DIASTEREOSELECTIVE LITHIATION OF N-SILYL-PROTECTED (S)-TETRAHYDRO-1H-PYRROLO[1,2-c]IMIDAZOL-3(2H)-ONE

Costa Metallinos,* Seyed Iraj Sadraei, and Nadezda Zhukovskaya

Department of Chemistry, Brock University, 500 Glenridge Avenue, St. Catharines, Ontario L2S 3A1, Canada

Abstract – An L-proline-derived imidazolone protected with an N-triethylsilyl (N-TES) group undergoes diastereoselective lithiation–electrophile quench to give C5-substituted products with syn stereochemistry. Unlike the previous N-t-Bu analogues, the N-TES derivatives may be easily N-desilylated to give secondary ureas that serve as precursors to N-phenyl chiral bicyclic guanidines.

INTRODUCTION

The stereoselective synthesis of variously substituted pyrrolidines by lithiation–substitution reactions continues to evolve as a valuable tool in synthetic chemistry.1 Based initially on (−)-sparteine-mediated deprotonation on N-Boc pyrrolidine (1, Scheme 1) reported by Beak and coworkers,2 recent advances in ligand design3 have allowed for the synthesis of enantiomeric products, or the use of sub-stoichiometric amounts of ligand4 under dynamic thermodynamic resolution conditions.5 It is also now possible to install aryl and vinyl substituents with retention of stereochemical integrity of the chiral carbanion.6 As part of efforts to find alternate syntheses of chiral reagents with a pyrroloimidazol(in)e framework,7 we reported previously the diastereoselective lithiation–substitution of t-Bu protected urea 4 to afford a series of C5-substituted products with syn stereochemistry.5 This approach was modeled on Beak’s observation of syn-selective lithiation–substitution in chiral cyclic carbamates 6.2 Although lithiation of urea 4 was effective for providing diastereomerically enriched imidazolinones, it posed two challenges for development of a more general approach leading to variously N-substituted pyrroloimidazolinium salt precatalysts: First, the synthesis of 4 from L-proline-derived Cbz-protected t-Bu amide 3 gave inconsistent yields upon scale-up. Second, removal of the N-t-Bu group from the C5-substituted products 5 required prolonged exposure to refluxing trifluoroacetic acid, which posed stability issues for substituents in certain
derivatives. In this paper, we report that an L-proline hydantoin-derived N-silyl protected version of 4 undergoes analogous diastereoselective lithiation–substitution to give C5-substituted products that may be readily N-desilylated with dilute acid at room temperature to give secondary ureas. The chiral products thus obtained may be subjected to standard N-arylation protocols leading to chiral pyrroloimidazolinones of greater structural diversity than would otherwise be accessible.

RESULTS AND DISCUSSION
The ease of preparation of L-proline hydantoin (8, Scheme 2) and its utility as a precursor to a chiral auxiliary for diastereoselective lithiation of ferrocenes made it an attractive starting material for the synthesis of C5-substituted imidazolinones. To this end, reduction of 8 with lithium aluminum hydride in THF at room temperature gave 9 in ample quantities and without racemization of the pyrrolidine chiral center. Imidazolinone 9 was initially N-protected by deprotonation of nitrogen with i-PrLi/TMEDA, followed by addition of TMSCl. Although product 10 was air-stable and could be purified by flash column chromatography, subsequent attempts to induce diastereoselective lithiation at the C5 position by sequential treatment with i-PrLi/TMEDA at −78 °C in diethyl ether, followed by TMSCl quench, resulted in the formation of the N-[bis(trimethylsilyl)methyl]dimethylsilyl product 12. The observed regiochemistry was presumably due to the greater acidity of the α-silylmethyl groups over the C5 position. This result was notably different from the behavior of N-trimethylsilyl-protected aryl-O-carbamate 13.
reported by Hoppe (Scheme 2),\textsuperscript{16} which undergoes preferential ortho-lithiation to give phenol 15 after electrophile quench, \textit{N}-desilylation, and hydrolysis of the secondary carbamate (14).

To avoid \(\alpha\)-silyl carbanion formation, the \(N\)-triethylsilyl (\(N\)-TES) analogue 11 was prepared with the expectation that the \(\alpha\)-silyl methylene groups would be less prone to deprotonation. As anticipated, exposure of 11 to 1.2 equivalents of \(i\)-PrLi/TMEDA at \(-78^\circ\text{C}\) followed by TMSCl quench afforded exclusively the desired syn-C5-trimethylsilyl adduct in 86\% yield (Scheme 3). Repetition of this procedure followed by electrophile quench with MeI, benzophenone, \(n\)-Bu\(_3\)SnCl or allyl bromide (the latter after transmetalation with CuCN-2LiCl) gave additional C5-substituted products with \(\text{syn}\)-stereochemistry in yields ranging from 47-60\%. In contrast to the previously reported \(N\)-\(t\)-Bu derivatives,\textsuperscript{8} products 16a-e underwent smooth \(N\)-desilylation upon treatment with 2M aqueous HCl for 30 min at room temperature to give secondary ureas 17a-e in good yields (71-91\%). It is notable that potentially sensitive substituents such as the diphenylhydroxymethyl group of 16c or the stannane of 16d remained intact under these conditions.
The ability to remove the N-TES group in the preceding products allows for the introduction of new N-substituents. For example, N-phenylation of either 17a or 17b could be conducted with a mixture of cuprous iodide/TMEDA, potassium carbonate and iodobenzene in refluxing toluene to give 18a,b in 40% and 74% yield, respectively (Scheme 4). Ureas 18a,b were treated sequentially with POCl₃ to generate intermediate chlorimidazolinium salts that, without purification, were exposed to aqueous ammonia/triethylamine to afford guanidines 19a,b.

