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N,*N*′-Carbonyldiimidazole-Mediated Cyclization of Amino Alcohols to Substituted Azetidines and Other *N*-Heterocycles

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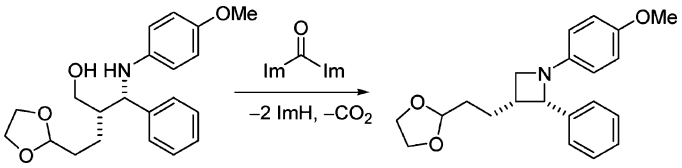


Amino alcohols are important synthons for *N*-heterocycles. We have developed an efficient method to activate hydroxyl groups, which avoids the use of toxic reagents and tolerates a wide variety of functional groups. Our strategy has been applied to the synthesis of functionalized *p*-methoxyphenyl-protected azetidines, pyrrolidines, and piperidines. The required amino alcohols were synthesized according to an optimized proline-catalyzed Mannich protocol. An azetidine analogue of ezetimibe was synthesized to demonstrate the potential for the synthesis of drug-like molecules.

Introduction

Saturated *N*-heterocycles[1] represent an important class of compounds that exhibit biological activity. Despite the development of many useful strategies for their synthesis, the intramolecular displacement of a hydroxyl group with an amino group remains the most predictable. Coupled together with the Mannich reaction,[2] many natural and non-natural bioactive compounds could be accessed in an efficient manner, as illustrated in Figure 1.[3]

To induce the cyclization of a given amino alcohol, the hydroxyl group requires activation (Scheme 1). Insensitive substrates can be activated with the aid of strong mineral acids, such as hydrobromic acid, leading to cyclic amines as their hydrobromide salts (eq 1). Often, however, these harsh conditions are incompatible with functional groups. Therefore, milder protocols have been developed that involve the activation of the hydroxyl group, for example, as a mesylate (eq 2), followed by base-induced ring closure.[4] The most common methods today involve Mitsunobu-type activation[5] with DEAD (eq 3) or Appel-type protocols using carbon tetrabromide and triphenylphosphine.[6] The drawback of these protocols is the use of toxic and

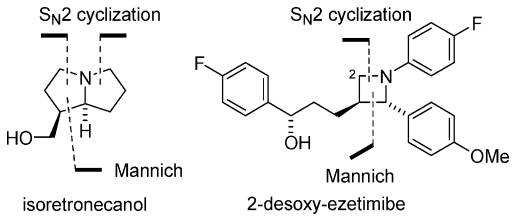
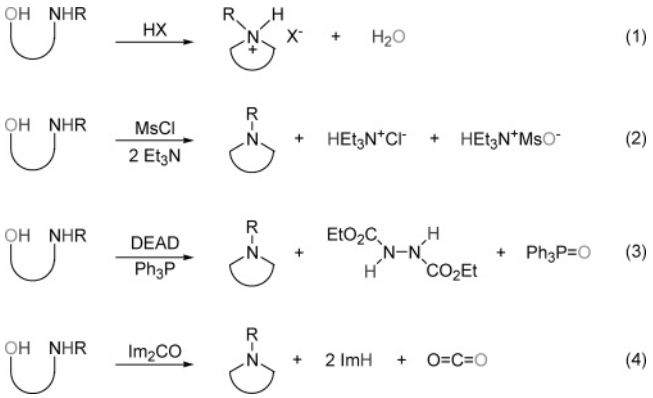


FIGURE 1. Mannich-Cyclization approach to *N*-heterocycles.

SCHEME 1. Mass Balance of Cyclization Processes



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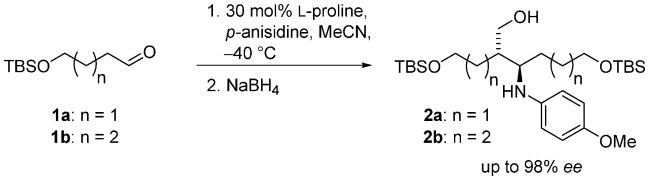
expensive reagents. In addition, byproducts are formed that are difficult to separate or to recycle. Our new method employs readily available and nontoxic 1,1-carbonyldiimidazole (CDI) and affords imidazole and carbon dioxide as the byproducts (eq 4).

In a recent communication,[7] we reported the synthesis of 1,2-disubstituted *N*-heterocycles, comprised of a proline-catalyzed Mannich reaction,[8,9] followed by a cyclization with Staab's reagent[10] (1,1-carbonyldiimidazole). In this paper, we want to give a full account of our studies and extend the strategy to the synthesis of higher substituted heterocycles. In addition, the unexpected oxidative cleavage of diarylazetidines provides access to chiral amino ketones.

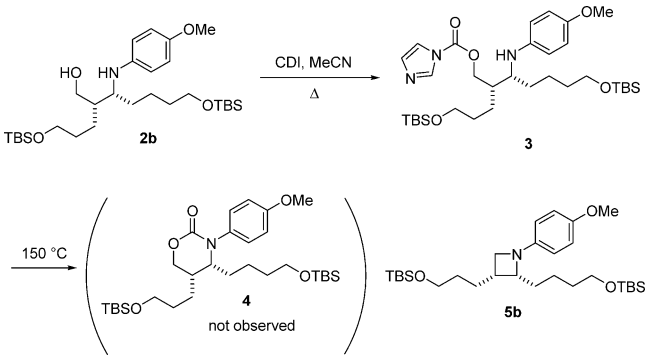
Results and Discussion

As an organocatalytic[11] entry into *N*-heterocyclic systems, we were investigating the proline-catalyzed self-Mannich reaction or Mannich dimerization of aldehydes,[12] bearing an additional site for functionalization. After a good deal of experimentation, we found that the Mannich reaction with *tert*-butyldimethylsiloxy-protected aldehydes[13] **1a** and **1b** gave the desired products **2a** and **2b** in up to 98% ee (Scheme 2).

SCHEME 2. Mannich Dimerization of Functionalized Aldehydes



SCHEME 3. Cyclization of γ-Amino Alcohols



Acetonitrile as the solvent and a very low temperature (−40 °C) were the essentials for a high selectivity.

To determine the relative configuration of the major diastereomer, we wanted to convert amino alcohol **2b** into the cyclic carbamate derivative **4**. For *N*,*N*-dialkyl *β*-amino alcohols, the CDI method usually affords the corresponding oxazinones in high yields.[14] However, when **2b** and CDI were refluxed in acetonitrile for 12 h, not even a trace of the desired 1,3-oxazin-2-one **4** was detected. Instead, carbamate **3** had formed, which refused to cyclize to **4**. Disappointed by this result, in a final attempt, crude **3** was heated to 150 °C in a Kugelrohr apparatus under high vacuum. To our surprise, not the desired carbamate,[15] but the azetidine **5b** was formed (Scheme 3).

To test the scope and limitation of this azetidine synthesis,[16,17] a series of amino alcohols derived from proline-catalyzed Mannich reactions was subjected to our cyclization protocol. Benzylic (Table 1, entries 3, 8−10) as well as aliphatic *p*-methoxyphenyl (PMP) amines (Table 1, entries 1−2, 4−7) were used in the reaction. In addition, standard protecting groups such as acetates (entries 4 and 5), TBS ethers (entries 1−3), and acetals (entries 9 and 10) were tested, which would allow for further functionalization of the products (vide infra). The method is not limited to the synthesis of 2,3-*cis*-azetidines (entry 5), though we mainly examined *syn*-amino alcohols as a result of their preferential formation in the proline-catalyzed Mannich process.[18]

All reactions were carried out in a Kugelrohr apparatus. The imidazole formed in the reaction as well as azetidines of low

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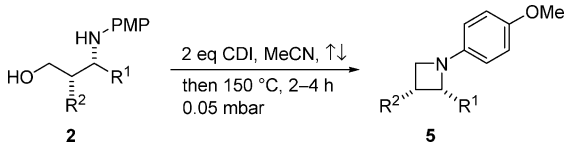
TABLE 1. Synthesis of Azetidines

