JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

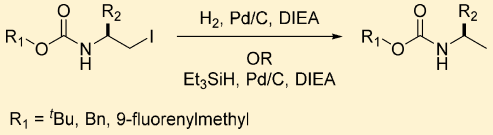
Hydrodehalogenation of Alkyl Iodides with Base-Mediated Hydrogenation and Catalytic Transfer Hydrogenation: Application to the Asymmetric Synthesis of N-Protected α-Methylamines

Pijus K. Mandal, J. Sanderson Birtwistle, and John S. McMurray*

Department of Experimental Therapeutics, The University of Texas M. D. Anderson Cancer Center, 1901 East Road, Houston, Texas 77054, United States

Supporting Information

ABSTRACT: We report a very mild synthesis of N-protected α-methylamines from the corresponding amino acids. Carboxyl groups of amino acids are reduced to iodomethyl groups via hydroxymethyl intermediates. Reductive deiodination to methyl groups is achieved by hydrogenation or catalytic transfer hydrogenation under alkaline conditions. Basic hydrodehalogenation is selective for the iodomethyl group over hydrogenolysis-labile protecting groups, such as benzyloxycarbonyl, benzyl ester, benzyl ether, and 9-fluorenyloxymethyl, thus allowing the conversion of virtually any protected amino acid into the corresponding N-protected α-methylamine.



In the field of peptidomimetic drug development, the goal is to incorporate nonproteinogenic amino acid surrogates into candidate compounds to introduce new ligand−receptor interactions, to reduce proteolytic susceptibility, and to increase bioavailability. α-Methylamines represent a class of amino acid replacements in which the carboxyl group of the amino acid is converted to a methyl group and which, therefore, can serve as C-terminal amino acid mimics. Indeed, our laboratory reported that replacing the CONHBn group of a C-terminal Gln-NHBn with a methyl group increased cellular potency approximately 50-fold in a set of STAT3 phosphorylation inhibitors[1] (Figure 1). In addition to peptidomimetics, α-methylamines are components of several important drug classes, such as adrenergic receptor agonists,[2−5] α-methylhistamine and analogues,[6,7] inhibitors of phenylethanolamine *N*-methyl transferase,[8] amphetamine analogues,[9] dopamine analogues,[10] potassium channel modulators,[11] and cathepsin K inhibitors,[12] to name but a few (Figure 1).

Complete reduction of the carboxyl group of α-amino acids to a methyl group is a common strategy for the stereospecific synthesis of α-methylamines. This is a multistep process, and typical strategies involve reduction of the carboxyl group to a hydroxymethyl group, followed by derivatization to moieties that are further reduced to the methyl group. The following examples illustrate varying approaches to the several steps in the synthesis. Starting with L-histidinol (in which the carboxyl group of histidine was reduced to the hydroxymethyl group), Friary et al. converted the hydroxyl group to the chloride, then reduced the chloromethyl group with catalytic transfer hydrogenolysis using ammonium formate in refluxing methanol.[7] Donner reduced free carboxyl groups of *N*-Boc-protected amino acids with borane to hydroxymethyl groups and converted these to the corresponding ethyl thioethers via tosylates.[13] Desulfurization with Raney nickel afforded the *N*-Boc-protected α-methylamine. This methodology was applied to a variety of amino acids, including bis-Boc histidine, Boc-Tyr(Me), and Boc-Ser(Bn). The side-chain benzyl protecting group of serine was removed by the Raney nickel. Khono et al. reported the synthesis of (*R*)-2-amino-1-(4-methoxyphenyl)-propane starting with tyrosine in which the amino, side-chain hydroxyl, and carboxyl groups were protected with benzyloxycarbonyl, methyl, and ethyl groups, respectively (Cbz-Tyr(Me)-OEt).[4] The carboxyl ester was reduced to the hydroxymethyl group with $NaBH_4$. After activation as a tosyl ester, the tosylate was reduced with Zn powder in the presence of NaI in refluxing aqueous dimethoxyethane. The Cbz group was stable to these conditions, and it was subsequently removed using standard hydrogenation. Quagliato et al. reduced the carboxyl group of free amino acids using $LiBH_4$, followed by Boc protection of the amino group.[11] The hydroxymethyl group was transformed to an iodomethyl group with I_2 and polymer supported triphenylphosphine. The iodomethyl group was reduced to the methyl group using L-Selectride. Some of these methods required elevated temperatures, and not all amino and side-chain protecting groups were stable to all of the reduction steps. We, therefore, sought a methodology that could be used to convert α-amino acids bearing standard protecting groups to N-protected and "side-chain"-protected α-methylamines.

Our laboratory reported a catalytic transfer hydrogenation (CTH) method using triethylsilane (TES) and 10% Pd/C to remove benzyl-type protecting groups and to reduce nitro groups, imines, azides, and both conjugated and nonconjugated multiple bonds under neutral conditions.[14] Though a wide variety of functional groups were reduced, TES/Pd−C-mediated reduction of organic halides was not explored. Herein, we report that CTH as well as conventional

