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Selective C-2 Alkylation of Tryptophan by a Pd(II)/Norbornene-Promoted C−H Activation Reaction

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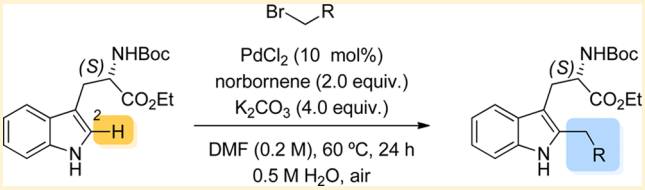
Supporting Information

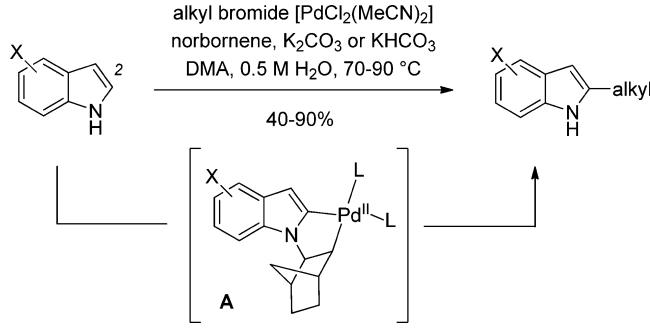
ABSTRACT: A palladium(II)-catalyzed norbornene-mediated regioselective alkylation at the C-2 indole position of *N*-*tert*-butyloxycarbonyl (Boc)-protected (*S*)-tryptophan ethyl ester is reported. The protocol employs mild reaction conditions and is tolerant of a range of functional groups. The reaction proceeds without racemization at the stereogenic center of the amino acid.



Tryptophan stands out among all proteinogenic amino acids because it is the only amino acid that contains an indole ring. Molecular recognition of tryptophan in biological processes is frequently based on binding of this unique structure element, and tryptophan recognition is a key feature in numerous protein−protein interactions.[1] In addition, the indole core is part of many biologically active substances, which interact with typical tryptophan binding domains.[2] Representative examples for tryptophan motifs include the U2AF homology motif, which is important for protein splicing,[3] or the Pex5 motif, which is relevant to protein import.[4] In a recent research program we planned to study the use of 2-alkylated tryptophans as substitutes for tryptophan[5] in a tryptophan-containing recognition motif, and we therefore searched for potential ways to access this compound class. Concise routes toward this goal include the attachment of a serine type side chain to position C-3 of a 2-alkylated indole[6] or the immediate alkylation of tryptophan with an unprotected indolic nitrogen atom. The most frequently used protocol based on the latter strategy relies on an initial activation of an appropriately protected tryptophan ester via the respective 3-chloroindolenine intermediate, which can then be substituted by appropriate nucleophiles.[7] More recently, a direct benzylation at carbon atom C-2 of *N*-methoxycarbonyltryptophan methyl ester has been reported in the context of a more extensive study on Ru-catalyzed C−H alkylation[8] reactions of alkenes.[9] In this paper, we disclose our results on the direct, racemization-free alkylation[10] of *N*-*tert*-butyloxycarbonyl (Boc) (*S*)-tryptophan ethyl ester with various alkyl bromides employing a Pd-catalyzed, norbornene-mediated C−H activation reaction.

The starting point of our investigation was a selective C-2 alkylation reaction of indoles (Scheme 1) that had been previously developed in our group.[11] In this reaction, norbornene[12] serves as a cocatalyst that transposes the palladium metal from the initially attacked indolic nitrogen atom to the position C-2 of the indole core. A five-membered

Scheme 1. Previous Work on Indole C-2 Alkylation by a Pd(II)-Catalyzed, Norbornene-Mediated C−H Activation



palladacycle **A** was identified as an intermediate in this reaction, and kinetic evidence was in line with a rate-determining oxidative addition of alkyl bromide occurring at this intermediate. Upon reductive elimination and retro-amino-palladation, the metal catalyst turns over and enters a new catalytic cycle. Upon appropriate choice of base, it was possible to use a large variety of substituted indoles as substrates in this reaction.

Although the reaction was performed, by applying an alkyl iodide as electrophile, with a single substrate that bears a 3-substituent (CH_2CH_2OTBS; TBS = *tert*-butyldimethylsilyl),[11b] it was uncertain whether the procedure was applicable to tryptophan derivatives. One issue of concern was the fact that the acidic NH-position of the amino acid might interfere with palladation at the indolic nitrogen atom; the other issue of concern was the question of whether the stereogenic center of tryptophan would withstand the basic conditions at elevated temperature.