Scheme 3

Scheme 4
Previous studies by Basavaiah and coworkers\textsuperscript{18} showed that borane-mediated reduction of phenacyl bromide (20a) catalyzed by guanidine 19c (Scheme 5) gave R-configured alcohol 21 in up to 83\% ee when the reaction was performed in refluxing toluene, but afforded (S)-21 in 32\% ee when the reaction was conducted at room temperature. Attempts to improve the enantioselectivity of this reduction by employing the bulkier guanidines reported here gave 21 in only 8\% ee (S-configuration) using 19a, or as a racemate using 19b. Reduction of acetophenone (20b) under identical conditions gave (S)-22 in marginally better 24\% ee for 19a and 10\% ee for 19b. Both sets of experiments had to be performed in refluxing toluene as there was no observable reduction at room temperature. Yields for all transformations ranged from 77-86\%. It is clear from the reduction of 20a that the additional stereocenter at C5 is detrimental to the enantioselectivity of this process, possibly by virtue of a “mismatch” with the sense of chirality that is induced by the original stereogenic center of L-proline. Additional support for this hypothesis would require synthesis of the \textit{anti} stereoisomers of 19a,b which unfortunately are not accessible by the current synthetic method. Research efforts are now being directed towards converting N-arylureas such as 18a,b into N-heterocyclic carbenes for transition metal catalysis. Work in this area will be reported as results permit.

\begin{center}
\textbf{Scheme 5}
\end{center}

\begin{center}
\textbf{EXPERIMENTAL}
\end{center}

\textbf{General.} All reagents were purchased from commercial sources and used as received unless otherwise indicated. Tetrahydrofuran (THF) was freshly dried and distilled over sodium/benzophenone ketyl under an atmosphere of nitrogen. Diethyl ether was distilled over LiAlH\textsubscript{4} and stored under an argon atmosphere. All alkyllithium bases were titrated against \textit{N}-benzylbenzamide\textsuperscript{19} to a blue endpoint. All reactions were performed under argon in flame- or oven-dried glassware using syringe-septum cap techniques unless
otherwise indicated. Column chromatography was performed on silica gel 60 (70-230 mesh). NMR spectra were obtained on a Bruker Avance 300 or 600 MHz instrument and are referenced to TMS or to the residual proton signal of the deuterated solvent for $^1$H spectra, and to the carbon multiplet of the deuterated solvent for $^{13}$C spectra according to known values. Enantiomeric ratios were determined on an Agilent 1100 series HPLC system at $\lambda = 254$ nm using a Chiralcel OD-H column, and were compared against racemic material. FT-IR spectra were obtained on an ATI Mattson Research Series spectrometer as KBr pellets for solids or on KBr discs for liquids. Optical rotations were measured on a Rudolph Research Autopol III automatic polarimeter. Mass spectra were obtained on an MSI/Kratos Concept 1S Mass Spectrometer. Melting points were determined on a Kofler hot-stage apparatus on recrystallized material unless otherwise indicated, and are uncorrected.

$(-)-(S)$-Tetrahydro-1$H$-pyrrolo[1,2-c]imidazol-3(2$H$)-one (9). A solution of L-proline hydantoin (8, 3.00 g, 0.02 mol) in THF (130 mL) was transferred by cannula into a stirred suspension of lithium aluminum hydride (2.45 g, 0.06 mol) in THF (130 mL) at 0 °C and the mixture was thereafter allowed to stir to at room temperature for 16 h. After cooling to 0 °C in an ice-water bath, workup was performed by sequential addition of water (2.5 mL), 15% aqueous NaOH solution (2.5 mL), and after 15 min, additional water (2.5 mL). The crude mixture containing aluminum salts was passed through a pad of Celite, rising with CH$_2$Cl$_2$. The organic phase was separated, dried over anhyd. Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. Column chromatography (silica gel, 95:5 CH$_2$Cl$_2$:MeOH, R$_f$ = 0.33) gave 9 as a colorless solid that was recrystallized from CH$_2$Cl$_2$ (1.52 g, 56%); mp 178-180 °C (CH$_2$Cl$_2$); $[\alpha]_{D}^{20}$ −102 (c 0.50, CHCl$_3$); IR (KBr) $\nu_{\text{max}}$ 3264, 2955, 2886, 1693, 1481, 1433, 1404, 1313, 1260, 1193, 1091, cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.47 (b, 1H), 3.78−3.71 (m, 1H), 3.65-3.53 (m, 2H) 3.32 (dd, 1H, $J$ = 8.9, 2.4 Hz) 3.06-2.98 (m, 1H), 2.00-1.87 (m, 2H), 1.84-1.72 (m, 1H), 1.49-1.36 (m, 1H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 166.3, 59.4, 45.0, 42.9, 30.3, 25.1; EIMS [m/z] 126 (M$^+$, 7), 98 (67), 70 (35), 55 (100), 41 (34); HRMS (EI) calcd for C$_6$H$_{10}$N$_2$O: 126.0793; found: 126.0794.