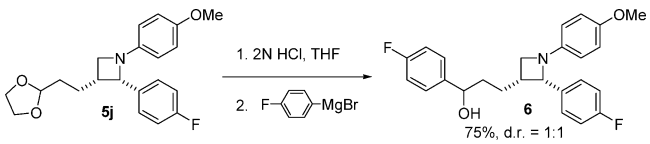


2 **5**

entry	amino alcohol	azetidine	R^2	R^1	yield (%)
1	**2a**	**5a**	$(CH_2)_2OTBS$	$(CH_2)_3OTBS$	73
2	**2b**	**5b**	$(CH_2)_3OTBS$	$(CH_2)_4OTBS$	71
3	**2c**	**5c**	$(CH_2)_3OTBS$	Ph	74
4	**2d**	**5d**	$(CH_2)_2OAc$	$(CH_2)_3OAc$	82
5[a]	**2e**	**5e**	$(CH_2)_2OAc$	$(CH_2)_3OAc$	84
6	**2f**	**5f**	Me	Et	71
7	**2g**	**5g**	Et	Pr	75
8	**2h**	**5h**	Me	Ph	82
9	**2i**	**5i**	$(CH_2)_3CH$-[O−$(CH_2)_2$−O]	Ph	86
10	**2j**	**5j**	$(CH_2)_3CH$-[O−$(CH_2)_2$−O]	4-C_6H_4F	90

[a] The minor *anti*-diastereomer from the Mannich reaction was used to obtain the corresponding azetidine with *anti*-configuration.

SCHEME 4. Functionalization of 5j



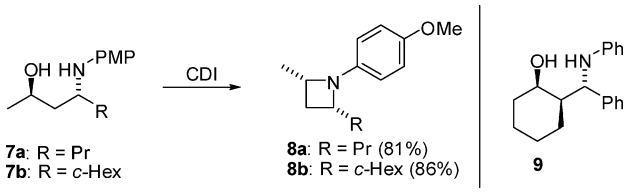
5j

molecular weight condense in the receiving flask. The nonpolar azetidines are easily separated by filtration through silica gel. The relative stereochemistry in the azetidine ring can be easily deduced from NOE experiments. For compound **5i**, an X-ray structure (see the Supporting Information) was obtained that supports our structural assignment.

All azetidines were accessible in just two synthetic steps. To demonstrate their facile conversion into drug-like molecules, **5j** was treated with acid, which resulted in the liberation of the carbonyl group. The addition of commercially available 4-fluorophenylmagnesium bromide to the crude aldehyde afforded an azetidine relative (**6**) of ezetimibe[19] as a separable 1:1 mixture of diastereomers (Scheme 4). Recently, Carreira et al. have shown that azetidine analogues are as potent as their parent β-lactams.[20] Similar as in β-lactam drugs such as ezetimibe, the central azetidine moiety can be regarded as a scaffold that places the pharmacophoric groups in the correct orientation. We, therefore, investigated the possibility of extending this methodology to azetidines with other substitution patterns.

The synthesis of 2,4-disubstituted azetidines has been achieved by displacement of 1,3-dibromides or -mesylates with a monosubstituted amine.[21] Formally, these heterocycles can also be accessed by a proline-catalyzed addition of ketones to imines, followed by reduction to the amino alcohols and subsequent

SCHEME 5. Synthesis of 2,4-Substituted Azetidines



7a: R = Pr
7b: R = *c*-Hex

8a: R = Pr (81%)
8b: R = *c*-Hex (86%)

9

CDI-mediated cyclization. We submitted the known[22] amino alcohols **7a** and **7b** to our cyclization reaction with CDI (Scheme 5). The corresponding azetidines **8a** and **8b** were obtained in good to excellent yields, whereas the amino alcohol **9**[23] failed to cyclize to the desired bicyclic system.

Interestingly, the above-mentioned cyclizations occur with clean inversion of configuration at the C−O carbon atom (**7a** → **8a**, Scheme 6, eq 1). This clearly supports an S_N2-type mechanism, where the C−N bond formation and the decarboxylation occur simultaneously. Our results nicely complement the findings of Mulvihill[24] and Szmuszkovicz.[25] They showed that benzylic hydroxyl groups bearing a tertiary β-amino group can be substituted under retention of configuration with imidazole (**11** → **14**) using CDI. The observed stereochemical outcome was explained with the intermediacy of an aziridinium−imidazolyl ion pair **13** (eq 2). The question of why the formation of the four-membered *N*-heterocycle is faster than the ring closure to the cyclic carbamate cannot be answered at this point. Recent competition experiments[26] showed that the cyclizations to the azetidine can under certain circumstances even surpass the piperidine formation.

To apply our method to the synthesis of larger rings,[27] the primary alcohol **2a** was protected as TBDPS ether, and the TBS groups were subsequently removed with *p*-toluenesulfonic acid in methanol (Scheme 7). When the resulting diol **15** was heated with 3 equiv of CDI in acetonitrile, the cyclization occurred smoothly. The remaining carbamate was cleaved with 2 N NaOH/THF. Interestingly, the disubstituted pyrrolidine **16** was observed almost exclusively.

Piperidine **17** was obtained in two steps from **2c**, which was synthesized in a three-component Mannich reaction of 5-*tert*-butyldimethylsilyloxypentanal and benzaldehyde as a nonenolizable Mannich acceptor (Scheme 8). The TBS group was cleaved (TBAF), and the resulting diol was refluxed with CDI in acetonitrile for 2 h. After removal of the solvent, the reaction mixture was heated to 150 °C under high vacuum in a Kugelrohr apparatus to facilitate the decarboxylative cyclization. Hydrolysis of the remaining carbamate afforded piperidine **17** in 60% yield.

The PMP group of **5g** was removed easily by oxidation with ceric ammonium nitrate (CAN).[28] To facilitate the isolation, the crude amine was treated with Boc_2O to afford the Boc-protected azetidine **18** in 72% yield for two steps (Scheme 9, eq 1). However, when azetidine **5h** was subjected to this deprotection

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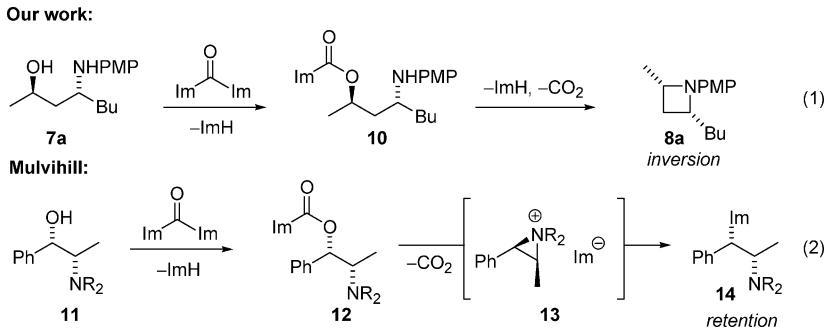
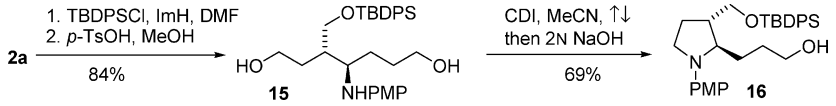
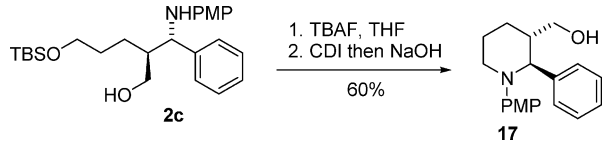
SCHEME 6. Mechanism of CDI-Mediated Cyclizations



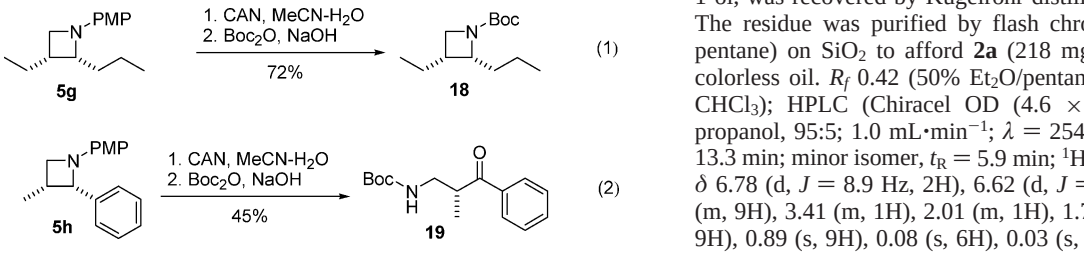
SCHEME 7. Synthesis of Pyrrolidine 16



SCHEME 8. Synthesis of Piperidine 17



SCHEME 9. Removal of PMP and the Unexpected Cleavage of the C−N Bond



protocol, oxidation occurred at the benzylic position leading to the corresponding amino ketone **19** (eq 2).

