4).

Protection of the primary alcohol present in **18** was accomplished by exposure to an excess of *tert*-butyldimethylsilyl chloride in the presence of catalytic amounts of 4-(dimethylamino)pyridine and provided the mono-silyl ether **19** in good yield. Minor quantities of unreacted **18** and the corresponding di-silyl ether (not characterized or shown) were also observed during this transformation. Treatment of **19** at low temperature with trifluoromethanesulfonic anhydride in the presence of excess 2,6-lutidine, followed by subsequent warming to room temperature, resulted in clean conversion to the pyridinium salt **20** which could surprisingly be isolated by flash column chromatography in good yield. Simultaneous *O*-demethylation and desilylation was accomplished by

(13) Deoxygenation of the halogenation reaction medium and use of the corresponding Boc-protected aminopyridine as a halogenation substrate did not result in significant yield improvements.

(14) Sakamoto, T.; Kondo, Y.; Yamanaka, H. *Heterocycles* **1988**, *27*, 453.

(15) For a review of catalytic asymmetric dihydroxylation methods, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(16) (a) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. (b) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785. (c) Becker, H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 448. See also: Hoye, T. R.; Mayer, M. J.; Vos, T. J.; Ye, Z. *J. Org. Chem.* **1998**, *63*, 8554.

(17) The absolute configuration shown for diol **18** is based on literature precedent.[16] The absolute configurations of intermediates **19**−**22** and compound **1** are derived from that of **18**.

exposure of **20** to tetrabutylammonium fluoride for several hours at room temperature and provided pyridone **21** in good yield after purification on silica gel. When conducting large-scale operations, pyridinium salt **20** was not routinely isolated and the crude mono-silyl ether **19** was instead converted directly to pyridone **21** in moderate overall yield.

With the bicyclic 2-pyridone framework assembled, we then examined the oxidation of the alcohol moiety present in **21** to the carboxylic acid level. After some experimentation, a two-step procedure was found to be most effective and commenced with Swern oxidation of **21** to afford aldehyde **22**.[18] A low-temperature quench was employed in this operation in order to minimize possible racemization of the stereogenic center contained in **22**.[19] Aldehyde **22** was not purified but was instead further oxidized by exposure to buffered, aqueous $KMnO_4$ to give the desired pyridone **1** in moderate overall yield after flash column chromatography.[20,21] Pyridone **1** prepared in this manner was typically of sufficient purity for subsequent chemical transformations (e.g., amide bond formation). Comparison to an independently prepared racemic standard determined the optical purity of **1** to be 60% (ee) and indicated that the synthetic operations which convert diol **18** to **1** resulted in minor racemization (see Supporting Information for additional details).

In summary, we describe the preparation of optically active bicyclic 2-pyridone **1** in eleven steps from commercially available 2-hydroxy-6-methylnicotinonitrile (3.3% overall yield). Although certain aspects of this first-generation synthesis may possibly be improved upon in the future, we believe that the present route affords **1** in quantities sufficient to allow its incorporation into a variety of peptidomimetic structures.

Experimental Section[22]

All reactions were performed in septum-sealed flasks under a slight positive pressure of argon unless otherwise noted. All commercial reagents were used as received from their respective suppliers with the following exceptions. Tetrahydrofuran was distilled from sodium−benzophenone ketyl prior to use. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride prior to use. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. ^{1}H and ^{13}C NMR chemical shifts are reported in parts per million (δ) downfield relative to internal tetramethylsilane or residual solvent peaks, and coupling constants are given in hertz. Melting points were determined using a Mel-Temp II apparatus and are uncorrected.