$(-)-(S)$-2-(Trimethylsilyl)tetrahydro-1$H$-pyrrolo[1,2-c]imidazol-3(2$H$)-one (10). A solution of 9 (500 mg, 3.96 mmol) and TMEDA (0.71 mL, 4.75 mmol) in THF (20 mL) at 0 °C was treated with $i$-PrLi (6.10 mL, 4.75 mmol), which was added dropwise over 15 min. After stirring for an additional 15 min, TMSCl (0.76 mL, 5.90 mmol) was added and the mixture was allowed to stir at room temperature for 16 h. The reaction mixture was cooled in an ice-water bath, worked up by addition of water (20 mL), and extracted with CH$_2$Cl$_2$ (4 x 20 mL). The combined organic phase was dried over anhyd. Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 7:3 hexane:EtOAc, R$_f$ = 0.28) to give 10 as a colorless oil (310 mg, 46%); $[\alpha]_{D}^{20}$ −53.7 (c 1.00,
CHCl$_3$; IR (KBr, neat) $\nu_{\text{max}}$ 2953, 1681, 1481, 1460, 1392, 1318, 1249, 1162 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.54-3.22 (m, 3H), 3.20 (dd, 1H, $J = 7.8$, 1.5 Hz), 3.03-2.95 (m, 1H), 1.94-1.75 (m, 3H), 1.33-1.26 (m, 1H), 0.24 (s, 9H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 167.5, 59.1, 45.8, 45.3, 30.6, 25.0, -1.2; EIMS $[m/z(\%)]$ 198 (M$^+$, 8), 183 (100), 100 (29), 55 (62), HRMS (EI) calcd for C$_9$H$_{18}$N$_2$OSi: 198.1188; found: 198.1190.

$(-)$-$(S)$-2-((Bis(trimethylsilyl)methyl)dimethylsilyl)tetrahydro-$1H$-pyrrolo[1,2-c]imidazol-3(2$H$)-one (12). A solution of 10 (40 mg, 0.32 mmol) and TMEDA (0.10 mL, 0.67 mmol) in THF (4 mL) at $-78 \, ^{\circ}\text{C}$ was treated with $i$-PrLi (0.60 mL, 0.67 mmol). After 2 h, the reaction mixture was quenched with TMSCl (0.09 mL, 0.67 mmol) and, after 15 min, was stirred at room temperature for 16 h. After cooling in an ice-water bath, the reaction mixture was worked up by addition of water (7 mL) and extracted with CH$_2$Cl$_2$ (4 x 7 mL). The combined organic phase was dried over anhyd. Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 7:3 hexane:EtOAc, $R_f = 0.66$) to give 12 as a colorless glass (29 mg, 26%); $[\alpha]_D^{20} -26.9$ (c 0.27, CHCl$_3$); IR (KBr) $\nu_{\text{max}}$ 2955, 1675, 1481, 1397, 1319, 1256, 1010 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.69-3.53 (m, 3H), 3.21 (dd, 1H, $J = 7.8$, 1.6 Hz), 3.03-2.94 (m, 1H), 1.96-1.83 (m, 2H), 1.82-1.71 (m, 1H), 1.36-1.23 (m, 2H), 0.25 (d, 6H, $J = 3.7$ Hz), 0.1 (s, 18H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 167.5, 58.8, 46.1, 45.4, 30.8, 25.0, 2.9, 2.3, 1.7; EIMS $[m/z(\%)]$ 342 (M$^+$, 88), 217 (62), 129 (73), 73 (100); HRMS (EI) calcd for C$_{15}$H$_{34}$N$_2$OSi$_3$: 342.1979; found: 342.1978.

$(-)$-$(S)$-2-((Triethylsilyl)tetrahydro-$1H$-pyrrolo[1,2-c]imidazol-3(2$H$)-one (11). A solution of 9 (800 mg, 6.34 mmol) and TMEDA (1.13 mL, 7.60 mmol) in THF (35 mL) at 0 °C was treated with $i$-PrLi (5.85 mL, 1.3 M, 7.60 mmol), added dropwise over 15 min. After stirring for an additional 15 min, chlorotriethylsilane (1.60 mL, 9.51 mmol) was added and the mixture was allowed to stir at room temperature for 16 h. The reaction mixture was cooled in an ice-water bath, worked up by addition of water, and extracted with CH$_2$Cl$_2$ (4 x 30 mL). The combined organic phase was dried over anhyd. Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography (silica gel, 7:3 hexane:EtOAc, $R_f = 0.54$) to give 11 as a colorless oil (1.17 g, 77%); $[\alpha]_D^{20} -46.2$ (c 0.10, CHCl$_3$); IR (KBr, neat), $\nu_{\text{max}}$ 2953, 1681, 1481, 1460, 1392, 1318, 1249, 1162, 1007 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.74-3.59 (m, 3H), 3.25 (d, 1H, $J = 7.8$ Hz), 3.05-2.97 (m, 1H), 2.00-1.86 (m, 2H), 1.83-1.73 (m, 1H), 1.40-1.26 (m, 1H), 0.96 (t, 9H, $J = 7.1$ Hz), 0.77 (q, 6H, $J = 7.1$ Hz); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 167.9, 59.2, 46.4, 45.5, 30.6, 25.0, 6.9, 3.4; EIMS $[m/z(\%)]$ 240 (M$^+$, 7), 211 (100), 100 (11); HRMS (EI) calcd for C$_{12}$H$_{24}$N$_2$Si: 240.1658; found: 240.1661.
(−)-(5S,7aS)-2-(Triethylsilyl)-5-(trimethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (16a). A solution of 11 (800 mg, 3.33 mmol) and TMEDA (0.60 mL, 4.00 mmol) in Et₂O (32 mL) at –78 °C was treated with i-PrLi (2.50 mL, 1.60 M, 4.00 mmol). After 2 h, TMSCl (0.64 mL, 5.00 mmol) was added and the reaction mixture was allowed to warm up slowly to room temperature. The reaction mixture was cooled in an ice-water bath and worked up by addition of water (30 mL). After separation of the layers, the aqueous phase was extracted with CH₂Cl₂ (4 x 30 mL), and the combined organic extract was dried over anhyd Na₂SO₄, filtered and concentrated under reduced pressure. The product was purified by flash column chromatography (silica gel, 9:1 hexane:EtOAc, Rf = 0.54) to give 16a as a colorless oil (893 mg, 86%); [α]D²⁰ = −45.1 (c 0.59, CHCl₃); IR (KBr, neat) νmax 2953, 1689, 1461, 1399, 1251, 1134, 1005 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 3.74-3.70 (m, 1H), 3.61 (t, 1H, J = 9.0 Hz), 3.18 (d, 1H, J = 9.6 Hz), 2.46 (t, 1H, J = 9.0 Hz), 2.02-1.97 (m, 1H), 1.92-1.86 (m, 1H), 1.71-1.66 (m, 1H), 1.49-1.45 (m, 1H), 0.96 (t, 9H, J = 7.8 Hz), 0.84-0.76 (m, 6H), 0.19 (s, 9H); ¹³C NMR (150.9 MHz, CDCl₃) δ 166.1, 60.5, 49.7, 47.7, 31.6, 27.9, 6.8, 3.4, −1.0; EIMS [m/z (%)] 312 (M⁺, 12), 297 (100), 283 (70), 239 (58), 87 (36), 73 (32), 59 (40); HRMS (EI) calcd for C₁₅H₃₂N₂O₂Si: 312.2053; found: 312.2045.