Conclusion

Employing our newly developed CDI-mediated ring closure, we have synthesized a variety of *N*-heterocycles, ranging from azetidines to piperidines. We have further shown that the initial products can be easily converted into drug-like molecules. In combination with the rapidly expanding repertoire of enantioselective Mannich reactions, this strategy will provide access to structurally diverse PMP-protected *N*-heterocycles. We are currently trying to apply this methodology to the synthesis of small alkaloid natural products and an azetidine library for screening purposes.

Experimental Section

The amino alcohols **2f**−**h** have been described previously.[8h] The compounds **2c**, **2i**, and **2j** were prepared according to refs 7 and 8h. The spectroscopic data of the minor diastereomers are given, although their absolute configurations were not determined.

Preparation of (2*S*,3*R*)-6-(*tert*-Butyldimethylsilyloxy)-2-[(2-*tert*-butyldimethylsilyloxy)ethyl]-3-(4-methoxyphenylamino)-hexan-1-ol (2a). To a stirred solution (−40 °C) of L-proline (17.3 mg, 0.15 mmol) and *p*-anisidine (61.6 mg, 0.5 mmol) in MeCN (5 mL) was added 4-*tert*-butyldimethylsilyloxybutanal (809 mg, 4 mmol). The mixture was stirred for 2 h at this temperature and then kept in a freezer (−30 °C) for 24 h. The mixture was diluted with Et_2O (2 mL) and allowed to reach 0 °C. After the addition of $NaBH_4$ (400 mg, 10.6 mmol), the reaction was stirred for 15 min at this temperature and poured into half-saturated aqueous NH_4Cl (50 mL). After 30 min, the mixture was extracted with Et_2O (3 × 50 mL), and the combined organic layers were dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded the crude product as a colorless oil. The byproduct, 4-*tert*-butyldimethylsilyloxybutan-1-ol, was recovered by Kugelrohr distillation (100 °C, 0.2 mbar). The residue was purified by flash chromatography (50% Et_2O/pentane) on SiO_2 to afford **2a** (218 mg, 0.43 mmol, 85%) as a colorless oil. R_f 0.42 (50% Et_2O/pentane); $[\alpha]^{25}_D$ −17.2 (*c* 0.98, $CHCl_3$); HPLC (Chiracel OD (4.6 × 250 mm); *n*-heptane/2-propanol, 95:5; 1.0 mL·min^{-1}; λ = 254 nm); major isomer, t_R = 13.3 min; minor isomer, t_R = 5.9 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78 (d, J = 8.9 Hz, 2H), 6.62 (d, J = 8.9 Hz, 2H), 3.80−3.55 (m, 9H), 3.41 (m, 1H), 2.01 (m, 1H), 1.70−1.48 (m, 6H), 0.91 (s, 9H), 0.89 (s, 9H), 0.08 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 141.7, 115.5 (2C), 114.9 (2C), 64.4, 62.7, 61.7, 58.0, 55.7, 40.1, 30.5, 29.8, 27.7, 25.9 (6C), 18.2 (2C), −5.4 (2C), −5.5 (2C); IR ($CHCl_3$) 3378, 2932, 2891, 2858, 1513, 1468, 1251, 1098, 1043, 836, 776 cm^{-1}; HRMS calcd for $C_{27}H_{53}NO_4Si_2$ (M^+), 511.3515; found, 511.3513. Anal. Calcd for $C_{27}H_{53}NO_4Si_2$: C, 63.35; H, 10.44; N, 2.74. Found: C, 62.91; H, 10.26; N, 3.17. **Epimer:** colorless oil; R_f 0.44 (50% Et_2O/pentane); $[\alpha]^{25}_D$ −3.2 (*c* 0.81, $CHCl_3$); HPLC (Chiracel OD (4.6 × 250 mm); *n*-heptane/2-propanol, 95:5; 1.0 mL·min^{-1}; λ = 254 nm); major isomer, t_R = 7.6 min; minor isomer, t_R = 5.9 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.75 (d, J = 8.9 Hz, 2H), 6.56 (d, J = 8.9 Hz, 2H), 3.80−3.45 (m, 9H), 3.39−3.30 (m, 1H), 1.82−1.93 (m, 1H), 1.79−1.43 (m, 6H), 0.89 (s, 9H), 0.88 (s, 9H), 0.06 (s, 6H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 142.3, 115.0 (2C), 114.6 (2C), 64.0, 62.9, 62.3, 57.2, 55.8, 42.0, 31.9, 29.3, 28.4, 25.9 (6C), 18.3, 18.2, −5.3 (2C), −5.5 (2C); IR ($CHCl_3$) 3391, 2933, 2859, 1514, 1468, 1251, 1097, 1042, 836, 774 cm^{-1}.

(2*S*,3*R*)-6-(*tert*-Butyldimethylsilyloxy)-2-[(3-*tert*-butyldimethylsilyloxy)propyl]-3-(4-methoxyphenylamino)-heptan-1-ol (2b). Colorless oil; R_f 0.40 (50% Et_2O/pentane); $[\alpha]^{25}_D$ −20.1 (*c* 0.80, $CHCl_3$); HPLC (Chiracel OD-H (4.6 × 250 mm); *n*-heptane/2-propanol, 98:2; 0.7 mL·min^{-1}; λ = 254 nm); major isomer, t_R = 63.4 min; minor isomer, t_R = 25.0 min; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81−6.74 (m, 2H), 6.70−6.62 (m, 2H), 3.75 (br s, 5H), 3.70−3.52 (m, 4H), 3.48−3.39 (m, 1H), 3.21 (br s, 2H), 1.89−1.24 (m, 11H), 0.91 (s, 9H), 0.87 (s, 9H), 0.06 (s, 6H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 141.7, 116.1 (2C), 114.9 (2C), 64.7, 63.1, 62.9, 58.8, 55.7, 41.6, 32.8, 31.5, 31.0, 26.0 (6C), 23.2, 22.2, 18.3 (2C), −5.3 (4C); IR (capillary) 3376, 2933, 2859,

1512, 1467, 1250, 1100, 1043, 837, 777 cm^{-1}; HRMS calcd for $C_{29}H_{57}NO_4Si_2$ (M^+), 539.3826; found, 539.3826; Anal. Calcd for $C_{29}H_{57}NO_4Si_2$: C, 64.51; H, 10.64; N, 2.59. Found: C, 64.28; H, 10.79; N, 2.34. **Epimer:** colorless oil; R_f 0.40 (50% Et_2O/pentane); $[\alpha]^{25}_D$ −1.3 (*c* 0.1, $CHCl_3$); HPLC (Chiracel OD-H (4.6 × 250 mm); *n*-heptane/2-propanol, 98:2; 0.7 mL·min^{-1}; λ = 254 nm); major isomer, t_R = 42.6 min; minor isomer, t_R = 27.6 min; ^1H NMR (300 MHz, $CDCl_3$) δ 6.78−6.72 (m, 2H), 6.63−6.58 (m, 2H), 6.86−6.79 (m, 1H), 6.74 (s, 3H), 6.73−6.64 (m, 1H), 3.61−3.52 (m, 4H), 3.39−3.30 (m, 1H), 3.20 (br s, 1H), 1.74−1.24 (m, 11H), 0.89 (s, 9H), 0.87 (s, 9H), 0.02 (s, 6H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 142.2, 115.5 (2C), 114.9 (2C), 64.4, 63.2, 62.9, 58.2, 55.8, 43.0, 32.9, 32.5, 30.4, 26.0, (6C), 24.8, 21.9, 18.3 (2C), −5.3 (4C); IR ($CHCl_3$) 3394, 2932, 2859, 1513, 1468, 1250, 1100, 1042, 837, 776 cm^{-1}.