(2-Hydroxy-6-methylpyridin-3-yl)carbamic Acid Benzyl Ester (9).[9] Triethylamine (44.6 mL, 320 mmol, 2.0 equiv) and diphenylphosphoryl azide (51.7 mL, 240 mmol, 1.5 equiv) were added sequentially to a suspension of 2-hydroxy-6-methylpyridine-3-carboxylic acid (24.5 g, 160 mmol, 1 equiv) in 1,4-dioxane (500 mL) at 23 °C. The resulting solution was heated to reflux for 18 h, then benzyl alcohol (33.1 mL, 320 mmol, 2.0 equiv) was added, and reflux was continued for an additional 23 h. The dark brown reaction mixture was cooled to 23 °C, and the volatiles were removed under reduced pressure. The resulting dark brown oil was partitioned between water (300 mL) and CH_2Cl_2 (2 × 300 mL), and the combined organic layers were dried over $MgSO_4$, gravity filtered, and concentrated. The solid thus obtained was triturated with EtOAc (250 mL) and was filtered through a medium frit, washed with Et_2O (3 × 70 mL), and air-dried to give **9** (21.3 g, 52%) as a tan powder: mp = 171−172 °C; R_f = 0.23 (50% EtOAc in hexanes); IR (cm^{-1}) 3388, 3323, 1732, 1643; ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3H), 5.13 (s, 2H), 5.98 (d, 1H, J = 7.5), 7.28−7.43 (m, 5H), 7.70 (d, 1H, J = 7.5), 8.22 (s, 1H), 11.92 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.1, 65.9, 103.7, 123.1, 125.9, 127.7, 127.9, 128.4, 136.6, 137.6, 153.2, 157.8; Anal. Calcd for $C_{14}H_{14}N_2O_3 \cdot 0.10H_2O$: C, 64.65; H, 5.50; N, 10.77. Found: C, 64.65; H, 5.46; N, 10.85.

(2-Methoxy-6-methylpyridin-3-yl)carbamic Acid Benzyl Ester (10). Trimethyloxonium tetrafluoroborate (12.7 g, 86.2 mmol, 1.05 equiv) was added to a solution of **9** (21.2 g, 82.1 mmol, 1 equiv) in CH_2Cl_2 at 23 °C. The resulting suspension was stirred at 23 °C for 36 h and then was partitioned between CH_2Cl_2 (2 × 200 mL) and 10% aqueous NaOH solution (300 mL). The combined organic layers were dried over Na_2SO_4 and concentrated, and the residue was purified by flash column chromatography (20% EtOAc in hexanes) to afford **10** (20.6 g, 92%) as a colorless oil: R_f = 0.32 (60% EtOAc in hexanes); IR (cm^{-1}) 3436, 1732; ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 3.95 (s, 3H), 5.20 (s, 2H), 6.71 (d, 1H, J = 7.8), 7.11 (s, br, 1H), 7.33−7.43 (m, 5H), 8.16 (s, br, 1H); ^{13}C NMR ($CDCl_3$) δ 23.6, 53.6, 67.2, 116.1, 120.0, 125.6, 128.5, 128.5, 128.8, 136.2, 148.8, 152.2, 153.5; Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.37; H, 5.93; N, 10.38.

(1,6-Dimethyl-2-oxo-1,2-dihydropyridin-3-yl)carbamic Acid Benzyl Ester (11). Tetrabutylammonium bromide (4.00 g, 12.4 mmol, 2.0 equiv), sodium hydroxide (0.50 g, 12.5 mmol, 2.0 equiv), and iodomethane (3.86 mL, 62.0 mmol, 10.0 equiv) were added sequentially to a biphasic solution of **9** (1.60 g, 6.19 mmol, 1 equiv) in a 2:1 mixture of CH_2Cl_2 and water (90 mL). The pale green reaction mixture was stirred at 23 °C for 1 h and then was partitioned between water (150 mL) and CH_2Cl_2 (2 × 100 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. Purification of the residue by flash column chromatography (60% EtOAc in hexanes) afforded **11** (1.54 g, 91%) as a light brown solid: mp = 76−78 °C; R_f = 0.40 (60% EtOAc in hexanes); IR (cm^{-1}) 3254, 1714, 1647; ^{1}H NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.57 (s, 3H), 5.20 (s, 2H), 6.08 (d, 1H, J = 7.3), 7.30−7.41 (m, 5H), 7.82 (s, br, 1H), 7.91 (d, 1H, J = 7.3); ^{13}C NMR ($CDCl_3$) δ 20.4, 31.9, 67.0, 106.3, 120.0, 126.6, 128.2, 128.3, 128.7, 136.2, 137.6, 153.5, 158.2; Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.17; H, 5.90; N, 10.28.