Received: April 24, 2014
Published: August 12, 2014

   dx.doi.org/10.1021/jo500911v | J. Org. Chem. 2014, 79, 8422−8427

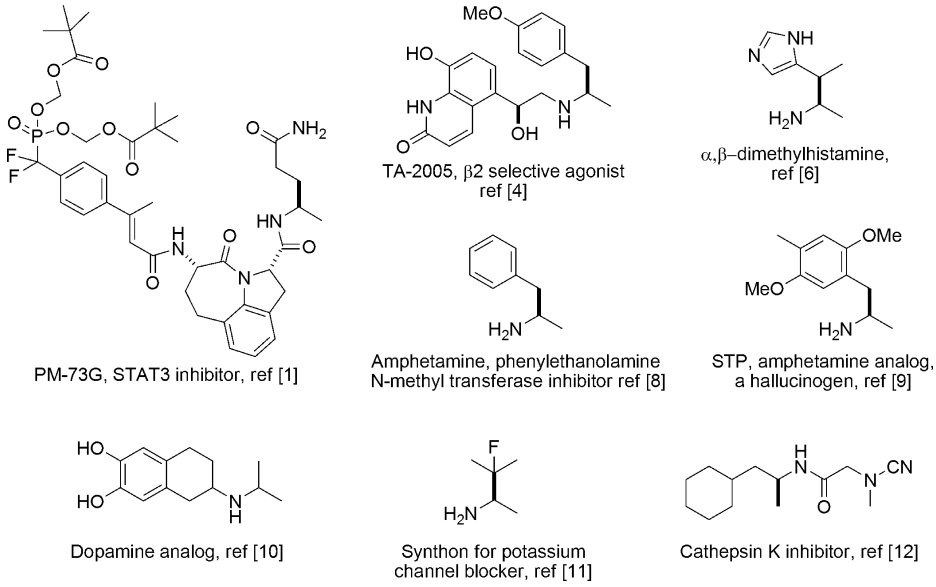
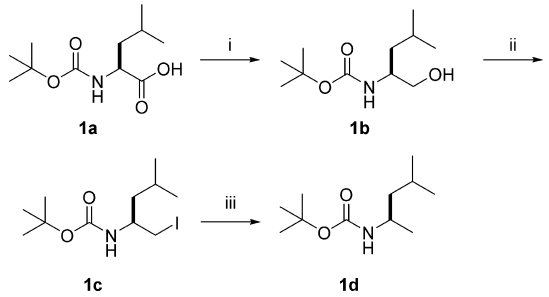


Figure 1. α-Methylamines utilized in pharmacological applications.

hydrogenation under alkaline conditions is an efficient and chemoselective method of hydrodehalogenation of alkyl iodides derived from the carboxyl groups of protected α-amino acids to produce chiral α-methylamines.

As illustrated with *tert*-butyloxycarbonyl-leucine (Scheme 1), protected amino acids were reduced to the corresponding β-amino alcohols by activation of the carboxyl group as a mixed carbonic anhydride (MCA) using *iso*-butyl chloroformate (IBCF), followed by in situ reduction with sodium borohydride.[15−17] The hydroxyl group was replaced by an iodide by treatment with iodine, triphenylphosphine, and imidazole to give the iodomethyl intermediate, **1c**.[18]

Scheme 1. [a]



[a]Reagents and conditions. (i) a, IBCF, NMM, −15 °C; b, $NaBH_4$, quantitative; (ii) I_2, Ph_3P, imidazole 67%; (iii) H_2, or TES, Pd/C, DIEA (see Table 1 for yields).

Using standard CTH conditions, addition of TES to a stirred suspension of **1c** in MeOH/THF in the presence of 10% Pd−C under argon resulted in the immediate evolution of hydrogen gas, as is normally observed.[14] However, there was no evidence of deiodination, even after stirring for the extended reaction time of 24 h. Conventional hydrogenation in MeOH/THF in the presence of 10% Pd−C also failed to reduce the iodo intermediate. Interestingly, addition of 2 equiv of the tertiary amine, diisopropylethylamine (DIEA), to the TES Pd/C-mediated CTH reaction resulted in complete reduction of the iodide to the corresponding *N*-Boc-α-methylamine (**1d**). Conventional hydrogenation in MeOH/THF over 10% Pd−C in the presence of 1.5−2 equiv of DIEA also resulted in reductive deiodination to the α-methyl group. This suggested that the formation of HI poisons the Pd catalyst and that DIEA neutralizes the acid. Dehydrohalogenation of iodomethyl intermediates is complete in 4 h for both reduction methods as judged by reverse phase HPLC.

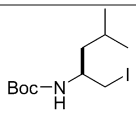
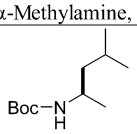
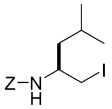
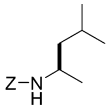
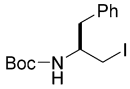
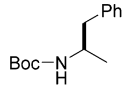
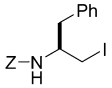
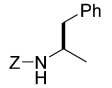
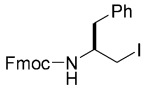
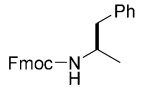
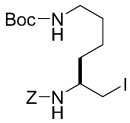
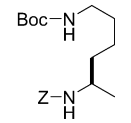
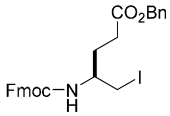
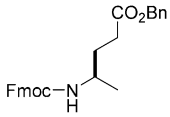
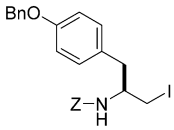
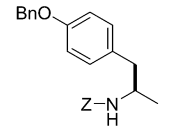
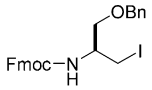
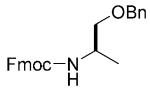
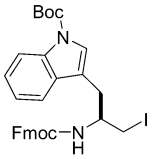
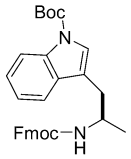
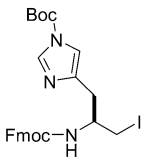
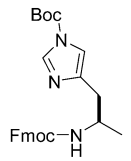
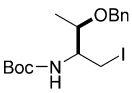
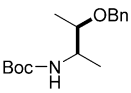
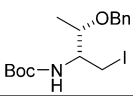
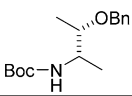
Reductive deiodination of alkyl iodides derived from a variety of protected amino acids was performed under both conditions, CTH with TES/Pd−C and conventional hydrogenation with H_2/Pd−C, in the presence of DIEA (Table 1). These basic conditions are selective for deiodination and leave untouched benzyl-based amino or hydroxyl protecting groups, such as benzyloxycarbonyl (Z), benzyl ester (OBzl) and benzyl ether, and 9-fluorenyloxymethyl (Fmoc), which are cleaved by standard hydrogenation reactions. Thus, our methodology allows the preparation of α-methylamines containing a wide variety of protected functionalities, e.g., the side-chain amino group of lysine (entry 6), the side-chain carboxyl group glutamic acid (entry 7), and by inference aspartic acid, the hydroxyl groups of tyrosine and serine (entries 8 and 9, respectively), the indole of tryptophan (entry 10), and the imidazole of histidine (entry 11). In our studies, we have chosen to keep the amino α-protecting groups intact for stability on storage. At the appropriate time, these protecting groups can be removed using standard deprotection conditions.