(*S*)-5-(*tert*-Butyldimethylsilyloxy)-2-((*S*)-(4-methoxyphenylamino)(phenyl)methyl)pentan-1-ol (2c). Colorless foam; R_f 0.35 (25% EtOAc/pentane); $[\alpha]^{25}_D$ −20.0 (*c* 0.50, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 4H), 7.24−7.19 (m, 1H), 6.68 (d, *J* = 8.9 Hz, 2H), 6.51 (d, *J* = 8.9 Hz, 2H), 4.56 (d, *J* = 4.2 Hz, 1H), 3.70−3.67 (m, 5H), 3.60−3.53 (m, 1H), 2.05−1.96 (m, 1H), 1.66−1.29 (m, 4H), 0.88 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 141.4, 141.3, 128.7 (2C), 127.0 (2C), 126.8, 115.1 (2C), 114.6 (2C), 64.0, 63.1, 61.4, 55.7, 46.3, 30.7, 26.0 (3C), 22.5, 18.4, −5.2 (2C); IR (KBr) 3309, 3186, 2936, 2856, 1513, 1473, 1247, 1105, 1036, 835, 776, 706 cm^{-1}; HRMS calcd for $C_{25}H_{39}NO_3Si$ (M^+), 429.2699; found, 429.2697. **Epimer:** colorless solid; R_f 0.35 (25% EtOAc/pentane); ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.27 (m, 4H), 7.23−7.17 (m, 1H), 6.66 (d, *J* = 8.9 Hz, 2H), 6.50 (d, *J* = 8.0 Hz, 2H), 4.34 (d, *J* = 6.1 Hz, 1H), 3.80 (dd, *J* = 11.8, 2.8 Hz, 1H), 3.70 (dd, *J* = 11.4, 5.8 Hz, 1H), 3.68 (s, 3H), 3.55 (t, *J* = 5.9 Hz, 2H), 1.97−1.87 (m, 1H), 1.65−1.34 (m, 4H), 0.86 (s, 9H), 0.01 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 142.2, 140.7, 128.4 (2C), 126.9 (3C), 115.8 (2C), 114.6 (2C), 63.8 (2C), 63.2, 55.7, 45.9, 30.3, 26.0 (3C), 25.2, 18.4, −5.2 (2C); IR ($CHCl_3$) 3421, 3293, 2933, 2863, 1512, 1466, 1284, 1232, 1103, 1038, 834, 779, 743, 703 cm^{-1}.

(3*S*,4*R*)-3-(Hydroxymethyl)-4-(4-methoxyphenylamino)heptane-1,7-diyl diacetate (2d). Colorless oil; HPLC (Daicel AD (4.6 × 250 mm); 2-propanol/*n*-heptane, 1:10; 0.7 mL·min^{-1}; λ = 230 nm); major enantiomer, t_R = 44.3 min; minor enantiomer, t_R = 48.1 min; $[\alpha]^{25}_D$ −12.2 (*c* 0.14, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.80−6.84 (m, 2H), 6.65−6.60 (m, 2H), 4.22−3.99 (m, 4H), 3.76−3.74 (m, 5H), 3.54−3.52 (m, 1H), 2.05 (s, 3H), 2.03 (s, 3H), 1.96−1.81 (m, 1H), 1.80−1.50 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 171.0, 152.6, 141.6, 115.5 (2C), 115.0 (2C), 64.2, 63.9, 62.9, 57.3, 55.7, 39.5, 28.6, 26.0, 25.6, 20.9 (2C); IR ($CHCl_3$) 3506, 3394, 2951, 1733, 1514, 1465, 1368, 823, 757 cm^{-1}.

(3*R,4*R**)-3-(Hydroxymethyl)-4-(4-methoxyphenylamino)-heptane-1,7-diyl diacetate (2e).** Colorless oil; HPLC ((*S*,*S*)-Whelk01 (4.6 × 250 mm); ethanol/*n*-heptane, 1:10; 0.5 mL·min^{-1}; λ = 254 nm); major enantiomer, t_R = 57.1 min; minor enantiomer, t_R = 53.5 min; $[\alpha]^{25}_D$ −6.4 (*c* 0.81, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.78−6.73 (m, 2H), 6.61−6.50 (m, 2H), 4.10−3.99 (m, 4H), 3.90−3.82 (m, 1H), 3.74 (s, 3H), 3.73−3.64 (m, 1H), 3.53−3.43 (m, 2H), 2.92 (br s, 1H), 2.03 (s, 3H), 2.00 (s, 3H), 1.90−1.46 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 171.1, 152.2, 141.7, 115.0 (2C), 114.8 (2C), 64.2, 63.2, 62.8, 56.2, 55.8, 40.0, 28.7, 27.3, 25.4, 20.9 (2C); IR ($CHCl_3$) 3499, 3397, 3018, 2955, 1732, 1513, 1465, 1368, 1241, 1039, 822, 757 cm^{-1}; HRMS calcd for $C_{19}H_{29}NO_6$ (M^+), 367.1995; found, 349.1993.

(*S*)-4-(1,3-Dioxolan-2-yl)-2-((*S*)-(4-methoxyphenylamino)(phenyl)methyl)butan-1-ol (2i). Colorless solid; R_f = 0.35 (33% pentane/Et_2O); $[\alpha]^{25}_D$ −23.8 (*c* 0.51, $CDCl_3$); HPLC (Chiralpac AS (4.6 × 250 mm); *n*-heptane/2-PrOH, 7:3; 0.8 mL·min^{-1}; λ = 230 nm); major isomer, t_R = 8.33 min; minor isomer, t_R = 11.02 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.26 (m, 4H), 7.24−7.17 (m, 1H), 6.70−6.64 (m, 2H), 6.53−6.40 (m, 2H), 4.79 (t, *J* = 4.5 Hz, 1H), 4.53 (d, *J* = 4.4 Hz, 1H), 3.95−3.79 (m, 1H), 3.70−3.64 (m, 4H), 2.07−1.96 (m, 1H), 1.81−1.37 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 152.2, 141.5, 141.3, 128.4 (2C), 127.1 (2C), 126.9, 115.2 (2C), 114.7 (2C), 104.4, 64.9, 64.8, 63.7, 31.5, 55.7, 46.3, 31.6, 20.3; IR (KBr) 3314, 3193, 2949, 2880, 1510, 1479, 1409, 1286, 1256, 1232, 865, 1030, 818, 700 cm^{-1}; Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found C, 70.42; H, 8.05; N, 3.70.

(*S*)-4-(1,3-Dioxolan-2-yl)-2-((*S*)-(4-fluorophenyl)(4-methoxyphenylamino)methyl)butan-1-ol (2j). Colorless solid; mp 89−91 °C; $[\alpha]^{24}_D$ +1.37 (*c* 1.02, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (ddd, *J* = 2.0, 5.0, 6.2 Hz, 2H), 6.91 (t, *J* = 8.2 Hz, 2H), 6.61 (d, *J* = 8.5 Hz, 2H), 6.43 (d, *J* = 8.8 Hz, 2H), 4.72 (t, *J* = 4.4 Hz, 1H), 4.45 (d, *J* = 3.0 Hz, 1H), 3.85 (m, 2H), 3.75 (m, 2H), 3.61 (m, 5H), 1.85 (m, 1H), 1.61 (m, 2H), 1.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 and 160.5 (*J* = 244.0 Hz), 152.2, 141.0, 137.0, 128.7 and 128.6 (2C, *J* = 8.4 Hz), 115.4 and 115.2 (2C, *J* = 12.9 Hz), 115.1 (2C), 114.7 (2C), 104.4, 65.0, 64.9, 63.6, 61.0, 55.8, 46.3, 31.6, 20.4; ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.0; IR ($CHCl_3$) 3309, 2930, 2878, 1512, 1244, 1141, 1033, 820 cm^{-1}. Anal. Calcd for $C_{21}H_{26}FNO_4$: C, 67.18; H, 6.98; N, 3.73. Found: C, 67.31; H, 6.82; N, 3.74.