(6-Bromomethyl-2-methoxypyridin-3-yl)carbamic Acid Benzyl Ester (12). *N*-Bromosuccinimide (18.3 g, 103 mmol, 1.4 equiv) and benzoyl peroxide (0.357 g, 1.47 mmol, 0.02 equiv) were added sequentially to a solution of **10** (20.05 g, 73.6 mmol, 1 equiv) in CCl_4 at 23 °C. The resulting suspension was heated to reflux for 18 h and then was cooled to 23 °C and filtered through a medium frit. The red/brown filtrate was concentrated under reduced pressure, and the residue was passed through a plug of silica gel, eluting with 15% EtOAc in hexanes. Fractions containing the desired product were combined and concentrated, and the residue was allowed to stand overnight. The resulting red/brown solid was triturated with CH_3OH (50 mL), filtered through a medium frit, and washed with hexanes (30 mL) to provide **12** (3.06 g, 12%) as a yellow solid: mp = 88−89 °C; R_f = 0.48 (10% EtOAc in hexanes; 2 elutions); IR (cm^{-1}) 3433, 1734; ^{1}H NMR ($CDCl_3$) δ 3.99 (s, 3H), 4.45 (s, 2H), 5.21 (s, 2H), 6.99 (d, 1H, J = 7.4), 7.22 (s, br, 1H), 7.33−7.43 (m, 5H), 8.28 (d, 1H, J = 7.4); ^{13}C NMR ($CDCl_3$) δ 34.5, 54.0, 67.5, 117.1, 122.6, 125.1, 128.6, 128.7, 128.9, 135.9, 146.5, 152.4, 153.3; Anal. Calcd for $C_{15}H_{15}BrN_2O_3$: C, 51.30; H, 4.30; N, 7.98. Found: C, 51.72; H, 4.31; N, 8.01.

(18) (a) Tidwell, T. T. *Synthesis* **1990**, 857. (b) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(19) DeCamp, A. E.; Kawaguchi, A. T.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1991**, *32*, 1867.

(20) Abiko, A.; Roberts, J. C.; Takemasa, T.; Masamune, S. *Tetrahedron Lett.* **1986**, *27*, 4537.

(21) Caution must be exercised during the conversion of **22** to **1** since prolonged reaction times (>15 min) resulted in extensive decomposition of the 2-pyridone ring system. The use of buffered $NaClO_2$ to effect the **22** to **1** transformation was unpredictable and often resulted in the formation of chlorinated 2-pyridone side products.

(22) General experimental procedures and instrumentation are described in: Dragovich, P. S.; Prins, T. J.; Zhou, R. *J. Org. Chem.* **1995**, *60*, 4922.

(6-But-3-enyl-2-methoxypyridin-3-yl)carbamic Acid Benzyl Ester (13). Allylmagnesium bromide (19.5 mL of a 1.0 M solution in Et_2O, 19.5 mmol, 1.0 equiv) was added via cannula over 10 min to a solution of **12** (6.84 g, 19.4 mmol, 1 equiv) in THF (200 mL) at 0 °C. Upon completion of the addition, the reaction mixture was warmed to 50 °C whereupon a second portion of allylmagnesium bromide (38.9 mL of a 1.0 M solution in Et_2O, 38.9 mmol, 2.0 equiv) was added. The resulting orange solution was maintained at 50 °C for 30 min, then was cooled to 23 °C, and was partitioned between 0.5 M HCl (150 mL) and a 1:1 mixture of EtOAc and hexanes (2 × 150 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by careful flash column chromatography (5% EtOAc in hexanes) afforded **13** (2.24 g, 37%) as a pale yellow oil (containing minor impurities by ^{1}H NMR): R_f = 0.84 (50% EtOAc in hexanes); IR (cm^{-1}) 3432, 1733; ^{1}H NMR ($CDCl_3$) δ 2.42−2.49 (m, 2H), 2.73 (t, 2H, J = 7.6), 3.96 (s, 3H), 4.94−5.07 (m, 2H), 5.20 (s, 2H), 5.80−5.94 (m, 1H), 6.71 (d, 1H, J = 7.9), 7.11 (s, br, 1H), 7.32−7.43 (m, 5H), 8.16 (s, br, 1H); ^{13}C NMR ($CDCl_3$) δ 33.3, 36.4, 53.3, 67.0, 114.7, 115.4, 120.0, 125.2, 128.3, 128.3, 128.6, 135.9, 138.2, 151.6, 152.1, 153.3; Anal. Calcd for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 69.35; H, 6.44; N, 8.94.