Oba and colleagues introduced deuterium in leucine derivatives by free-radical-mediated Bu_3SnD/AIBN reduction of methyl iodides.[19,20] In a similar vein, we found that the iodine atom could be readily replaced with a deuterium using TES-*d* in the catalytic transfer hydrogenation reaction, as illustrated for Fmoc-Phe$\psi$$CH_2$D (**5e**) in Scheme 2. Although methanol is a potential hydrogen source, no trace of the trihydrogen species was found, indicating that, during TES-mediated CTH, triethylsilane is the sole source of hydrogen.

In the case of 4-iodophenylalanine, mass spectroscopic analysis of the hydrogenation reactions, using both H_2 and TES, at various time points revealed that the aromatic side chain is deiodinated first. This is in keeping with dehalogenation of aromatic halides with hydrogenation, which is known to

dx.doi.org/10.1021/jo500911v | J. Org. Chem. 2014, 79, 8422−8427

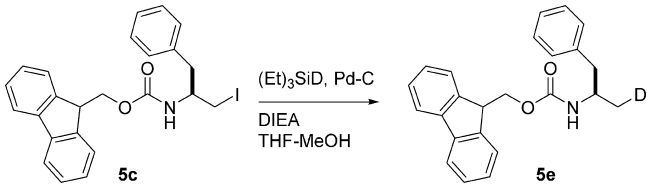
Table 1. Yields of the Conversion of α-Iodomethylamines to α-Methylamines by Base-Mediated Dehydrohalogenation

	Iodomethyl Substrate **c**	Protected α-Methylamine, **d**	% Yield [a] H_2-Pd/C	% Yield [a] TES-Pd/C
1			91	88
2			64	91
3			91	b
4			81	76
5			89	82
6			83	65
7			90	81
8			78	83
9			92	88
10			77	84
11			85	81
12			88	81
13			84	80

[a]Yields are calculated from weights of final products after chromatographic purification. [b]The N-protected α-methylamine was not separable from nonpolar, silane-based side products resulting from the TES in the CTH reaction.

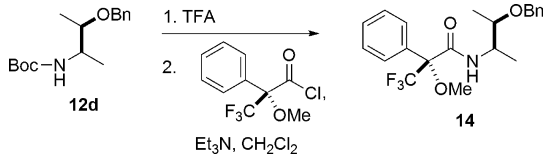
be very rapid.[21] Attempts to deiodinate the iodomethyl derivative of 4-nitrophenylalanine, using both procedures, resulted in mixtures of compounds, indicating that the conditions are not selective with respect to the reduction of nitro groups.

Scheme 2



To test for epimerization of the α-carbon during these procedures, we converted both L- and D-Boc-Thr(Bn)-OH to the corresponding α-methylamines, **12d** and **13d**, respectively, using both H_2 and TES conditions. As threonine has two chiral centers, it was reasoned that the potential diastereomers resulting from the synthesis would be readily detected. Chiral HPLC indicated the presence of single diastereomers. Neither ^{1}H nor ^{13}C NMR spectra indicated the presence of more than one stereoisomer. As further proof, the Boc group was removed from **12d** and the α-methylamine was derivatized with Mosher's reagent to give a product with three stereocenters (**14**, Scheme 3). Chiral HPLC of the unpurified product showed one peak, and ^{1}H and ^{19}F NMR showed only one set of resonances. Thus, the chirality of the α-carbon remains intact during all phases of the transformation. This is in keeping with the work of Quagliato et al., who reported that reduction of α-iodomethylamines derived from *N*-Boc-amino acids either with H_2/Pearlman's catalyst or with L-Selectride to form α-methylamines did not epimerize the α-carbon.[11]

Scheme 3



In summary, dehydrohalogenation of the alkyl amines derived from N-protected amino acids can be accomplished by conventional hydrogenolysis or CTH in the presence of a tertiary amine. Hydrogenation under alkaline conditions leaves intact side-chain protecting groups, thus allowing the conversion of virtually any protected amino acid into the corresponding α-methylamine. Removal of the amino protecting group would permit facile incorporation into peptidomimetic or other drug candidates.

EXPERIMENTAL SECTION

Preparation of N-Protected β-Amino Alcohols (General Procedure).[16,17] The preparation of Boc-LeuψCH_2OH, **1b**, is given as an example. A solution of Boc-Leu-OH (4.34 g, 18.8 mmol) in dry THF (40 mL) was cooled to −10 °C under an argon atmosphere. *N*-Methylmorpholine (NMM) (2.5 mL, 22.6 mmol, 1.2 equiv) was added, followed by dropwise addition of isobutyl chloroformate (2.9 mL, 22.6 mmol, 1.2 equiv). After stirring at −10 °C for 10 min, the reaction was allowed to increase to room temperature over 60 min. The precipitated NMM hydrochloride was filtered off, and the filtrate cooled to −10 °C. $NaBH_4$ (1.07 g, 28.2 mmol, 1.5 equiv) was added. After 15 min, the reaction was quenched with 2% $KHSO_4$ (25 mL) until the effervescence ceased. Ethyl acetate (200 mL) was added, and the solution was washed with water (200 mL) and 5% $NaHCO_3$ (100 mL), followed by brine (100 mL), before drying over $MgSO_4$. Filtering

dx.doi.org/10.1021/jo500911v | J. Org. Chem. 2014, 79, 8422−8427

and removal of the solvent under reduced pressure gave the protected amino alcohol of sufficient purity to proceed to the next reaction. Analysis was done by TLC and/or HPLC and NMR.

Alternate Procedure: Preparation of Boc-Leucinol, 1b. In this case, a procedure different from the above was utilized. Leucine methyl ester hydrochloride (1 equiv; 27.5 mmol) and Boc-anhydride (1.5 equiv; 41.3 mmol) were dissolved in CH_2Cl_2 (135 mL), and triethylamine (1.5 equiv, 41.3 mmol, 5.5 mL) was added. The mixture was stirred for 3 h at room temperature. The solution was washed with 2% $KHSO_4$ (100 mL) and 5% $NaHCO_3$ (100 mL), followed by brine (50 mL), before drying over $MgSO_4$. Removal of the solvent under reduced pressure gave the Boc-leucine methyl ester as a clear oil. The Boc-leucine methyl ester and $NaBH_4$ (4 equiv, 88.9 mmol) were dissolved in dry THF (110 mL) under an argon atmosphere, and methanol (24 equiv, 22 mL) was added dropwise. The vigorous effervescence was controlled by a cold water bath. After 3 h, the volume of the solution was reduced under reduced pressure to ca. 80 mL and quenched with water (100 mL) before extracting with ethyl acetate (2 × 100 mL). The extract was washed with brine (100 mL) and dried over $MgSO_4$. Filtering and removal of the solvent gave the product as a clear oil.