(2*S*,3*R*)-7-(*tert*-Butyldimethylsilyloxy)-2-(3-(*tert*-butyldimethylsilyloxy)propyl)-3-(4-methoxyphenylamino)heptyl 1*H*-Imidazole-1-carboxylate (3). Colorless oil; R_f 0.15 (50% Et_2O/pentane); $[\alpha]^{25}_D$ −6.8 (*c* 0.53, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.38 (s, 1H), 7.07 (s, 1H), 6.72 (d, *J* = 8.9 Hz, 2H), 6.50 (d, *J* = 8.3 Hz, 2H), 4.43 (d, *J* = 5.5 Hz, 2H), 3.72 (s, 3H), 3.64 (t, *J* = 5.7 Hz, 2H), 3.56 (t, *J* = 6.0 Hz, 2H), 3.47 (m, 1H), 3.15 (br s, 1H), 2.13 (m, 1H), 1.70−1.30 (m, 6H), 0.89 (s, 9H), 0.86 (s, 9H), 0.50 (s, 6H), 0.00 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 148.6, 141.9, 136.9, 130.6, 116.9, 115.0 (2C), 114.1 (2C), 68.8, 62.8, 62.7, 55.7, 55.0, 40.4, 32.6, 31.9, 30.9, 25.9 (6C), 23.4, 23.3, 18.3, 18.2, −5.4 (4C); IR ($CHCl_3$) 3322, 3129, 2933, 2858, 1764, 1514, 1469, 1403, 1317, 1242, 1176, 1100, 837, 775, 652 cm^{-1}; HRMS calcd for $C_{33}H_{59}N_3O_5Si_2$ (M^+), 633.3993; found, 633.3993.

General Procedure for the Preparation of the Azetidines 5. A solution of the corresponding amino alcohol (0.2 mmol) and 1,1′-carbonyldiimidazole (0.4 mmol) in MeCN (10 mL) was refluxed for 2 h. The solvent was evaporated in vacuo, and the intermediate carbamates were heated to 150 °C in a Kugelrohr oven under high vacuum (0.1 mbar) for 2 h. Products of lower molecular weight were collected in the receiving flask. The residue was purified by flash chromatography on silica gel to afford the azetidines.

(2*S*,3*R*)-3-(2-(*tert*-Butyldimethylsilyloxy)ethyl)-2-(3-(*tert*-butyldimethylsilyloxy)propyl)1-(4-methoxyphenyl)-azetidine (5a). Colorless oil; R_f 0.50 (17% Et_2O/pentane); $[\alpha]^{25}_D$ −95.6 (*c* 0.96, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, *J* = 9.0 Hz, 2H), 6.52 (d, *J* = 9.0 Hz, 2H), 3.95 (q, *J* = 7.7, 1 Hz), 3.75 (s, 3H), 3.74−3.55 (m, 6H), 2.72−2.57 (m, 1H), 2.06−1.80 (m, 4H), 1.60 (m, 2H), 0.92 (s, 9H), 0.91 (s, 9H), 0.08 (s, 6H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 147.1, 114.5 (2C), 113.4 (2C), 66.2, 62.8, 61.4, 56.7, 55.7, 32.4, 30.1, 29.5, 27.4, 25.9 (6C), 18.3 (2C), −5.3 (2C), −5.4 (2C); IR (capillary) 2933, 2896, 2857, 1513, 1469, 1244, 1101, 836, 777 cm^{-1}; HRMS calcd for $C_{27}H_{51}NO_3Si_2$ (M^+), 493.3407; found, 493.3408.

(2*S*,3*R*)-2-(4-(*tert*-Butyldimethylsilyloxy)butyl)-3-(3-(*tert*-butyldimethylsilyloxy)propyl)1-(4-methoxyphenyl)-azetidine (5b). Colorless oil; R_f 0.40 (17% Et_2O/pentane); $[\alpha]^{25}_D$ −55.0 (*c* 0.76, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, *J* = 8.8 Hz, 2H), 6.50 (m, 2H), 3.89 (m, 1H), 3.75 (s, 3H), 3.68−3.56 (m, 6H), 2.58−2.42 (m, 1H), 1.90−1.28 (m, 10H), 0.91 (s, 18H), 0.06 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 147.2, 114.6 (2C), 113.5 (2C), 66.6, 63.2, 63.0, 56.8, 33.2, 33.1, 30.9, 30.8, 26.9 (6C), 25.7, 22.8, 18.4 (2C), −5.2 (4C); IR ($CHCl_3$) 2933, 2858, 1511, 1468, 1245, 1102, 1044, 837, 777 cm^{-1}; HRMS calcd for $C_{29}H_{55}NO_3Si_2$ (M^+), 521.3721; found, 521.3721.

(2*S*,3*R*)-1-(4-Methoxyphenyl)-3-(3-(*tert*-butyldimethylsilyloxy)-propyl)-2-phenylazetidine (5c). Colorless oil; R_f 0.50 (9% Et_2O/

pentane); $[\alpha]^{25}_D$ −103.3 (*c* 0.26, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.24 (m, 5H), 6.85 (d, J = 8.9 Hz, 2H), 6.35 (d, J = 8.9 Hz, 2H), 5.01 (d, J = 8.3 Hz, 1H), 3.80 (t, J = 7.1 Hz, 1H), 3.74 (s, 3H), 3.65 (dd, J = 6.7, 3.0 Hz, 1H), 3.46 (t, J = 6.2 Hz, 2H), 2.80−2.65 (m, 1H), 1.50−1.10 (m, 4H), 0.84 (s, 9H), −0.03 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 146.4, 139.5, 128.1 (2C), 127.0, 126.9 (2C), 114.5 (2C), 113.3 (2C), 69.4, 63.0, 55.8, 55.3, 35.4, 30.3, 27.1, 25.9 (3C), 18.3, −5.4 (2C); IR ($CHCl_3$) 3003, 2950, 2856, 1511, 1470, 1242, 1100, 1043, 834, 758 cm^{-1}; HRMS calcd for $C_{25}H_{37}NO_2Si$ (M^+), 411.2593; found, 411.2595.

3-((2*R*,3*R*)-3-(2-Acetoxyethyl)-1-(4-methoxyphenyl)azetidin-2-yl)propyl acetate (5d). Colorless oil; R_f 0.32 (50% Et_2O/pentane); $[\alpha]^{25}_D$ −72.0 (*c* 0.83, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.80 (d, J = 8.9 Hz, 2H), 6.49 (d, J = 8.9 Hz, 2H), 4.15−4.07 (m, 4H), 3.95 (q, J = 6.6 Hz, 1H), 3.75 (s, 3H), 3.65 (dd, J = 3.5, 7.1 Hz, 1H), 3.61 (t, J = 7.5 Hz, 1H), 2.61 (m, 1H), 2.15−2.08 (m, 1H), 2.07 (s, 3H), 2.06 (s, 3H), 2.05−1.96 (m, 1H), 1.88−1.82 (m, 2H), 1.70−1.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1 (2C), 152.6, 146.6, 114.6 (2C), 113.5, 65.5, 64.2, 62.7, 56.3, 55.7, 30.1, 28.4, 27.5, 25.4, 20.9; IR ($CHCl_3$) 2953, 2847, 1739, 1511, 1468, 1367, 1241, 1040, 822 cm^{-1}; HRMS calcd for $C_{19}H_{27}NO_5$ (M^+), 349.1889; found, 349.1890.