6-But-3-enyl-2-hydroxynicotinonitrile (14). *n*-Butyllithium (100 mL of a 1.6 M solution in hexanes, 160 mmol, 2.5 equiv) was added via cannula over 10 min to a solution of diisopropylamine (22.4 mL, 160 mmol, 2.5 equiv) in THF (600 mL) at −78 °C. The resulting pale yellow solution was stirred at −78 °C for 5 min and then was warmed to 0 °C for an additional 5 min. 2-Hydroxy-6-methylnicotinonitrile (**8**) (8.58 g, 64.0 mmol, 1 equiv) was added as a solid in small portions over 15 min, and the deep orange solution thus obtained was stirred for 1 h at 0 °C. Allyl bromide (8.31 mL, 96.0 mmol, 1.5 equiv) was then added, and the reaction mixture was warmed to 23 °C, maintained at that temperature for 30 min, and partitioned between 1.0 M HCl (300 mL) and EtOAc (2 × 250 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. The resulting orange solid was triturated with boiling Et_2O (100 mL) and subsequently cooled to 23 °C and then was filtered through a medium frit, washed with Et_2O (2 × 50 mL), and air-dried to give **14** (6.42 g, 58%) as a tan solid: mp = 122−125 °C; R_f = 0.48 (10% CH_3OH in CH_2Cl_2); IR (KBr pellet, cm^{-1}) 2223, 1654; ^{1}H NMR (DMSO-d_6) δ 2.32−2.37 (m, 2H), 2.62 (t, 2H, J = 7.6), 4.96−5.06 (m, 2H), 5.69−5.83 (m, 1H), 6.23 (d, 1H, J = 7.3), 8.03 (d, 1H, J = 7.3), 12.55 (s, br, 1H); ^{13}C NMR (DMSO-d_6) δ 31.8, 31.9, 100.0, 104.6, 116.1, 116.7, 136.5, 148.9, 156.7, 160.8; Anal. Calcd for $C_{10}H_{10}N_2O\cdot0.10H_2O$: C, 68.24; H, 5.84; N, 15.92. Found: C, 68.07; H, 5.95; N, 15.66.

6-But-3-enyl-2-hydroxynicotinamide (15). Hydrogen peroxide (30 wt % solution in water, 45 mL) was added to a solution of **14** (12.1 g, 70.2 mmol) in a mixture of EtOH (150 mL) and 10% aqueous NaOH (280 mL) at 23 °C. The reaction mixture was heated to 50 °C for 18 h and then was cooled to 23 °C, and the volatiles were removed under reduced pressure. The residue was acidified with 12 M HCl to pH 2−3, and the resulting precipitate was filtered, washed with water (2 × 50 mL), and air-dried to afford **15** as a yellow solid (13.4 g, 100%): mp = 195−198 °C; R_f = 0.24 (10% CH_3OH in CH_2Cl_2); IR (cm^{-1}) 3329, 3134, 1688, 1642; ^{1}H NMR (DMSO-d_6) δ 2.31−2.38 (m, 2H), 2.64 (t, 2H, J = 7.6), 4.96−5.05 (m, 2H), 5.71−5.84 (m, 1H), 6.29 (d, 1H, J = 7.3), 7.45 (s, br, 1H), 8.21 (d, 1H, J = 7.3), 9.00 (s, br, 1H), 12.37 (s, br, 1H); ^{13}C NMR (DMSO-d_6) δ 31.4, 32.0, 105.1, 116.0, 117.9, 136.7, 144.3, 154.0, 162.9, 164.8; Anal. Calcd for $C_{10}H_{12}N_2O_2\cdot0.15H_2O$: C, 61.61; H, 6.28; N, 14.37. Found: C, 61.84; H, 6.18; N, 14.11.