(−)-(5S,7aS)-5-Methyl-2-(triethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (16b). A solution of 11 (500 mg, 2.08 mmol) and TMEDA (0.37 mL, 2.50 mmol) in Et₂O (30 mL) at –78 °C was treated with i-PrLi (1.92 mL, 1.30 M, 2.50 mmol). After 2 h, Me₂SO₄ (0.40 mL, 3.12 mmol) was added and the reaction mixture was allowed to warm up slowly to room temperature. The reaction mixture was cooled in an ice-water bath, worked up with water (10 mL), and extracted with CH₂Cl₂ (4 x 10 mL). The combined organic phase was dried over anhyd Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, Rf = 0.32) gave 16b as a colorless oil (315 mg, 60%); [α]D²⁰ = −24.4 (c 1.01, CHCl₃); IR (KBr, neat) νmax 2954, 2875, 1678, 1460, 1400, 1266, 1132, 1006 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.01-3.96 (m, 1H), 3.69-3.57 (m, 1H), 3.49 (t, 1H, J = 8.9 Hz), 3.12 (dd, 1H, J = 7.1, 2.5 Hz), 2.16-2.13 (m, 1H), 1.92-1.81 (m, 1H), 1.75-1.70 (m, 1H), 1.62-1.49 (m, 1H), 1.39 (d, 3H, J = 6.4 Hz), 0.98 (t, 9H, J = 7.5 Hz), 0.82-0.75 (m, 6H); ¹³C NMR (75.5 MHz, CDCl₃) δ 163.9, 56.4, 46.3, 45.9, 38.5, 30.7, 24.9, 12.7, −2.5; EIMS [m/z (%)] 254 (M⁺, 12), 297 (100), 283 (70), 239 (58), 87 (36), 73 (32), 59 (40); HRMS (EI) calcd for C₁₃H₂₆N₂O₂Si: 312.2053; found: 312.2045.

(+)-(5R,7aS)-5-(Hydroxydiphenylmethyl)-2-(triethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (16c). A solution of 11 (500 mg, 2.08 mmol) and TMEDA (0.37 mL, 2.50 mmol) in Et₂O (30 mL) at –78 °C was treated with i-PrLi (1.56 mL, 1.60 M, 2.50 mmol). After 2 h, a solution of benzophenone (568 mg, 3.12 mmol) in THF (5 mL) was added slowly by cannula, and the reaction mixture was allowed to warm slowly to room temperature. The reaction mixture was cooled in an ice-water bath, worked up with...
water (10 mL) and extracted with CH$_2$Cl$_2$ (4 × 10 mL). The combined organic phase was dried over anhyd. Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 9:1 hexane:EtOAc, R$_f$ = 0.62) gave 16c as a colourless oil (495 mg, 56%); [α]$_D^{20}$ +153.0 (c 1.10, CHCl$_3$; IR (KBr, neat) $\nu_{max}$ 3206, 2954, 1647, 1414, 1262, 1145, 1006 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.64 (d, 2H, $J$ = 7.5 Hz), 7.45 (d, 2H, $J$ = 7.5 Hz), 7.34-7.16 (m, 6H), 4.32-4.26 (m, 1H), 3.90-3.85 (m, 1H), 3.63 (t, 1H, $J$ = 7.5 Hz), 3.20 (dd, 1H, $J$ = 7.6, 3.1 Hz), 2.17-2.04 (m, 1H), 1.97-1.83 (m, 1H), 1.58-1.45 (m, 1H), 1.42-1.30 (m, 1H), 0.94 (t, 9H, $J$ = 7.5 Hz), 0.80-0.72 (m, 6H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 166.0, 147.7, 146.3, 128.2, 127.8, 127.7, 126.4, 126.3, 126.0, 76.8, 66.9, 60.7, 47.8, 29.2, 25.9, 6.8, 3.3; EIMS [m/z (%)] 422 (M$^+$, 21), 239 (25), 182 (53), 105 (92), 77 (100), 51 (64); HRMS (EI) calcd for C$_{25}$H$_{34}$N$_2$O$_2$Si: 422.2390; found: 422.2384.