3-((2*R,3*S**)-3-(2-Acetoxyethyl)-1-(4-methoxyphenyl)azetidin-2-yl)propyl acetate (5e).** Colorless oil; R_f 0.32 (50% Et_2O/pentane); $[\alpha]^{25}_D$ −16.8 (*c* 0.41, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (d, J = 8.9 Hz, 2H), 6.46 (d, J = 8.9 Hz, 2H), 4.15−4.01 (m, 5H), 3.75 (s, 3H), 3.66−3.58 (m, 1H), 3.20 (t, J = 7.0 Hz, 1H), 2.55−2.41 (m, 1H), 2.06 (s, 3H), 2.05 (s, 3H), 2.00−1.66 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 171.0, 152.4, 146.7, 114.7 (2C), 113.0 (2C), 70.1, 64.4, 62.5, 56.5, 55.8, 34.2, 33.3, 32.4, 24.1, 21.0, 20.9; IR ($CHCl_3$) 2950, 1738, 1511, 1241, 1040, 757 cm^{-1}; HRMS calcd for $C_{19}H_{27}NO_5$ (M^+), 349.1889; found, 349.1889.

(2*R*,3*R*)-2-Ethyl-1-(4-methoxyphenyl)-3-methylazetidine (5f). Colorless oil; R_f 0.29 (9% Et_2O/pentane); $[\alpha]^{25}_D$ −146.5 (*c* 1.04, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, J = 8.9 Hz, 2H), 6.51 (d, J = 8.9 Hz, 2H), 3.77 (m, 1H), 3.75 (s, 3H), 3.62 (dd, J = 8.0, 6.8 Hz, 1H), 3.48 (dd, J = 6.8, 3.2 Hz, 1H), 2.65 (m, 1H), 1.83 (m, 2H), 1.30 (d, J = 7.2 Hz, 3H), 0.92 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 147.4, 114.5 (2C), 113.5 (2C), 67.9, 58.1, 55.7, 27.5, 23.8, 14.7, 10.2; IR (capillary) 2961, 2873, 2834, 1511, 1465, 1293, 1240, 1120, 1041, 819 cm^{-1}; HRMS calcd for $C_{13}H_{19}NO$ (M^+), 205.1467; found, 205.1467.

(2*R*,3*R*)-3-Ethyl-1-(4-methoxyphenyl)-2-propylazetidine (5g). Colorless oil; R_f 0.50 (17% Et_2O/pentane); $[\alpha]^{25}_D$ −170.0 (*c* 0.90, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, J = 9.0 Hz, 2H), 6.52 (d, J = 9.0 Hz, 2H), 3.89 (dt, J = 8.4, 4.4 Hz, 1H), 3.76 (s, 3H), 3.61−3.56 (m, 2H), 2.48−2.32 (m, 1H), 1.65−1.65 (m, 4H), 1.43−1.29 (m, 2H), 1.00 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 147.4, 114.5 (2C), 113.4 (2C), 66.4, 56.5, 55.7, 35.2, 33.3, 22.3, 19.7, 14.3, 11.7; IR (capillary) 2956, 2867, 2835, 1510, 1464, 1240, 1042, 820 cm^{-1}; HRMS calcd for $C_{15}H_{23}NO$ (M^+), 233.1780; found, 233.1780.

(2*S*,3*R*)-1-(4-Methoxyphenyl)-3-methyl-2-phenylazetidine (5h). Colorless oil; R_f 0.44 (9% Et_2O/pentane); $[\alpha]^{25}_D$ −267.8 (*c* 0.84, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41−7.27 (m, 5H), 6.78 (d, J = 9.0 Hz, 2H), 6.42 (d, J = 9.0 Hz, 2H), 5.00 (d, J = 8.3 Hz, 1H), 3.86 (dd, J = 7.7, 6.7 Hz, 1H), 3.74 (s, 3H), 3.59 (dd, J = 6.6, 2.8 Hz, 1H), 2.88 (m, 1H), 0.93 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 146.4, 139.6, 128.0 (2C), 126.8, 126.7 (2C), 114.5 (2C), 113.3 (2C), 69.5, 57.0, 55.8, 30.2, 16.2; IR (capillary) 2965, 2932, 2875, 2802, 1447, 1406, 1247, 1140, 1107, 1081, 879, 859, 755, 692, 639, 552, 529, 505 cm^{-1}; HRMS calcd for $C_{17}H_{19}NO$ (M^+), 253.1467; found, 253.1467.

(2*S*,3*R*)-3-(2-(1,3-Dioxolan-2-yl)ethyl)-1-(4-methoxyphenyl)-2-phenylazetidine (5i). Colorless solid; R_f 0.35 (25% Et_2O/pentane); $[\alpha]^{25}_D$ −154.0 (*c* 0.83, $CHCl_3$); HPLC (Chiralpac AS (4.6 × 250 mm); *n*-heptane/*i*-PrOH, 6:4; 0.7 mL·min^{-1}; λ =214 nm); major isomer, t_R = 15.29 min; minor isomer, t_R = 10.56 min; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36−7.25 (m, 5H), 6.75−6.72 (m, 2H), 6.38−6.35 (m, 2H), 5.00−4.98 (m, 1H), 4.69−4.66 (m, 1H), 3.87−3.65 (m, 9H), 2.75 (m, 1H), 1.53−1.31 (m, 4H); ^{13}C (75 MHz, $CDCl_3$) δ 152.3, 146.3, 139.3, 128.2 (2C), 127.1, 126.9 (2C), 114.5 (2C), 113.3 (2C), 104.3, 69.2, 64.7, 55.8, 55.2, 35.4, 31.5, 25.2; IR ($CHCl_3$) 2952, 1511, 1241, 1136, 1038, 756, 704 cm^{-1}. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.24; N, 4.13. Found: C, 73.90; H, 7.45; N, 3.81.

(2*S*,3*R*)-3-(2-(1,3-Dioxolan-2-yl)ethyl)-2-(4-fluorophenyl)-1-(4-methoxyphenyl)azetidine (5j). Colorless solid; mp 85−88 °C; R_f 0.66 (Et_2O); $[\alpha]^{24}_D$ −6.94 (*c* 1.11, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (ddd, J = 3.0, 5.4, 8.4 Hz, 2H), 6.96 (t, J = 8.8 Hz, 2H), 6.67 (dd, J = 2.2, 6.7 Hz, 2H), 6.30 (dd, J = 2.2, 6.7 Hz, 2H), 4.89 (d, J = 8.4 Hz, 1H), 4.62 (t, J = 4.6 Hz, 1H), 3.80 (m, 2H), 3.71 (m, 2H), 3.64 (s, 3H), 3.59 (d, J = 3.2 Hz, 1H), 3.57 (d, J = 3.0 Hz, 1H), 2.66 (m, 1H), 1.43 (m, 2H), 1.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6 and 160.3 (J = 245.0 Hz), 152.3, 145.9, 134.9, 128.4 and 128.3 (2C, J = 8.0 Hz), 115.1 and 114.9 (2C, J = 21.7 Hz), 114.4 (2C), 113.2 (2C), 104.1, 68.4, 64.6 (2C), 55.6, 55.0, 35.2, 31.3, 25.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.8; IR ($CHCl_3$) 2940, 2848, 1509, 1239, 1038, 817 cm^{-1}. Anal. Calcd for $C_{21}H_{24}FNO_3$: C, 70.57; H, 6.77; N, 3.92. Found: C, 70.38; H, 6.48; N, 3.80.