Preparation of Protected Amino Iodides (General Procedure).[18] The preparation of Boc-Leu$\psi$$CH_2$I, **1c**, is provided as an example. Iodine (7.99 g, 27.6 mmol, 2 equiv) was added to triphenyl phosphine (7.23 g, 27.6 mmol, 3 equiv) and imidazole (3.13 g, 46 mmol, 5 equiv) dissolved in CH_2Cl_2 (60 mL), and the mixture was stirred for 30 min. Boc-leucinol (2.00 g, 9.2 mmol, 1 equiv) dissolved in CH_2CL_2 (20 mL) was added dropwise. After 2 h, the white precipitate was filtered and the filtrate was washed with brine (2 × 100 mL) before drying over $MgSO_4$. Removal of the solvent under reduced pressure gave a brown solid that was purified by silica gel chromatography using 10−20% ethyl acetate in hexane. Yield 2.0 g, 67%, starting from 9.2 mmol of **1b**. Identical to that reported by Caputo et al.[22] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93−1.00 (m, 6H), 1.36 (t, J = 7.0 Hz, 2H), 1.46 (s, 9H), 1.57−1.72 (m, 1H), 3.26−3.33 (m, 1H), 3.36−3.52 (m, 2H), 4.5 (brs, 1H).

*Z-Leu$\psi$$CH_2$I, **2c**.* Yield 2.5 g, 88%, starting from 7.96 mmol of **2b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90−0.94 (m, 6H), 1.36 (m, 2H), 1.62 (m, 1H), 3.26 (m, 1H), 3.4−3.54 (m, 2H), 4.9 (d, J = 9.0 Hz, 1H), 5.1 (s, 2H), 7.3−7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.4, 22.5, 22.7, 24.7, 44.2, 48.5, 66.9, 128.1, 128.2, 128.6, 136.4, 155.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{21}INO_2$ 362.0617; Found 362.0662.

*Boc-Phe$\psi$$CH_2$I, **3c**.* Yield 2.16 g, 65%, starting from 9.2 mmol of **3b**. Identical to that reported by Quagliato et al.[11] and Caputo et al.[22] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.8 (dd, J = 8.1 and 13.2 Hz, 1H), 2.93 (dd, J = 5.7 and 13.5 Hz, 1H), 3.18 (dd, J = 4.0 and 10.1 Hz, 1H), 3.42 (dd, J = 4.1 and 10.0 Hz, 1H), 3.62 (m, 1H), 4.7 (brs, 1H), 7.25−7.36 (m, 5H).

*Z-Phe$\psi$$CH_2$I, **4c**.* Yield 1.2 g, 85%, starting from 4.2 mmol of **4b**. Identical to that reported by Caputo et al.[22] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82 (dd, J = 8.0 and 13.6 Hz, 1H), 2.95 (dd, J = 6.0 and 13.9 Hz, 1H), 3.2 (dd, J = 4.0 and10.3 Hz, 1H), 3.43 (dd, J = 4.4 and 10.1 Hz, 1H), 3.71 (m, 1H), 4.95 (d, J = 7.7 Hz, 1H), 5.1 (s, 2H), 7.22−7.43 (m 10H).

*Fmoc-Phe$\psi$$CH_2$I, **5c**.* Yield 2.3 g, 85%, starting from 5.2 mmol of **5b**. Identical to that reported by Caputo et al.[22] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.0−2.8 (m, 2H), 3.2 (dd, J = 3.6 and 10.0 Hz, 1H), 3.45 (dd, J = 4.2 and 10.2 Hz, 1H), 3.7 (m, 1H), 4.24 (t, J = 6.8 Hz, 1H), 4.42 (d, J = 6.7 Hz, 2H), 4.93 (d, J = 8.1 Hz, 1H), 7.26−7.36 (m, 7H), 7.4−7.46 (m, 2H), 7.56−7.62 (m, 2H), 7.8 (d, J = 7.5 Hz, 2H).

*Z-Lys(Boc)$\psi$$CH_2$I, **6c**.* Yield 2.0 g, 76%, starting from 5.46 mmol of **6b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.3−1.6 (m, 15H), 3.1 (m, 2H), 3.31 (m, 1H), 3.41 (m, 2H), 4.6 (brs, 1H), 5.0 (brs, 1H), 5.1 (s, 2H), 7.3−7.4 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.8, 28.5, 29.7, 34.6, 40.1, 50.4, 66.9, 79.1, 128.1, 128.2, 128.6, 136.3, 155.7, 156.1. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{30}IN_2O_4$ 477.1250; Found 477.1288.

*Fmoc-Glu(OBn)$\psi$$CH_2$I, **7c**.* Yield 1.3 g, 68%, starting from 3.5 mmol of **7b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ1.9 (m, 2H), 2.43 (m, 2H), 3.3 (m, 1H), 3.4 (m, 1H), 3.5 (m, 1H), 4.2 (t, J = 7.0 Hz, 1H), 4.41 (m, 2H), 4.93 (d, J = 9.0 Hz, 1H), 5.1 (s, 2H), 7.27−7.42 (m, 9H), 7.6 (d, J = 7.5 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.5, 30.1, 30.6, 47.3, 50.3, 66.6, 66.8, 120.0, 125.0, 127.1, 127.7, 128.3, 128.4, 128.6, 135.7, 141.3, 143.8, 155.6, 172.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{27}INO_4$ 556.0985; Found 556.1021.