(--)-(5S,7aS)-2-(Tributylstannyl)-5-(trimethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (16d). A solution of 11 (207 mg, 0.86 mmol) and TMEDA (0.15 mL, 1.03 mmol) in Et$_2$O (10 mL) at –78 °C was treated with i-PrLi (0.65 mL, 1.03 mmol). After 2 h, Bu$_3$SnCl (0.35 mL, 1.29 mmol) was added, and the reaction mixture was allowed to warm up slowly to room temperature. The reaction mixture was cooled in an ice-water bath, worked up with water (10 mL) and extracted with Et$_2$O (4 × 10 mL). The combined organic extract was dried over anhyd. Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, R$_f$ = 0.92) gave 16d as a colorless oil (358 mg, 60%); [α]$_D^{20}$ –17.8 (c 0.59, CHCl$_3$; IR (KBr, neat) $\nu_{max}$ 2954, 1674, 1462, 1401, 1257, 1204, 1123, 1005 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 3.69-3.63 (m, 1H), 3.59 (t, 1H, $J$ = 9.0 Hz), 3.18 (dd, 1H, $J$ = 7.4, 1.6 Hz), 2.69 (t, 1H, $J$ = 8.3 Hz), 2.07-1.92 (m, 2H), 1.83-1.73 (m, 1H), 1.58-1.46 (m, 6H), 1.39-1.26 (m, 7H), 0.99-0.74 (m, 24H), 0.81-0.74 (m, 6H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 167.5, 59.7, 46.6, 44.9, 31.6, 29.7, 29.3, 27.6, 13.8, 11.4, 6.8, 3.4; EIMS [m/z (%)] 473 (M-C$_4$H$_9$, 71), 239 (32), 209 (69), 41 (100); HRMS (EI) calcd for C$_{20}$H$_{41}$N$_2$OSiSn: 473.2010; found: 473.2006.

(+)-(5R,7aS)-5-Allyl-2-(triethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (16e). A solution of 11 (1.00 mg, 4.16 mmol) and TMEDA (0.74 mL, 5.00 mmol) in THF (30 mL) at –78 °C was treated with i-PrLi (3.84 mL, 1.3 M, 5.00 mmol). After 2 h, a solution of CuCN (185 mg, 2.08 mmol) and LiCl (176 mg, 4.16 mmol) in THF (5 mL) was added slowly by cannula, and stirring was continued at –78 °C. After 1 h, allyl bromide (0.43 mL, 4.50 mmol) was added and the reaction mixture was allowed to warm up slowly to room temperature. The reaction mixture was cooled in an ice-water bath, worked up with water (30 mL) and extracted with CH$_2$Cl$_2$ (4 × 30 mL). The combined organic extract was dried over anhyd. Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, R$_f$ = 0.33) gave 16e as a colorless oil (518 mg, 47%); [α]$_D^{20}$ +10.2 (c 0.75, CHCl$_3$; IR
(KBr, neat) \( v_{\text{max}} \) 2955, 1687, 1460, 1393, 1251, 1124, 1005 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 5.86-5.73 (m, 1H), 5.15-5.04 (m, 2H), 4.04-3.93 (m, 1H) 3.60-3.50 (m, 2H), 3.18 (dd, 1H, \( J = 7.4, 2.1 \) Hz), 3.04-2.96 (m, 1H), 2.44-2.33 (m, 1H), 2.14-2.00 (m, 1H), 1.94-1.85 (m, 2H), 1.56-1.45 (m, 1H), 0.98 (t, 9H, \( J = 7.5 \) Hz), 0.82-0.77 (m, 6H), 0.98 (t, 9H, \( J = 7.5 \) Hz), 0.82-0.77 (m, 6H); \(^{13}\)CNMR (75.5 MHz, CDCl\(_3\)); \( \delta \) 163.0, 135.5, 117.1, 60.6, 48.9, 35.2, 32.5, 29.9, 6.9, 3.5; EIMS \([m/z(\%)]\) 280 (M\(^+\), 4), 251 (30), 239 (100), 115 (36), 87 (53), 59 (35); HRMS (EI) calcd for C\(_{15}\)H\(_{28}\)N\(_2\)O: 280.1971; found: 280.1974.

\((-\text{)}-(5S,7aS)-5-(\text{Trimethylsilyl})\text{tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one} (17a). A solution of 16a (413 mg, 1.32 mmol) in MeOH (1.8 mL) was treated with 2 M aq. HCl (10 mL). The mixture was stirred at room temperature for 30 min and worked up by careful addition of a saturated solution of aqueous NaHCO\(_3\) (10 mL). The crude mixture was extracted with CH\(_2\)Cl\(_2\) (4 × 10 mL), and the combined organic phase was dried over anhyd. Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, \( R_f = 0.13 \)) gave 17a as a colorless solid (238 mg, 91%) that was recrystallized from EtOAc/hexane; mp 100-103 °C (EtOAc/hexane); \([\alpha]_D^{20} – 67.1 \) (c 0.52, CHCl\(_3\)); IR (KBr) \( \nu_{\text{max}} \) 3259, 2948, 1682, 1490, 1446, 1411, 1272, 1243, 1126 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 4.40 (b, 1H), 3.92-3.81 (m, 1H), 3.65 (t, 1H, \( J = 8.5 \) Hz), 3.26 (dd, 1H, \( J = 8.7, 3.4 \) Hz), 2.47 (dd, 1H, \( J = 7.8, 2.4 \) Hz), 2.12-1.88 (m, 2H), 1.79-1.52 (m, 2H), 0.18 (s, 9H); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 164.1, 60.6, 49.2, 44.0, 31.2, 27.9, −1.1; EIMS \([m/z(\%)]\) 199 (M\(+\H\), 37) 183 (100), 73 (36); HRMS (FAB) calcd for C\(_9\)H\(_{19}\)N\(_2\)O: 199.1267; found: 199.1266.