Preparation of (*R*)-1-(4-Fluorophenyl)-3-((2*S*,3*R*)-2-(4-fluorophenyl)-1-(4-methoxyphenyl)azetidin-3-yl)propan-1-ol and (*S*)-1-(4-Fluorophenyl)-3-((2*S*,3*R*)-2-(4-fluorophenyl)-1-(4-methoxyphenyl)azetidin-3-yl)propan-1-ol (6). To a solution of **5j** (0.31 g, 0.86 mmol) in THF (5 mL) was added a solution of 2 N HCl (3 mL). The mixture was stirred for 4 h at room temperature. The mixture was quenched with a solution of $NaHCO_3$ and then extracted three times with CH_2Cl_2 (5 mL). The combined organic layers were dried with Na_2SO_4. Removal of the solvent on a rotary evaporator and filtration on Celite with CH_2Cl_2 gave the aldehyde as a yellow oil, which was used without purification in the next step. To a cold solution of the aldehyde (0.25 g, 0.8 mmol) in THF (8 mL) at −70 °C was added over 5 min (4-fluorophenyl)-magnesium bromide (1.2 mL, 1 M solution in THF, 1.2 mmol). After 2 h of stirring at −70 °C, the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with water and extracted with CH_2Cl_2 (3 × 10 mL). The organic fractions were combined and washed successively with water and brine. After drying (Na_2SO_4), filtration, and concentration, the crude compound was chromatographed on silica gel (pentane/AcOEt, 7:3) to give **6** (0.243 g, 0.59 mmol, 75%) as a colorless solid. **Less polar diastereomer:** mp 108−111 °C; R_f 0.59 (25% Et_2O/pentane); $[\alpha]^{25}_D$ −34.09 (*c* 1.03, $CHCl_3$); HPLC (LI60.M (250 × 4 mm); pentane/Et_2O, 6:4; 0.5 mL·min^{-1}; λ = 254 nm); major isomer, t_R = 12.5 min; minor isomer, t_R = 11.3 min; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (td, J = 2.6, 8.0 Hz, 2H), 7.08 (td, J = 2.5, 8.2 Hz, 2H), 6.93 (m, 4H), 6.65 (d, J = 8.8 Hz, 2H), 6.24 (d, J = 8.5 Hz, 2H), 4.87 (d, J = 8.0 Hz, 1H), 4.38 (t, J = 5.7 Hz, 1H), 3.68 (d, J = 4.5 Hz, 1H), 3.62 (s, 3H), 3.50 (d, J = 4.9 Hz, 1H), 2.62 (m, 1H), 1.67 (m, 1H), 1.32 (m, 1H), 1.25 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 and 160.8 (2C, J = 244.0 Hz), 152.3, 145.9, 140.2, 135.0, 128.6 and 128.5 (2C, J = 7.6 Hz), 127.3 and 127.2 (2C, J = 8.4 Hz), 115.3 and 115.2 (2C, J = 8.4 Hz), 115.1 and 115.0 (2C, J = 8.4 Hz), 114.6 (2C), 113.3 (2C), 73.9, 68.6, 55.9, 55.3, 36.9, 35.6, 27.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.0, −115.5; IR ($CHCl_3$) 3378, 3014, 2939, 2852, 1509, 1225, 757 cm^{-1}; HRMS calcd for $C_{25}H_{25}F_2NO_2$ (M^+), 409.1854; found, 409.1853. **More polar diastereomer:** mp 100−104 °C; $[\alpha]^{25}_D$ −43.4 (*c* 1.07 $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (td, J = 2.2, 6.0 Hz, 2H), 7.01 (td, J = 3.2, 6.0 Hz, 2H), 6.91 (m, 4H), 6.64 (d, J = 8.8 Hz, 2H), 6.24 (d, J = 8.8 Hz, 2H), 4.86 (d, J = 8.0 Hz, 1H), 4.33 (t, J = 6.0 Hz, 1H), 3.80 (d, J = 4.4 Hz, 1H), 3.62 (s, 3H), 3.52 (d, J = 4.4 Hz, 1H), 2.60 (m, 1H), 1.72 (m, 1H), 1.51 (m, 1H), 1.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 and 160.8 (2C, J = 245.0 Hz), 152.4, 145.9, 140.2, 135.0, 128.6 and 128.5 (2C, J = 7.6 Hz), 127.3 and 127.2 (2C, J = 8.4 Hz),

115.3 and 115.2 (2C, $J = 5.3$ Hz), 115.1 and 115.0 (2C, $J = 5.3$ Hz), 114.6 (2C), 113.3 (2C), 73.9, 68.5, 55.9, 55.3, 36.9, 35.6, 27.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −115.1, −115.6; IR ($CHCl_3$) 3346, 3010, 2942, 2855, 1509, 1227, 758 cm^{-1}; HRMS calcd for $C_{25}H_{25}F_2NO_2$ (M^+), 409.1854; found, 409.1853.

(±)-(2*R,4*S**)-2-Butyl-1-(4-methoxyphenyl)-4-methylazetidine (8a).** Colorless oil; R_f 0.62 (9% Et_2O/pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (d, $J = 9.0$ Hz, 2H), 6.58 (d, $J = 9.0$ Hz, 2H), 3.82−3.61 (m, 2H), 3.76 (s, 3H), 2.51 (dd, $J = 10.6$, 8.0 Hz, 1H), 2.00−1.87 (m, 1H), 1.75−1.59 (m, 2H), 1.47 (d, $J = 6.1$ Hz, 3H), 1.44−1.24 (m, 2H), 0.98 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 147,6, 114.6 (2C), 113.2 (2C), 61.1, 58.3, 55.8, 40.4, 32.2, 24.2, 18.2, 14.2; IR (capillary) 2958, 2928, 2862, 1510, 1242, 1042, 819 cm^{-1}; HRMS calcd for $C_{14}H_{21}NO$ (M^+), 219.1623; found, 219.1624.

(±)-(2*S,4*S**)-2-Cyclohexyl-1-(4-methoxyphenyl)-4-methylazetidine (8b).** Colorless solid; R_f 0.49 (9% Et_2O/pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81−6.74 (m, 2H), 6.59−6.53 (m, 2H), 3.74 (s, 3H), 3.83−3.65 (m, 1H), 3.61−3.50 (m, 1H), 2.41−2.29 (m, 1H), 1.92−1.60 (m, 7H), 1.43 (d, $J = 6.1$ Hz, 3H), 1.30−0.87 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 148.0, 114.6 (2C), 113.3 (2C), 66.1, 58.6, 55.8, 44.0, 29.8, 28.2, 27.2, 26.8, 26.4, 26.2, 24.0; IR ($CHCl_3$) 2925, 2852, 1509, 1242, 1042, 820, 758 cm^{-1}; HRMS calcd for $C_{17}H_{25}NO$ (M^+), 259.1936; found, 259.1936.

(±)-(1*R,2*R**)-2-((*S**)-Phenyl(phenylamino)methyl)cyclohexanol (9).** Prepared from (±)-(*R**)-2-((*S**)-phenyl(phenylamino)-methyl)cyclohexanone[23] by reduction with excess $NaBH_4$ in methanol. Colorless solid; R_f 0.36 (33% Et_2O/pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.15 (m, 5H), 7.09−7.01 (m, 2H), 6.61−6.44 (m, 3H), 4.45 (d, $J = 7.5$ Hz, 1H), 4.01 (br s, 1H), 1.85−1.16 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.6, 142.8, 129.1 (2C), 128.4 (2C), 126.9 (2C), 126.7 (2C), 116.7, 113.2, 66.9, 61.1, 47.5, 34.1, 25.9, 25.3, 20.1; IR (KBr) 3544, 3369, 2923, 2857, 1605, 1504, 1312, 974, 750, 699 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.22; H, 8.31; N, 4.91.

(3*S*,4*R*)-3-(*tert*-Butyldiphenylsilyloxy)methyl-4-(4-methoxyphenylamino)-heptane-1,7-diol (15). Imidazole (310 mg, 4.56 mmol) and *tert*-butyldiphenylsilylchloride (1.00 g, 3.65 mmol) were added to a solution of **5a** (1.60 g, 3.04 mmol) in DMF (20 mL) at ambient temperature. After 2 h, the solution was diluted with ether (200 mL), washed with saturated aqueous $NaHCO_3$ (2 × 100 mL), dried ($MgSO_4$), and evaporated to dryness. The residue was filtered over a plug of silica, eluting with 10% ether/pentane. The filtrate was concentrated and dissolved in MeOH (10 mL). A catalytic amount of *p*-toluenesulfonic acid was added, and the solution was stirred at ambient until TLC analysis revealed complete conversion to the product. The reaction mixture was diluted with EtOAc and extracted with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated to dryness. Flash chromatography (EtOAc) afforded the tile compound (1.33 g, 84%, two steps) as colorless oil: R_f 0.43 (EtOAc); $[\alpha]^{25}_D$ +21.3 (*c* 0.74, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−6.58 (m, 4H), 7.49−7.30 (m, 6H), 6.79−6.71 (m, 2H), 6.61−6.55 (m, 2H), 3.75 (s, 3H), 3.74−3.42 (m, 7H), 2.80 (br s, 3H), 1.99 (m, 1H), 1.71−1.38 (m, 6H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 141.9, 135.6 (2C), 135.5 (2C), 133.2, 133.0, 129.8 (2C), 127.7 (4C), 115.2 (2C), 115.0 (2C), 65.0, 62.7, 61.4, 56.3, 55.8, 41.1, 31.5, 30.1, 28.5, 26.9 (3C), 19.1; IR ($CHCl_3$) 3374, 2933, 2860, 1513, 1468, 1429, 1237, 1109, 1046, 822, 756, 705, 614, 506 cm^{-1}; HRMS calcd for $C_{31}H_{43}NO_4Si$ (M^+), 521.2961; found, 521.2965.