*Z-Tyr(Bn)$\psi$$CH_2$I, **8c**.* Yield 2.3 g, 89%, starting from 5.2 mmol of **8b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.68 (dd, J = 8.0 and 13.2 Hz, 1H), 2.8 (dd, J =5.6 and 13.2 Hz, 1H), 3.13 (dd, J = 3.34 and10.5 Hz,1H), 3.35 (dd, J = 3.5 and 9.4 Hz, 1H), 3.6 (m, 1H), 4.86 (d, J = 8.0 Hz, 1H), 5.00 (s, 2H), 5.05 (s, 2H), 6.8 (d, J = 8.1 Hz, 2H), 7.1 (d, J = 8.1 Hz, 2H), 7.25−7.6 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.9, 155.4, 137.0, 136.3, 133.3, 133.2, 131.3, 131.2, 130.2, 129.6, 129.0, 128.8, 128.7, 128.6, 128.6, 128.2, 128.1, 128.0, 127.5, 115.1, 70.1, 66.9, 51.7, 39.7, 13.5. HRMS (ESI-TOF) m/z:$[M + NH_4]^+$ Calcd for $C_{24}H_{28}IN_2O_3$ 519.1145; Found 519.1154.

*Fmoc-Ser(Bn)$\psi$$CH_2$I, **9c**.* Yield 1.8 g, 72%, starting from 4.95 mmol of **9b**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38 (m, 2H),3.5 (m, 1H), 3.7 (m, 1H), 3.8 (m, 1H), 4.2 (t, J = 7.4 Hz, 1H), 4.42 (m, 2H), 4.52 (s, 2H), 5.2 (d, J = 8.2 Hz, 1H), 7.27−7.42 (m, 9H), 7.6 (d, J = 7.5 Hz, 2H), 7.75 (d, J = 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 47.3, 51.1, 67.0, 70.4, 73.5, 120.1, 125.1, 127.1, 127.8, 127.8, 128.0, 128.2, 128.6, 137.6, 141.4, 143.9, 155.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{25}INO_3$ 514.0879; Found 514.0890.

*Fmoc-Trp(Boc)$\psi$$CH_2$I, **10c**.* Yield 1.4 g, 57%, starting from 4.0 mmol of **10b**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.71 (s, 9H), 2.98 (m, 1H), 3.09 (m, 1H), 3.32(m, 1H),3.48 (m, 1H),3.9 (m, 1H), 4.27 (t, J = 7.0 Hz,1H), 4.41−4.49 (m, 2H), 5.1 (d, J = 7.75 Hz, 1H),7.3−7.46 (m, 7H), 7.56−7.63 (m, 3H), 7.7 (d, J = 8.0 Hz, 1H), 7.8 (d, J = 7.6 Hz, 2H), 8.18 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.6, 149.6, 143.8, 141.3, 135.5, 130.2, 127.8, 127.1, 125.1, 124.7, 124.2, 122.8, 120.1, 119.1, 115.7, 115.4, 83.8, 67.0, 50.3, 47.2, 30.5, 28.2, 13.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{31}H_{32}IN_2O_4$ 623.1407; Found 623.1409.

*Fmoc-His(Boc)$\psi$$CH_2$I, **11c**.* Yield 1.6 g, 63%, starting from 4.4 mmol of **11b**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.63 (s, 9H), 2.90 (m, 1H), 3.04 (m, 1H), 3.26 (m, 1H), 3.39 (m. 1H), 3.97 (m, 1H), 4.26 (m, 1H), 4.38 (m, 2H), 6.06 (d, J = 8.1 Hz, 1H), 7.29 (s, 1H), 7.32−7.35 (m, 2H), 7.41−7.43 (m, 2H), 7.61−7.64 (m, 2H), 7.78 (d, J = 7.5.Hz, 2H), 8.08 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 155.6, 146.8, 143.9, 141.3, 138.6, 137.0, 127.7, 127.1, 125.2, 120.0, 115.1, 85.9, 66.9, 50.9, 47.2, 31.6, 27.9, 18.9, 10.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{29}IN_3O_4$ 574.1203; Found 574.1214.

*Boc-L-Thr(OBzl)$\psi$$CH_2$I, **12c**.* Yield 1.0 g, 73%, starting from 3.4 mmol of Boc-L-Thr(OBzl)-CH_2OH. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22 (d, J = 6.3 Hz, 3H), 1.44 (s, 9H), 3.24−3.3 (m, 2H), 3.72 (m, 1H), 4.02 (m, 1H), 4.41 (d, J = 11.3 Hz, 1H), 4.63 (d, J = 11.3 Hz, 1H), 5.00(d, J = 9.0 Hz, 1H), 7.27−7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 6.9, 16.7, 28.4, 56.3, 71.3, 73.5, 79.7, 127.9, 128.0, 128.5, 138.0, 155.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{25}INO_3$ 406.0879; Found 406.0872.

*Boc-D-Thr(OBzl)$\psi$$CH_2$I, **13c**.* Yield 1.04 g, 76%, starting from 3.4 mmol of Boc-D-Thr(OBzl)-CH_2OH. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22 (d, J = 6.3 Hz, 3H), 1.44 (s, 9H), 3.24−3.3 (m, 2H), 3.72 (m, 1H), 4.02 (m, 1H), 4.40 (d, J = 11.3 Hz, 1H), 4.63 (d, J = 11.3 Hz, 1H), 5.00(d, J = 9.0 Hz, 1H), 7.27−7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 6.9, 16.7, 28.4, 56.3, 71.3, 73.5, 79.7, 127.9, 128.0, 128.5, 138.0, 155.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{25}INO_3$ 406.0879; Found 406.0882.

Dehalogenation of N-Protected β-Amino Iodides (General Procedure). The conversion of Boc-Leu$\psi$$CH_2$I, **1c**, to Boc-Leu$\psi$$CH_3$, **1d**, is given as an example.

Method A, Conventional Hydrogenation. Boc-Leu$\psi$$CH_2$I, **1c** (2.00 g, 6.11 mmol, 1 equiv), and DIEA (1.60 mL, 9.17 mmol, 1.5 equiv) were dissolved in a mixture of THF (27 mL) and methanol (55 mL), and 10% palladium on charcoal (0.200 g) was added. The mixture was hydrogenated at 49 psi and room temperature for 24 h in a Parr apparatus. The solvent was removed, and the residue was dissolved in 100 mL of EtOAc and filtered through Celite. The filtrate

dx.doi.org/10.1021/jo500911v | J. Org. Chem. 2014, 79, 8422−8427

was concentrated under vacuum, and the crude product was purified by silica gel chromatography eluting with 10−20% ethyl acetate in hexane.