6-But-3-enyl-2-hydroxynicotinic Acid (16). A solution of **15** (13.4 g, 70.1 mmol) in 10% aqueous KOH (350 mL) was refluxed for 20 h and subsequently cooled to room temperature. The reaction mixture was acidified with 12 M HCl to pH 2−3, and the resulting precipitate was filtered, washed with water (2 × 50 mL), and dried under vacuum to afford **16** as a yellow solid (12.4 g, 92%): mp = 151−155 °C; R_f = 0.20 (10% CH_3OH in CH_2Cl_2); IR (cm^{-1}) 2905 (br), 1736, 1652; ^{1}H NMR (DMSO-d_6) δ 2.34−2.29 (m, 2H), 2.73 (t, 2H, J = 7.6), 4.96−5.07 (m, 2H), 5.72−5.85 (m, 1H), 6.56 (d, 1H, J = 7.5), 8.28 (d, 1H, J = 7.5), 13.26 (s, br, 1H), 14.64 (s, br, 1H); ^{13}C NMR (DMSO-d_6) δ 31.7, 32.0, 107.9, 113.7, 116.3, 136.5, 146.0, 156.5, 165.1, 165.1; Anal. Calcd for $C_{10}H_{11}NO_3\cdot0.10H_2O$: C, 61.59; H, 5.79; N, 7.18. Found: C, 61.67; H, 5.71; N, 7.17.

(6-But-3-enyl-2-hydroxypyridin-3-yl)carbamic Acid Benzyl Ester (17). Triethylamine (13.9 mL, 99.7 mmol, 2.0 equiv) and diphenylphosphoryl azide (16.1 mL, 74.7 mmol, 1.5 equiv) were added sequentially to a suspension of **16** (9.63 g, 49.8 mmol, 1 equiv) in 1,4-dioxane (450 mL) at 23 °C. The resulting solution was heated to reflux for 7.5 h, then benzyl alcohol (10.3 mL, 99.5 mmol, 2.0 equiv) was added, and reflux was continued for an additional 16 h. The dark brown reaction mixture was cooled to 23 °C, and the volatiles were removed under reduced pressure. The resulting dark brown oil was partitioned between water (300 mL) and EtOAc (2 × 250 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated. The solid thus obtained was triturated with Et_2O (150 mL) and was filtered through a medium frit, washed with Et_2O (2 × 50 mL), and air-dried to give **17** (7.34 g, 49%) as an off-white powder: mp = 179−180 °C; R_f = 0.34 (50% EtOAc in hexanes); IR (cm^{-1}) 3386, 1727, 1645; ^{1}H NMR ($CDCl_3$) δ 2.39−2.46 (m, 2H), 2.65 (t, 2H, J = 7.5), 4.97−5.07 (m, 2H), 5.21 (s, 2H), 5.73−5.87 (m, 1H), 6.10 (d, 1H, J = 7.5), 7.32−7.44 (m, 5H), 7.68 (s, br, 1H), 8.06 (s, br, 1H), 12.74 (s, br, 1H); ^{13}C NMR ($CDCl_3$) δ 32.3, 32.9, 67.2, 105.8, 116.3, 123.1, 126.6, 128.4, 128.5, 128.8, 136.2, 136.7, 140.4, 153.5, 159.3; Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N,. 9.39. Found: C, 68.25; H, 6.20; N, 9.38.

(6-But-3-enyl-2-methoxypyridin-3-yl)carbamic Acid Benzyl Ester (13) (Alternate Preparation). Trimethyloxonium tetrafluoroborate (2.0 g, 13.5 mmol, 1.2 equiv) and 2,6-di-*tert*-butylpyridine (1.52 mL, 6.76 mmol, 0.6 equiv) were added to a solution of **17** (3.36 g, 11.26 mmol, 1 equiv) in CH_2Cl_2 (80 mL) at 23 °C. The reaction mixture was stirred at that temperature for 65 h and then was partitioned between water (100 mL) and CH_2Cl_2 (2 × 200 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. The residue was purified by flash column chromatography (5% EtOAc in hexanes) to afford **13** (3.19 g, 91%) as colorless oil.