\((-\text{)}-(5S,7aS)-5-Methyl\text{tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one} (17b). A solution of 16b (333 mg, 1.32 mmol) in MeOH (1.3 mL) was treated with 2 M aq. HCl (8 mL). The mixture was stirred at room temperature for 30 min and worked up by careful addition of a saturated solution of aqueous NaHCO\(_3\) (10 mL). The crude mixture was extracted with CH\(_2\)Cl\(_2\) (4 × 10 mL), and the combined organic phase was dried over anhyd. Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, \( R_f = 0.10 \)) gave 17b as a colorless solid (155 mg, 84%) that was recrystallized from EtOAc/hexane; mp 65-67 °C (EtOAc/hexane); \([\alpha]_D^{20} – 20.9 \) (c 1.00, CHCl\(_3\)); IR (KBr) \( \nu_{\text{max}} \) 3298, 2968, 1697, 1487, 1440, 1271, 1155, 1125, 1093 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 4.77 (b, 1H), 4.13-4.03 (m, 1H), 3.74-3.68 (m, 1H), 3.58 (t, 1H, \( J = 8.5 \) Hz), 3.24 (t, 1H, \( J = 8.2 \) Hz), 2.26-2.13 (m, 1H), 2.01-1.92 (m, 1H), 1.79-1.69 (m, 1H), 1.67-1.56 (m, 1H), 1.43 (d, 3H, \( J = 6.8 \) Hz); \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \( \delta \) 162.0, 60.9, 51.8, 46.0, 35.8, 29.5, 18.3; EIMS \([m/z(\%)]\) 140 (M\(+\), 26), 125 (100), 69 (71); HRMS (EI) calcd for C\(_7\)H\(_{12}\)N\(_2\)O: 140.0950; found: 140.0947.
(+)-(5R,7aS)-5-(Hydroxydiphenylmethyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (17c). A solution of 16c (100 mg, 0.24 mmol) in MeOH (1 mL) was treated with 2 M aq. HCl (4 mL). The mixture was stirred at room temperature for 30 min and worked up by careful addition of a saturated solution of aqueous NaHCO₃ (10 mL). The crude mixture was extracted with CH₂Cl₂ (4 × 7 mL), and the combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, Rf = 0.19) gave 17c as a colorless oil (58 mg, 80%); [α]D²⁰ +146.0 (c 0.65, CHCl₃); IR (KBr, neat) νmax 3206, 2955, 1668, 1487, 1448, 1416, 1266, 1150, 1005 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.66 (d, 2H, J = 7.5 Hz), 7.47 (d, 2H, J = 7.5 Hz), 7.34-7.17 (m, 6H), 5.34 (b, 1H), 4.30-4.24 (m, 1H), 3.95-3.92 (m, 1H), 3.56 (t, 1H, J = 8.4 Hz), 3.20 (dd, 1H, J = 8.4, 1.8 Hz), 2.17-2.03 (m, 1H), 2.00-1.88 (m, 1H), 1.66-1.60 (m, 1H), 1.36-1.29 (m, 1H); ¹³C NMR (75.5 MHz, CDCl₃) δ 163.6, 147.5, 145.9, 127.9, 127.8, 126.6, 126.5, 126.4, 125.8, 77.2, 66.6, 60.6, 44.0, 28.9, 25.7; EIMS [m/z (%)] 308 (M⁺, 17), 182 (44), 125 (68), 105 (100), 77 (40); HRMS (EI) calcd for C₁₉H₂₀N₂O₂: 308.1525; found: 308.1529.

(–)-(5S,7aS)-5-(Tributylstannyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (17d). A solution of 16d (239 mg, 0.58 mmol) in MeOH (1 mL) was treated with 2 M aq. HCl (8 mL). The mixture was stirred at room temperature for 30 min and worked up by careful addition of a saturated solution of aqueous NaHCO₃ (10 mL). The crude mixture was extracted with CH₂Cl₂ (4 × 10 mL), and the combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, Rf = 0.17) gave 17d as a colorless oil (141 mg, 71%); [α]D²⁰ –16.5 (c 0.40, CHCl₃); IR (KBr, neat) νmax 3229, 2954, 1692, 1453, 1265, 1072; ¹H NMR (300 MHz, CDCl₃) δ 4.47 (b, 1H), 3.82-3.75 (m, 1H), 3.63 (t, 1H, J = 8.0 Hz), 3.24 (dd, 1H, J = 8.7, 2.4 Hz), 2.67 (t, 1H, J = 8.5 Hz), 2.07-1.98 (m, 2H), 1.84-1.74 (m, 1H), 1.55-1.47 (m, 6H), 1.36-1.29 (m, 7H), 0.93-0.88 (m, 15H); ¹³C NMR (75.5 MHz, CDCl₃) δ 165.8, 59.7, 44.4, 43.3, 31.5, 29.7, 29.3, 27.3, 13.8, 11.2; EIMS [m/z(%)] 359 (M⁺, 17), 182 (44), 125 (68) 105 (100), 77 (40); HRMS (EI) calcd for C₁₄H₂₇N₂OSn: 359.1145; found: 359.1149.

(–)-(5R,7aS)-5-Allyltetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (17e). A solution of 16e (238 mg, 0.89 mmol) in MeOH (1.2 mL) was treated with 2 M aq. HCl (6 mL). The mixture was stirred at room temperature for 30 min and worked up by careful addition of a saturated solution of aqueous NaHCO₃ (10 mL). The crude mixture was extracted with CH₂Cl₂ (4 × 10 mL), and the combined organic phase was dried over anhyd. Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography (silica gel, 7:3 hexane:EtOAc, Rf = 0.11) gave 17e as a colorless oil (111 mg, 82%); [α]D²⁰ –5.3 (c 1.01, CHCl₃); IR (KBr) νmax 3229, 2968, 1682, 1490, 1451, 1404, 1281, 1145, 1004 cm⁻¹; ¹H NMR (300 MHz,
CDCl$_3$ $\delta$ 5.84-5.72 (m, 1H), 5.18-5.04 (m, 2H), 4.13-4.02 (m, 1H), 3.63-3.54 (m, 2H), 3.23 (t, 1H, $J$ = 8.0 Hz), 3.08-3.00 (m, 1H), 2.36-2.26 (m, 1H), 2.16-2.03 (m, 1H), 1.97-1.90 (m, 2H), 1.65-1.52 (m, 1H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 161.4, 135.3, 117.4, 60.8, 55.4, 46.1, 35.4, 32.4, 29.3; EIMS [m/z(%)] 166 (M$^+$, 3), 125 (100); HRMS (EI) calcd for C$_9$H$_{14}$N$_2$O: 166.1106; found: 166.1105.