Method B, Catalytic Transfer Hydrogenation with TES. Boc-LeuψCH_2I, **1c** (0.700 g, 2.14 mmol1 equiv, 2.14 mmol), triethylsilane (3.4 mL, 21.4 mmol; 10 equiv), and DIEA (0.56 mL, 3.21 mmol, 1.5 equiv) were dissolved in a mixture of THF (24 mL) and methanol (47 mL), and 10% palladium on charcoal (70 mg) was added into it. The mixture was stirred at room temperature for 24 h.

The solvent was removed under vacuum, and the residue was dissolved in 50 mL of EtOAc and filtered through Celite. Solvent was removed, and the crude was then purified by silica gel chromatography as above.

Boc-LeuψCH_3, ***1d.*** Yield: Method A: 1.1 g, 88%, starting from 6.11 mmol of **1c**; Method B: 0.391 g, 91%, starting from 2.14 mmol of **1c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 (bs, 1H), 3.70 (bs, 1H), 1.68 (m, 1H), 1.43 (s, 9H), 1.36 (m, 2H), 1.10 (d, J = 7.0 Hz, 2H), 0.92 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.3, 78.9, 77.3, 77.0, 76.8, 46.7, 44.7, 28.6, 28.4, 25.0, 22.7, 22.6, 21.8. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{11}H_{23}NNaO_2$ 224.1626; Found 224.1616.

Z-NHLeuψCH_3, ***2d.*** Yield: Method A: 1.2 g, 64%, starting from 8.03 mmol of **2c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37−7.29 (m, 5H), 5.13−5.04 (m, 2H), 4.51 (d, J = 8.0 Hz, 1H), 3.82−3.77 m, 1H), 1.69−1.60 (m, 1H), 1.39−1.16 (m, 2H), 1.14 (d, J = 7.0 Hz, 3H), 0.93 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.8, 136.7, 128.6, 128.2, 128.2, 128.1, 128.1, 66.5, 46.6, 45.3, 25.0, 22.8, 22.5, 21.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{22}NO_2$ 236.1651; Found 236.1611.

Boc-PheψCH_3, ***3d.***[11] Yield: Method A: 1.23 g, 91%, starting from 5.73 mmol of **3c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24−7.17 (m, 5H), 4.36 (bd, 1H), 3.91 (m, 1H), 2.87 (m, 2H), 1.45 (s, 9H), 1.14 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2, 138.3, 129.7, 129.5, 129.3, 128.6, 128.5, 128.3, 126.5, 126.3, 49.1, 47.4, 43.0, 28.4, 20.2, 19.1. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{21}NNaO_2$ 258.1470; Found 258.1471.

Z-PheψCH_3, ***4d.*** Yield: Method A: 0.28 g, 81%, starting from 1.27 mmol of **4c**; Method B: 0.310 g, 76%, starting from 1.52 mmol of **4c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.15 (m, 10H), 5.09 (s, 2H), 4.60 (m, 1H), 4.00 (m, 1H), 2.8 (m, 2H), 1.14(d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.6, 137.9, 136.6, 129.5, 128.6, −128.4, 128.1, 126.5, 66.51, 48.0, 42.8, 20.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{20}NO_2$ 270.1494; Found 270.1536.

Fmoc-PheψCH_3, ***5d.*** Yield: Method A: 0.340 g, 89%, starting from 1.03 mmol of **5c**; Method B: 1.105 g, 82%, starting from 3.66 mmol of **5c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 7.5 Hz, 2H), 7.58 (m, 2H), 7.43−7.15 (m, 9H), 4.59 (bd, 1H), 4.48−4.18 (m, 4 H), 2.83 (m, 2H), 1.14 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.6, 144.0, 141.4, 137.9, 129.6, 128.4, 127.7, 127.1, 126.5, 125.1, 125.1, 120.0, 66.4, 48.0, 47.3, 42.7, 20.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{24}NO_2$ 358.1807; Found 358.1829.

Z-Lys(Boc)ψCH_3, ***6d.*** Yield: Method A: 0.795 g, 83%, starting from 2.85 mmol of **6c**; Method B: 0.24 g, 65%, starting from 1.06 mmol of **6c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.30 (m, 5H), 5.08 (s, 2H), 4.57 (m, 2H), 3.73 (m, 1H), 3.11 (m, 2H), 1,27−1.54 (m, 15H), 1.14 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.1, 155.9, 136.6, 128.5, 128.2, 128.1, 66.5, 47.0, 40.3, 36.7, 29.8, 23.1, 21.3. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{19}H_{31}N_2O_4$ 351.2284; Found 351.2285.

Fmoc-Glu(OBn)ψCH_3, ***7d.*** Yield: Method A: 0.28 g, 90%, starting from 0.72 mmol of **7c**; Method B: 0.383 g, 81%, starting from 1.1 mmol of **7c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 2H), 7.59 (d, 2H, J = 7.5 Hz), 7.43−7.30 (m, 9H), 5.10 (s, 2H), 4.62 (d, J = 8.7 Hz, 2H), 4.40 (d, J = 7.0 Hz, 2H), 4.00 (t, J = 7.0 Hz, 1H), 3.77 (m, 1H), 2.43 (t, J = 7.5 Hz, 2H), 1.60−1.93 (m, 2H), 1.18 (d, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.4, 155.9, 144.0, 143.9, 141.3, 135.9, 128.6, 128.3, 127.70, 127.52, 127.46, 127.07, 125.1, 120.22, 120.00, 66.4, 66.4, 60.46, 47.3, 46.9, 31.9, 31.1, 21.4. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{27}H_{28}NO_4$ 430.2018; Found 430.2011.

Z-Tyr(Bn)ψCH_3, ***8d.*** Yield: Method A: 0.295 g, 78%; Method B: 0.310 g, 83%, starting from 1.0 mmol of **8c**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.14 (d, J = 7.0 Hz, 3H), 2.7 (m, 1H), 2.8 (m, 1H), 3.98 (m, 1H), 4.62 (m, 1H), 5.07 (s, 2H), 5.11 (s, 2H), 6.93 (d, J = 8.5 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.33−7.42 (m, 6H), 7.45−7.48 (m, 3H), 7.52−7.55 (m, 1H), 7.58−7.63 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 157.5, 137.1, 133.3, 133.2, 131.3, 130.5, 130.2, 129.4, 129.1, 128.8, 128.7, 128.6, 128.5, 128.1, 127.9, 127.5, 114.8, 70.0, 66.5, 48.1, 41.9, 20.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{26}NO_3$ 376.1913; Found 376.1942.