(3′*R*)-[6-(3′,4′-Dihydroxybutyl)-2-methoxypyridin-3-yl]-carbamic Acid Benzyl Ester (18). To a 1:1 mixture of *t*-BuOH and water (300 mL) at 0 °C was sequentially added $(DHQD)_2$-AQN (0.148 g, 0.164 mmol, 0.01 equiv), $K_3Fe(CN)_6$ (16.2 g, 49.2 mmol, 3.0 equiv), K_2CO_3 (6.8 g, 49.2 mmol, 3.0 equiv), and potassium osmate dihydrate (0.024 g, 0.066 mmol, 0.004 equiv), followed by a solution of **13** (5.13 g, 16.4 mmol, 1 equiv) in *t*-BuOH (25 mL). The resulting mixture was stirred at 0 °C for 20 h, then was warmed to room temperature, and Na_2SO_3 (30 g) was added carefully. The mixture was then stirred at room temperature for 2 h, and the volatiles were removed under reduced pressure. The residue was partitioned between water (200 mL) and EtOAc (3 × 200 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (2% CH_3OH in CH_2Cl_2) to afford **18** (5.57 g, 98%) as pale yellow oil. The enantiomeric purity of this material was determined to be 83.4% (ee) by chiral HPLC analysis (see the Supporting Information for additional details): R_f = 0.20 (70% EtOAc in hexanes); IR (cm^{-1}) 3427 (br), 1731; ^{1}H NMR ($CDCl_3$) δ 1.76−1.87 (m, 2H), 2.07−2.11 (m, 1H), 2.80−2.89 (m, 2H), 3.46−3.53 (m, 1H), 3.60−3.67 (m, 1H), 3.71−3.77 (m, 1H), 3.96 (s, 3H), 4.64 (d, 1H, J = 3.2), 5.21 (s, 2H), 6.76 (d, 1H, J = 7.8), 7.12 (s, br, 1H), 7.34−7.43 (m, 5H), 8.22 (s, br, 1H); ^{13}C NMR ($CDCl_3$) δ 32.3, 33.2, 53.9, 66.9, 67.3, 71.8, 116.0, 120.7, 126.0, 128.5, 128.6, 128.8, 136.0, 151.5, 152.3, 153.5; Anal. Calcd for $C_{18}H_{22}N_2O_5$: C, 62.42; H, 6.40; N, 8.09. Found: C, 62.15; H, 6.47; N, 8.02.

(3′*R*)-{6-[4′-(*tert*-Butyldimethylsilanyloxy)-3′-hydroxybutyl]-2-methoxypyridin-3-yl}carbamic Acid Benzyl Ester (19). Triethylamine (1.55 mL, 11.1 mmol, 2.5 equiv), *tert*-butyldimethylsilyl chloride (1.07 g, 7.10 mmol, 1.6 equiv), and 4-(dimethylamino)pyridine (0.025 g, 0.20 mmol, 0.045 equiv) were added sequentially to a solution of **18** (1.54 g, 4.45 mmol, 1 equiv) in CH_2Cl_2 (50 mL) at 23 °C. The reaction mixture was

stirred for 19 h at 23 °C and then was partitioned between 0.5 M HCl (150 mL) and a 1:1 mixture of EtOAc and hexanes (2 × 150 mL). The combined organic layers were dried over Na_2SO_4 and were concentrated. Purification of the residue by flash column chromatography (20% EtOAc in hexanes) provided **19** (1.69 g, 82%) as a colorless oil: $R_f = 0.32$ (20% EtOAc in hexanes); IR (cm^{-1}) 3436, 1734; ^1H NMR ($CDCl_3$) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.72−1.94 (m, 2H), 2.72−2.88 m, 2H), 3.26 (d, 1H, $J = 3.1$), 3.50 (dd, 1H, $J = 9.8, 6.9$), 3.58−3.63 (m, 1H), 3.65−3.70 (m, 1H), 3.95 (s, 3H), 5.20 (s, 2H), 6.75 (d, 1H, $J = 8.1$), 7.11 (s, br, 1H), 7.33−7.43 (m, 5H), 8.20 (s, br, 1H); ^{13}C NMR ($CDCl_3$) δ −5.2, −5.1, 18.5, 26.1, 32.5, 33.3, 53.7, 67.3, 67.4, 71.6, 115.8, 120.4, 125.7, 128.5, 128.6, 128.8, 136.1, 152.0, 152.3, 153.5; Anal. Calcd for $C_{24}H_{36}N_2O_5Si$: C, 62.57; H, 7.88,; N, 6.08. Found: C, 62.49; H, 7.92; N, 6.09.