(2*R*,3*S*)-3-(*tert*-Butyldiphenylsilyloxymethyl)-1-(4-methoxyphenyl)-2-(3-hydroxypropyl)-pyrrolidine (16). A solution of **15** (100 mg, 0.19 mmol) and 1,1′-carbonyldiimidazole (100 mg, 0.62 mmol) in MeCN (10 mL) was refluxed for 2 h. The solvent was evaporated in vacuo, and the residue was taken up in THF/2 N aq NaOH, 1:1 (10 mL). This mixture was stirred for 2 h at room temperature. The aqueous layers were extracted with Et_2O (2 × 10 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and evaporated in vacuo. Flash chromatography on silica gel (50% Et_2O/pentane) afforded **16** as a colorless oil: R_f 0.33 (50% Et_2O/pentane); $[\alpha]^{25}_D$ −6.2 (*c* 0.55, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (m, 2H), 7.59 (m, 2H), 7.45−7.33 (m, 6H), 6.84 (m, 2H), 6.50 (m, 2H), 3.77 (s, 3H), 3.65 (m, 2H), 3.57 (m, 1H), 3.50 (m, 2H), 3.33 (t, $J = 8.6$ Hz, 1H), 3.07 (q, $J = 8.2$ Hz, 1H), 2.31 (m, 1H), 2.13 (m, 1H), 1.83 (m, 1H), 1.74 (m, 1H), 1.65−1.55 (m, 3H), 1.42 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 142.1, 135.6 (2C), 135.5 (2C), 133.6, 133.5, 129.6 (2C), 127.7 (2C), 127.6 (2C), 115.1 (2C), 112.9 (2C), 65.4, 62.9, 60.7, 56.0, 47.2, 45.5, 29.4, 29.0, 26.8 (3C), 25.5, 19.2; IR ($CHCl_3$) 3395, 3008, 2936, 2860, 1514, 1368, 1241, 1109, 1043, 817, 758, 705, 614, 505 cm^{-1}; HRMS calcd for $C_{31}H_{41}NO_3Si$ (M^+), 503.2856; found, 503.2856.

((2*S*,3*S*)-1-(4-Methoxyphenyl)-2-phenylpiperidin-3-yl)methanol (17). Tetra-*n*-butylammonium fluoride (1 M in THF, 1 mL, 1 mmol) was added to a solution of **2c** (100 mg, 0.23 mmol) in THF (5 mL) at ambient temperature. After 30 min, the reaction mixture was filtered through a plug of silica eluting with Et_2O. The filtrate is evaporated to dryness, and a solution of this crude alcohol and 1,1′-carbonyldiimidazole (100 mg, 0.62 mmol) in MeCN (10 mL) was refluxed for 2 h. The solvent was evaporated in vacuo, and the residue was heated to 150 °C under high vacuum before it was taken up in THF/2 N aq NaOH, 1:1 (10 mL). This mixture was stirred for 2 h at room temperature. The aqueous layers were extracted with Et_2O (2 × 10 mL), and the combined organic layers were dried with Na_2SO_4, filtered, and evaporated in vacuo. Flash chromatography on silica gel (50% Et_2O/pentane) afforded **17** in 60% yield as colorless oil: R_f 0.29 (50% Et_2O/pentane); $[\alpha]^{25}_D$ +3.5 (*c* 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.24 (m, 2H), 7.21−7.06 (m, 3H), 6.93 (d, $J = 9.0$ Hz, 2H), 6.65 (d, $J = 9.0$ Hz, 2H), 3.86 (d, $J = 8.7$ Hz, 1H), 3.68 (s, 3H), 3.46 (dd, $J = 10.9$, 4.4 Hz, 1H), 3.36−3.25 (m, 2H), 2.89 (ddd, $J = 11.8$, 10.2, 4.3 Hz, 1H), 2.05−1.83 (m, 4H), 1.55−1.40 (m, 1H), 1.27 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.1, 146.0, 142.1, 128.4 (2C), 128.0 (2C), 126.7, 125.1 (2C), 113.6 (2C), 67.4, 65.2, 56.6, 55.2, 45.9, 27.4, 25.5; IR ($CHCl_3$) 3396, 3007, 2935, 2835, 2795, 2706 (w, "Bohlmann band"), 1509, 1453, 1241, 1036, 833, 760, 703 cm^{-1}; HRMS calcd for $C_{19}H_{23}NO_2$ (M^+), 279.1729; found, 279.1729.

Preparation of (2*R*,3*R*)-*tert*-Butyl 3-ethyl-2-propylazetidine-1-carboxylate (18). CAN (2.45 g, 4.48 mmol) was added to a solution of **5g** (262 mg, 1.12 mmol) in a 3:1 mixture of MeCN/H_2O (28 mL) at ambient temperature. After 30 min, NaOH (1M) was added, and the mixture was extracted four times with CH_2Cl_2. The organic layers were combined, washed with brine, filtered through cotton, and concentrated to dryness. Di-*tert*-butyl carbonate (489 mg, 2.24 mmol) was added to the residue, and the resulting mixture was dissolved in a 2:1 mixture of PhMe/H_2O (6 mL). Sodium hydroxide (270 μL, 25 wt %, 1.68 mmol) was added, and the mixture was stirred at ambient temperature for 3 h. The reaction mixture was diluted with H_2O and extracted twice with ethyl acetate. The organic layers were combined, washed with brine, dried over $MgSO_4$, filtered, and concentrated to dryness. The residue was purified by flash chromatography (25% Et_2O/pentane) to afford the title compound as a colorless oil (183 mg, 72%, two steps): R_f 0.20 (17% Et_2O/pentane); $[\alpha]^{25}_D$ −108.8 (*c* 0.57, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (q, $J = 7.6$ Hz, 1H), 3.91 (t, $J = 8.5$ Hz, 1H), 3.40 (dd, $J = 8.3$, 5.7 Hz, 1H), 2.50−2.35 (m, 1H), 1.65−1.15 (m, 6H), 1.42 (s, 9H), 0.91 (t, $J = 7.3$ Hz, 3H), 0.81 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 79.0, 64.0, 53.0, 34.6, 32.6, 28.5 (3C), 21.9, 19.9, 14.3, 11.6; IR ($CHCl_3$) 2962-(s), 2876, 1703, 1390, 1364, 1143 cm^{-1}; HRMS calcd for $C_{13}H_{25}NO_2$ (M^+), 227.1885; found, 227.1886.

(*R*)-*tert*-Butyl 2-Methyl-3-oxo-3-phenylpropylcarbamate (19). The exact conditions for the synthesis of compound **18** afforded the title compound as a colorless oil: R_f 0.32 (25% Et_2O/pentane); $[\alpha]^{25}_D$ −45.4 (*c* 0.56, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98−7.91 (m, 2H), 7.58−7.51 (m, 1H), 7.48−7.41 (m, 2H), 5.03 (br s,

1H), 3.82−3.69 (m, 1H), 3.37 (m, 2H), 1.38 (s, 9H), 1.17 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.5, 156.0, 136.1, 133.2, 128.6 (2C), 128.4 (2C), 79.1, 42.8, 41.1, 28.3, 15.6; IR ($CHCl_3$) 3373, 2976, 2934, 1684, 1511, 1453, 1368, 1249, 1218, 1171, 972 cm^{-1}; HRMS calcd for $C_{15}H_{21}NO_3$ (M^+), 207.0895; found, 207.0896.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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