Fmoc-Ser(OBn)ψCH_3, ***9d.*** Yield: Method A: 0.345 g, 92%; Method B: 0.330 g, 88%, starting from 0.97 mmol of **9c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (d, J = 6.0 Hz, 3H), 3.45 (m, 2H), 3.92 (m, 1H), 4.2 (t, J = 7.0 Hz, 1H), 4.38 (d, J = 7.0 Hz, 2H), 4.52 (m, 2H), 4.98 (brs, 1H),7.25−7.43 (m, 9H), 7.6 (d, J = 7.5 Hz, 2H), 7.75 (d, J = 7.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.1, 47.3, 66.6, 73.1, 73.2, 120.0, 125.1, 127.0, 127.6, 127.7, 127.8, 128.5, 138.1, 141.3, 144.0, 155.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{25}H_{26}NO_3$ 388.1913; Found 388.1924.

Fmoc-Trp(Boc)ψCH_3, ***10d.*** Yield: Method A: 0.124 g, 77%; Method B: 0.135 g, 84%, starting from 0.32 mmol of **10c**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22 (m, 2H), 1.69 (s, 9H), 2.82 (m, 1H), 3.03 (m, 1H), 4.15 (m, 1H), 4.24 (m, 1H), 4.4−4.48 (m, 2H), 4.87 (m, 1H), 7.28 (m, 1H), 7.30−7.37 (m, 3H), 7.40−7.48 (m, 3H),7.57−7.61 (m, 2H), 7.66 (m, 1H), 7.79 (m, 2H), 8.16 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.8, 149.7, 144.0, 141.3, 130.9, 127.7, 127.1, 125.1, 124.4, 123.9, 122.6, 120.0, 119.3, 116.9, 115.3, 83.6, 66.6, 47.3, 47.0, 32.2, 28.2, 20.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{31}H_{33}N_2O_4$ 497.2440; Found 497.2456.

Fmoc-His(Boc)ψCH_3, ***11d.*** Yield: Method A: 0.200 g, 85%; Method B: 0.190 g, 81%, starting from 0.53 mmol of **11c**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.22 (d, J = 6.0 Hz, 3H), 1.62 (s, 9H), 2.75 (m, 1H), 2.82 (m, 1H), 4.08 (m, 1H), 4.25 (m, 1H), 4.34 (m, 1H), 4.40 (m, 1H), 5.63 (d, J = 6.5 Hz, 1H), 7.20 (s, 1H), 7.31−7.34 (m, 2H), 7.39−7.43 (m, 2H), 7.60−7.63 (m, 2H), 7.78 (d, J = 7.5 Hz, 2H), 8.06 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.8, 147.0, 144.1, 141.3, 136.7, 127.6, 127.0, 125.2, 120.0, 114.5, 85.5, 66.6, 47.3, 46.8, 34.2, 27.9, 20.5. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{26}H_{30}N_3O_4$ 448.2236; Found 448.2257.

Fmoc-PheψCH_2D, ***5e.*** To a stirred suspension of Fmoc-phenylalanino iodide (100 mg, 0.21 mmol), DIPEA (0.1 mL, 0.63 mmol), dissolved in a mixture of 10 mL of THF−MeOH (9:1), and 10% Pd−C (10 mg), was added Et_3SiD (10 equiv; 0.3 mL). It was stirred at room temperature for 12 h (HPLC analysis showed quantitative conversion), and the mixture was then centrifuged. The supernatant was then concentrated and purified by RPHPLC. The pure fractions were then collected and lyophilized to get a white solid (48 mg, Yield: 65%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.14 (s, 2H), 2.76 (m, 1H), 2.86 (m, 1H), 4.03 (m, 1H), 4.24 (t, J = 6.5 Hz, 1H), 4.37 (m, 1H), 4.48 (m, 1H), 4.65 (m,1H), 7.20 (m, 2H), 7.26 (m, 1H), 7.31−7.36 (m, 4H), 7.44 (m, 2H), 7.60 (m, 2H), 7.80 (d, J = 7.5 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 155.6, 144.0, 141.4, 137.9, 129.5, 128.4, 127.7, 127.1, 126.5, 125.1, 125.0, 120.0, 66.4, 47.9, 47.4, 42.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{24}H_{23}DNO_2$ 359.1870; Found 359.1886.

Boc-L-Thr(OBzl)ψCH_3, ***12d.*** Yield: Method A: 0.30 g, 88%; Method B: 0.28 g, 81%, starting from 1.23 mmol of Boc-L-Thr(OBzl)-CH_2I (**12c**). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.16−1.18 (m, 6H). 1.44 (s, 9H), 3.5 (m, 1H), 3.72 (m, 1H), 4.42 (d, J = 11.6 Hz, 1H), 4.6 (d, J = 11.6 Hz, 1H), 4.73 (m, 1H), 7.25−7.36 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.1, 18.1, 28.4, 50.3, 71.0, 78.9, 127.6, 127.7, 128.3, 138.6, 155.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{26}NO_3$ 280.1913; Found 280.1914. Chiral HPLC R_t: 22.06 min. (Chiralpak IC Column; mobile phase: water/MeCN, gradient 55−75% MeCN/50 min, 0.5 mL/min, monitored at 254 nm).

Boc-D-Thr(OBzl)ψCH_3, ***13d.*** Yield: Method A: 0.29 g, 84%; Method B: 0.276 g, 80%, starting from 1.23 mmol of Boc-D-Thr(OBzl)-CH_2I (**13c**). ^{1}H NMR (600 MHz, $CDCl_3$) δ1.16−1.18 (m, 6H), 1.44 (s, 9H), 3.5 (m, 1H), 3.72 (m, 1H), 4.42 (d, J = 11.6 Hz, 1H), 4.61 (d, J = 11.6 Hz, 1H), 4.74 (m, 1H), 7.26−7.36 (m, 5H). ^{13}C NMR (75 MHz,

dx.doi.org/10.1021/jo500911v | J. Org. Chem. 2014, 79, 8422−8427

$CDCl_3$): δ 16.1, 18.1, 28.4, 50.2, 71.0, 78.9, 127.6, 127.7, 128.3, 138.6, 155.8. HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{26}NO_3$ 280.1913; Found 280.1917. Chiral HPLC R_t: 22.86 min. (Chiralpak IC Column; mobile phase: water/MeCN, gradient 55−75% MeCN/50 min, 0.5 mL/min, monitored at 254 nm).