(3*S*)-[3-(*tert*-Butyldimethylsilanyloxymethyl)-5-methoxy-2,3-dihydro-1H-in dolizin-6-yl]carbamic Acid Benzyl Ester Trifuoromethanesulfonic Acid Salt (20). 2,6-Lutidine (0.216 mL, 1.85 mmol, 3.0 equiv) and trifluoromethanesulfonic anhydride (0.109 mL, 0.648 mmol, 1.05 equiv) were added sequentially to a solution of **19** (0.285 g, 0.619 mmol, 1 equiv) in CH_2Cl_2 (30 mL) at −78 °C. The colorless reaction mixture was stirred at −78 °C for 45 min, warmed to 23 °C for an additional 15 min, and then was partitioned between 0.5 M HCl (100 mL) and EtOAc (150 mL). The organic layer was dried over Na_2SO_4 and was concentrated. The residue thus obtained was purified by flash column chromatography (5% CH_3OH in CH_2Cl_2) to give **20** (0.275 g, 75%) as a colorless oil: $R_f = 0.28$ (10% CH_3OH in CH_2Cl_2); ^1H NMR ($CDCl_3$) δ −0.14 (s, 3H), −0.01 (s, 3H), 0.74 (s, 9H), 2.35−2.42 (m, 1H), 2.74−2.89 (m, 1H), 3.30−3.56 (m, 2H), 3.89 (dd, 1H, $J = 11.3, 1.9$), 4.13 (dd, 1H, $J = 11.3, 2.8$), 4.34 (s, 3H), 5.23 (s, 2H), 5.36−5.39 (m, 1H), 7.31−7.43 (m, 6H), 8.07 (s, br, 1H), 8.57 (d, 1H, $J = 8.4$); HRMS Calcd for $C_{24}H_{35}N_2O_4Si$ [M^+] 443.2366, found 443.2376.

(3*S*)-(3-Hydroxymethyl-5-oxo-1,2,3,5-tetrahydroindolizin-6-yl)carbamic Acid Benzyl Ester (21). 2,6-Lutidine (2.43 mL, 20.84 mmol, 4.0 equiv) and trifluoromethanesulfonic anhydride (1.31 mL, 7.82 mmol, 1.5 equiv) were added sequentially to a solution of **19** (2.40 g, 5.21 mmol, 1 equiv) in CH_2Cl_2 (100 mL) at −78 °C. The colorless reaction mixture was stirred at −78 °C for 45 min, warmed to 23 °C for an additional 15 min, and then partitioned between 0.5 M HCl (150 mL) and CH_2Cl_2 (2 × 150 mL). The organic layers were dried over Na_2SO_4 and were concentrated. The residue thus obtained was dissolved in THF (120 mL) at 23 °C and tetrabutylammonium fluoride (15.63 mL of a 1.0 M solution in THF, 15.63 mmol, 3.0 equiv) was added. The reaction mixture was stirred at that temperature for 1 h and then was partitioned between 0.5 M HCl (150 mL) and EtOAc (2 × 150 mL). The organic layers were dried over Na_2SO_4 and were concentrated. The residue thus obtained was purified by flash column chromatography (80% EtOAc in hexanes) to give **21** (0.953 g, 58%) as a colorless oil: $R_f = 0.36$ (10% CH_3OH in CH_2Cl_2); IR (cm^{-1}) 3379 (br), 1727, 1649; ^1H NMR ($CDCl_3$) δ 1.86−1.97 (m, 1H), 2.29−2.41 (m, 1H), 2.90−3.15 (m, 2H), 3.80−3.93 (m, 2H), 4.78−4.86 (m, 1H), 5.11−5.15 (m, 1H), 5.20 (s, 2H), 6.20 (d, 1H, $J = 7.5$), 7.30−7.41 (m, 5H), 7.75 (s, br, 1H), 8.07 (d, 1H, $J = 7.5$); ^{13}C NMR ($CDCl_3$) δ 25.5, 29.4, 65.3, 66.2, 66.9, 102.3, 122.1, 127.0, 128.1, 128.2, 128.5, 135.9, 142.3, 153.4, 157.3; Anal. Calcd for $C_{17}H_{18}N_2O_4 \cdot 0.75H_2O$: C, 62.28; H, 5.99; N, 8.54. Found: C, 62.03; H, 5.86; N, 8.46.