(--)-(5S,7aS)-2-Phenyl-5-(trimethylsilyl)tetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (18a). A 2-necked flask under argon was charged with 17a (100 mg, 0.51 mmol), CuI (77 mg, 0.40 mmol), TMEDA (0.01 mL, 0.10 mmol), iodobenzene (0.12 mL, 1.10 mmol), K$_2$CO$_3$ (139 mg, 1.00 mmol), and toluene (1 mL). The mixture was heated to reflux for 24 h, then cooled to room temperature, diluted with CHCl$_3$ (15 mL), filtered through Celite and washed with additional CHCl$_3$ (4 × 15 mL). The organic filtrate was washed with H$_2$O (4 × 15 mL), dried over anhyd. MgSO$_4$ and concentrated under reduced pressure. Flash column chromatography (silica gel, 9:1 hexane:EtOAc, $R_f$ = 0.41) gave 18a as a colorless solid (56 mg, 40%) that was recrystallized from EtOAc/hexane; mp 138-140 °C (EtOAc/hexane); $[\alpha]_{D}^{20}$ – 70.1 (c 1.50, CHCl$_3$); IR (KBr) $\nu_{max}$ 3396, 2917, 1704, 1600, 1502, 1481, 1402, 1317, 1243, 1153, 1128, 1076, 1027 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.57 (dd, 2H, $J$ = 7.8, 1.3 Hz), 7.54-7.39 (m, 2H), 7.03 (t, 1H, $J$ = 7.3 Hz), 4.03-4.00 (t, 1H, $J$ = 8.9 Hz), 3.88-3.79 (m, 1H), 3.66 (dd, 1H, $J$ = 9.0, 3.3 Hz), 2.56 (dd, 1H, $J$ = 10.2, 7.8 Hz), 2.19-2.10 (m, 1H), 1.92-1.84 (m, 1H), 1.80-1.71 (m, 1H), 1.64-1.60 (m, 1H), 0.23 (s, 9H); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 159.2, 140.6, 128.8, 122.4, 117.7, 56.5, 49.8, 48.9, 31.8, 27.9, –0.99; EIMS [m/z(%)] 274 (M$^+$, 11), 259 (81), 183 (76), 73 (100); HRMS (EI) calcd for C$_{15}$H$_{22}$N$_2$OSi: 274.1501; found: 274.1491.

(--)-(5S,7aS)-5-Methyl-2-phenyltetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-one (18b). A 2-necked flask under argon was charged with 17b (643 mg, 4.59 mmol), CuI (700 mg, 3.67 mmol), TMEDA (0.09 mL, 0.9 mmol), iodobenzene (1.13 mL, 10.1 mmol), K$_2$CO$_3$ (1.59 mg, 12.2 mmol), and toluene (6 mL). The mixture was heated to reflux for 24 h, then cooled to room temperature, diluted with CHCl$_3$ (50 mL), filtered through Celite and washed with additional CHCl$_3$ (4 × 30 mL). The organic filtrate was washed with H$_2$O (4 × 50 mL), dried over anhyd. MgSO$_4$ and concentrated under reduced pressure. Flash column chromatography (silica gel, 9:1 hexane:EtOAc, $R_f$ = 0.18) to give 18b as a colorless solid (738 mg, 74%) that was recrystallized from EtOAc/hexane; mp 110-112 °C (EtOAc/hexane); $[\alpha]_{D}^{20}$ – 22.5 (c 0.90, CHCl$_3$); IR (KBr) $\nu_{max}$ 2890, 1943, 1862, 1681, 1508, 1384, 1280, 1153, 1085, 1054 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.51-7.48 (m, 2H), 7.36-7.28 (m, 2H), 7.04-6.99 (m, 1H), 4.09-4.01 (m, 1H), 3.91 (t, 1H, $J$ = 8.4 Hz), 3.87-3.82 (m, 1H), 3.69 (t, 1H, $J$ = 8.4 Hz), 2.25-2.19 (m, 1H), 2.14-2.07 (m, 1H), 1.86-1.78 (m, 1H), 1.74-1.64 (m, 1H), 1.44 (d, 3H, $J$ = 6.3 Hz); $^{13}$C NMR (75.5 MHz, CDCl$_3$) $\delta$ 156.7, 140.7, 128.7, 122.04,
A solution of 18a (230 mg, 0.87 mmol) in POCl₃ (1 mL) in a sealed tube under argon was heated to 110 °C. After 16 h, the mixture was cooled to room temperature and the excess POCl₃ was removed under reduced pressure. The crude intermediate was dissolved in MeCN (1 mL) and transferred to a solution of aqueous ammonia (0.63 mL, 8.5 mmol) and triethylamine (5.77 mL, 33.3 mmol) in MeCN (1 mL) at 0 °C. The mixture was stirred for 1 h, made acidic by addition of 5% aqueous HCl (10 mL), and extracted with CH₂Cl₂ (3 × 10 mL). After evaporation of the combined organic extract, the residue was dissolved in water (15 mL) and washed with toluene (3 × 10 mL). The aqueous phase was made alkaline with 10% aqueous NaOH and extracted with CH₂Cl₂ (4 × 15 mL). The combined organic extract was dried over anhyd. Na₂SO₄, filtered, and concentrated under reduced pressure to yield 19a as a colorless oil (78 mg, 34%); [α]D²⁰ −19.3 (c 0.6, CHCl₃); IR (KBr, neat) νmax 3384, 2929, 1646, 1596, 1502, 1405, 1319, 1240, 1116, cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.39 (m, 2H), 7.31-7.25 (m, 2H), 7.19-7.09 (m, 1H), 4.18-4.03 (m, 1H), 3.98-3.86 (m, 1H), 3.77-3.65 (m, 1H), 2.28-1.80 (m, 3H), 1.67-1.56 (m, 1H), 0.24 (s, 9H); ¹³C NMR (75.5 MHz, CDCl₃) δ 158.6, 141.2, 129.3, 123.5, 121.0, 58.8, 53.3, 51.2, 31.0, 29.2, 0.1; EIMS [m/z(%)] 273 (M⁺, 9), 258 (100), 200 (72), 182 (47), 73 (44); HRMS (EI) calcd for C₁₅H₂₃N₃Si: 273.1661; found: 273.1669.