Preparation of Mosher's Adduct, 14. Boc deprotection of **12d** (100 mg) was done by treating with 0.5 mL of trifluoroacetic acid (TFA) for 1 h. Excess TFA was removed under vacuum and stripped off residual amount with CCl_4. The crude TFA salt (50 mg, 0.28 mmol) was then dissolved in 1.0 mL of dry CH_2Cl_2. To this solution, cooled in ice, 120 μL of triethylamine (0.84 mmol) followed by 52 μL, (0.28 mmol) of (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (Mosher's acid chloride), was added. After completion, as monitored by reverse phase HPLC, 100 μL of water was added and the mixtures were passed through a short silica gel column that was washed with an additional 10 mL of CH_2Cl_2. The organic eluate was concentrated under vacuum, yielding a colorless oil. (82 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.18 (d, *J* = 6.7 Hz, 3H), 1.2 (d, *J* = 6.3 Hz, 3H), 3.4 (s, 3H), 3.56 (m, 1H), 4.1 (m, 1H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.65 (d, *J* = 11.8 Hz, 1H), 7.0 (d, *J* = 8.5 Hz, 1H), 7.26−7.41 (m, 8H), 7.50−7.55 (m, 2H). ^{19}F NMR (470 MHz, $CDCl_3$) δ −68.75 (s, 3F). HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{25}F_3NO_3$ 396.1787; Found 396.1790. Chiral HPLC R_t: 26.64 min. (Chiralpak IC Column; mobile phase: water/MeCN, gradient 50−80% MeCN/30 min, 0.5 mL/min, monitored at 254 nm).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of alkyl iodides and final α-methylamines, ^{19}F NMR spectrum of **14**, and HPLC chromatograms of compounds **12d**, **13d**, and **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jmcmurra@mdanderson.org.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the American Asthma Foundation (Award Number: 11-0360) and the Center for Targeted Therapy for support of this work. We also acknowledge the NCI Cancer Center Support Grant P30 CA016672 at MDACC for support of the NMR facility and the Translational Chemistry Core Facility, which provided mass spectrometry.

■ REFERENCES

(1) Mandal, P. K.; Gao, F.; Lu, Z.; Ren, Z.; Ramesh, R.; Birtwistle, J. S.; Kaluarachchi, K. K.; Chen, X.; Bast, R. C.; Liao, W. S.; McMurray, J. S. *J. Med. Chem.* **2011**, *54*, 3549−3563.

(2) Dallanoce, C.; Frigerio, F.; De, A. M.; Dorsch, S.; Klotz, K.-N.; De, M. C. *Bioorg. Med. Chem.* **2007**, *15*, 2533−2543.

(3) Bloom, J. D.; Dutia, M. D.; Johnson, B. D.; Wissner, A.; Burns, M. G.; Largis, E. E.; Dolan, J. A.; Claus, T. H. *J. Med. Chem.* **1992**, *35*, 3081−3084.

(4) Kohno, H.; Iwakuma, T.; Yamada, K. *Synth. Commun.* **1998**, *28*, 1935−1945.

(5) Fuso, L.; Mores, N.; Valente, S.; Malerba, M.; Montuschi, P. *Curr. Med. Chem.* **2013**, *20*, 1477−1495.

(6) Lipp, R.; Arrang, J. M.; Garbarg, M.; Luger, P.; Schwartz, J. C.; Schunack, W. *J. Med. Chem.* **1992**, *35*, 4434−4441.

(7) Friary, R. J.; Mangiaracina, P.; Nafissi, M.; Orlando, S. C.; Rosenhouse, S.; Seidl, V. A.; Shih, N. Y. *Tetrahedron* **1993**, *49*, 1993−1996.

(8) Ye, Q.; Grunewald, G. L. *J. Med. Chem.* **1989**, *32*, 478−486.

(9) Nichols, D. E.; Snyder, S. E.; Oberlender, R.; Johnson, M. P.; Huang, X. *J. Med. Chem.* **1991**, *34*, 276−281.

(10) Gorczynski, R. J.; Anderson, W. G.; Stout, D. M. *J. Med. Chem.* **1981**, *24*, 835−839.

(11) Quagliato, D. A.; Andrae, P. M.; Matelan, E. M. *J. Org. Chem.* **2000**, *65*, 5037−5042.

(12) Barrett, D. G.; Deaton, D. N.; Hassell, A. M.; McFadyen, R. B.; Miller, A. B.; Miller, L. R.; Payne, J. A.; Shewchuk, L. M.; Willard, D. H., Jr.; Wright, L. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3039−3043.

(13) Donner, B. G. *Tetrahedron Lett.* **1995**, *36*, 1223−1226.

(14) Mandal, P. K.; McMurray, J. S. *J. Org. Chem.* **2007**, *72*, 6599−6601.

(15) Bandgar, B. P.; Modhave, R. K.; Wadgaonkar, P. P.; Sande, A. R. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1993−1994.

(16) Kokotos, G. *Synthesis* **1990**, 299−301.

(17) Rodriguez, M.; Linares, M.; Doulut, S.; Heitz, A.; Martinez, J. *Tetrahedron Lett.* **1991**, *32*, 923−926.

(18) Mondal, S.; Fan, E. *Synlett* **2006**, 306−308.

(19) Oba, M.; Kobayashi, M.; Oikawa, F.; Nishiyama, K.; Kainosho, M. *J. Org. Chem.* **2001**, *66*, 5919−5922.

(20) Oba, M.; Terauchi, T.; Miyakawa, A.; Kamo, H.; Nishiyama, K. *Tetrahedron Lett.* **1998**, *39*, 1595−1598.

(21) Anwer, M. K.; Spatola, A. F. *Tetrahedron Lett.* **1985**, *26*, 1381−1384.

(22) Caputo, R.; Cassano, E.; Longobardo, L.; Palumbo, G. *Tetrahedron* **1995**, *51*, 12337−12350.