(3*S*)-(3-Formyl-5-oxo-1,2,3,5-tetrahydroindolizin-6-yl)-carbamic Acid Benzyl Ester (22). Dimethyl sulfoxide (0.522 mL, 7.36 mmol, 2.6 equiv) was added dropwise to a solution of oxalyl chloride (0.321 mL, 3.68 mmol, 1.3 equiv) in CH_2Cl_2 (80 mL) at −78 °C. The reaction mixture was stirred for 20 min at that temperature, and then a solution of **21** (0.890 g, 2.83 mmol, 1 equiv) in CH_2Cl_2 (20 mL) was added via cannula. After stirring an additional 20 min at −78 °C, triethylamine (1.97 mL, 14.15 mmol, 5.0 equiv) was added dropwise. The reaction mixture was maintained at −78 °C for 1.5 h, and then acetic acid (15.57 mmol, 0.891 mL, 5.5 equiv) was added. The reaction mixture was warmed to 0 °C for 5 min and then was washed with water (50 mL), saturated $NaHCO_3$ (50 mL), and brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated to afford crude **22** as off-white foam. This material was utilized without further purification: ^1H NMR ($CDCl_3$) δ 2.38−2.46 (m, 2H), 3.05−3.11 (m, 2H), 5.15−5.25 (m, 3H), 6.22 (d, 1H, $J = 7.8$), 7.33−7.44 (m, 5H), 7.72 (s, br, 1H), 8.11 (d, 1H, $J = 7.8$), 9.74 (s, 1H).

(3*S*)-6-(Benzyloxycarbonylamino)-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylic Acid (1). A 5% aqueous NaH_2PO_4 solution (5 mL) and a 1.0 M aqueous $KMnO_4$ solution (7 mL) were added sequentially to a solution of crude **22** (1.27 mmol) in *t*-BuOH (8 mL) at 23 °C. The reaction mixture was stirred at room temperature for 5 min, and then a saturated aqueous solution of Na_2SO_3 (20 mL) was added. The resulting mixture was stirred at room temperature for 10 min, then was acidified with 1.0 M HCl to pH 3, and washed with CH_2Cl_2 (3 × 50 mL). The organic washings were dried over Na_2SO_4 and were concentrated. The residue thus obtained was purified by flash column chromatography (10% CH_3OH in CH_2Cl_2) to give **1** (0.134 g, 30%) as an off-white solid. The enantiomeric purity of this material was determined to be 60% (ee) by chiral HPLC analysis (see the Supporting Information for additional details): mp = 204−206 °C; $R_f = 0.18$ (10% CH_3OH in CH_2Cl_2); IR (cm^{-1}) 3298, 1722, 1564, 1208; ^1H NMR (DMSO-d_6) δ 2.17−2.55 (m, 2H), 2.45−2.59 (m, 2H), 4.98 (dd, 1H, $J = 9.6, 2.7$), 5.16 (s, 2H), 6.23 (d, 1H, $J = 7.5$), 7.34−7.45 (m, 5H), 7.83 (d, 1H, $J = 7.5$), 8.34 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 26.2, 29.5, 61.6, 66.0, 99.7, 123.9, 125.7, 127.7, 127.9, 128.4, 136.6, 143.9, 153.4, 155.7, 171.3; Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.08; H, 5.00; N, 8.54.

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Supporting Information Available: Procedures for the preparation of racemic mixtures of compounds **18** and **1** and conditions for HPLC analyses of these mixtures. This material is available free of charge via the Internet at http://pubs.acs.org.

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