(--)(5S,7aS)-5-Methyl-2-phenyltetrahydro-1H-pyrrolo[1,2-c]imidazol-3(2H)-imine (19b). A solution of 18b (218 mg, 1.02 mmol) in POCl₃ (1 mL) in a sealed tube under argon was heated to 110 °C. After 16 h, the mixture was cooled to room temperature and the excess POCl₃ was removed under reduced pressure. The crude intermediate was dissolved in MeCN (1 mL) and transferred to a solution of aqueous ammonia (0.53 mL, 10 mmol) and triethylamine (6.75 mL, 40 mmol) in MeCN (1 mL) at 0 °C. The mixture was stirred for 1 h, made acidic by addition of 5% aqueous HCl (10 mL), and extracted with CH₂Cl₂ (3 × 10 mL). After evaporation of combined organic solution, the residue was dissolved in water (15 mL) and washed with toluene (3 × 10 mL). The aqueous phase was made alkaline with 10% aqueous NaOH and extracted with CH₂Cl₂ (4 × 15 mL). The combined organic extract was dried over anhyd. Na₂SO₄, filtered, and concentrated under reduced pressure to yield 19b as colorless oil (82 mg, 41%); [α]D²⁰ −49.0 (c 0.35, CHCl₃); IR (KBr, neat) νmax 3457, 2919, 2057, 1629, 1500, 1018 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.35 (m, 4H), 7.10-7.05 (m, 1H), 4.17-4.05 (m, 1H), 3.22-3.10 (m, 1H), 3.10-2.95 (m, 1H), 2.95-2.80 (m, 1H), 1.67-1.56 (m, 1H), 1.44 (s, 3H, J = 6.4 Hz); ¹³C NMR (75.5 MHz, CDCl₃) δ 156.4, 141.0, 129.2, 123.1, 120.1, 58.6, 55.2, 52.1, 36.2, 28.7,
18.0; EIMS \([m/z(\%)]\) 215 (M\(^+\), 6), 160 (100), 106 (30); HRMS (EI) calcd for C\(_{13}\)H\(_{17}\)N\(_3\): 215.1422; found: 215.1421.

\((+)-(S)-2\text{-Bromo-1-phenylethanol (21).}\) A solution of guanidine \(19a\) (27 mg, 0.10 mmol) in toluene (3 mL) at room temperature was treated with added BH\(_3\)•SMe\(_2\) (0.50 mL, 0.50 mmol). After stirring at room temperature for 20 min, the reaction was mixture heated at 110 °C for 20 min. A solution of phenacyl bromide (100 mg, 0.50 mmol) in toluene (2 mL) was added slowly, and heating was continued for a further 20 min. After cooling to room temperature, the reaction mixture was quenched with MeOH (1 mL) and the solvent was removed under reduced pressure. Flash column chromatography (9:1 hexane:EtOAc) gave \((R)-21\) as a colorless oil (84 mg, 83%); \([\alpha]_D^{20} +3.6\) (c 1.00, CHCl\(_3\)) \(\) \([\alpha]_D^{25} -39\) (c 8.00, CHCl\(_3\)) for \((R)\) enantiomer; CSP HPLC analysis (Chiralcel OD-H, 90:10 hexanes:i-PrOH, 1.0 mL/min) determined an er of 54:46 (8% ee) \([t_R(\text{major}) = 7.77\text{ min}, t_R(\text{minor}) = 9.03\text{ min}]\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.49-7.34\) (m, 5H), 5.01-4.85 (m, 1H), 3.69-3.48 (m, 2H), 2.64 (b, 1H).

\((-)-(S)-1\text{-Phenylethanol (22).}\) A solution of guanidine \(19a\) (27 mg, 0.10 mmol) in toluene (1 mL) at room temperature was treated with added BH\(_3\)•SMe\(_2\) (0.50 mL, 0.50 mmol). After stirring at room temperature for 20 min, the reaction mixture was heated at 110 °C for 20 min. A solution of acetophenone (0.06 mL, 0.50 mmol) in toluene (1 mL) was added slowly, and heating was continued for a further 20 min. After cooling to room temperature, the reaction mixture was quenched with MeOH (1 mL) and the solvent was removed under reduced pressure. Flash column chromatography (9:1 hexane:EtOAc) gave \((S)-22\) as a colorless oil (47 mg, 77%); \([\alpha]_D^{20} -10.1\) (c 2.00, CHCl\(_3\)) \(\) \([\alpha]_D^{25} -57\) (c 5.13, CHCl\(_3\)) for \((S)\) enantiomer; CSP HPLC analysis (Chiralcel OD-H, 95:5 hexanes:i-PrOH, 0.4 mL/min) determined an er of 62:38 (24% ee) \([t_R(\text{minor}) = 19.49\text{ min}, t_R(\text{major}) = 23.72\text{ min}]\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta 7.38-7.28\) (m, 5H), 4.95-4.90 (m, 1H), 1.80-1.79 (b, 1H), 1.44 (d, 3H, \(J = 6.5\) Hz).

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9. This approach was modeled on Beak’s observation of syn-selective lithiation–substitution in an