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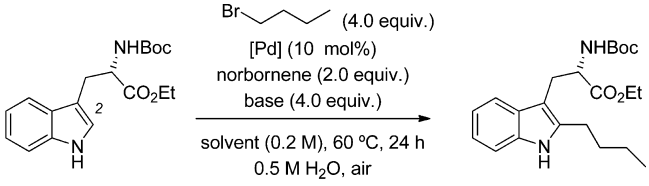
Initial screening experiments were performed with butyl bromide and tryptophan esters bearing different amino protecting groups. It was found that the 9-fluorenylmethoxycarbonyl (Fmoc) protecting group was unstable under the conditions of the Pd(II)-catalyzed, norbornene-mediated alkylation reaction. The use of 2,2,2-trichlorethoxycarbonyl was not very promising either, leading to a sluggish conversion after prolonged reaction times. Gratifyingly, it was found that the reaction conditions previously employed to alkylate the above-mentioned 3-substituted TBS-protected tryptophol with an alkyl iodide could be applied to the alkylation of the *N*-Boc-protected (*S*)-tryptophan ester **1**[13] with the less reactive butyl bromide (Table 1, entry 1). The yield, however, was moderate,

Table 1. Optimization of Reaction Conditions for the Alkylation of *N*-Boc Protected Tryptophan Ester 1 with Butyl Bromide



1 **2a**

entry	[Pd]	base	solvent	yield (%)
1	$PdCl_2$	K_2CO_3	DMF/DMSO (9/1)	61
2	$Pd(OAc)_2$	K_2CO_3	DMF/DMSO (9/1)	61
3	$PdCl_2(MeCN)_2$	K_2CO_3	DMF/DMSO (9/1)	44
4	$PdCl_2$	$KHCO_3$	DMF/DMSO (9/1)	54
5[a]	$PdCl_2$	$KHCO_3$	DMF/DMSO (9/1)	52
6	$PdCl_2$	K_2CO_3	DMA	67
7	$PdCl_2$	K_2CO_3	MeCN	14
8	$PdCl_2$	K_2CO_3	DMF	72
9	$PdCl_2$	Na_2CO_3	DMF	67

[a]The reaction was performed at a temperature of 90 °C.

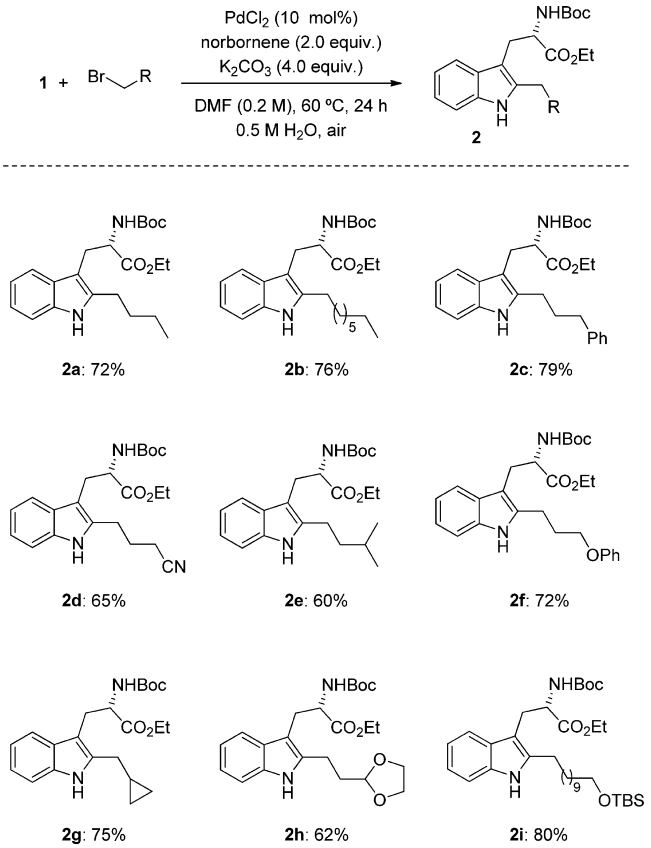
and we attempted to further improve it by modification of the reaction conditions (for a complete table of the different conditions, see the Supporting Information).

Changing the source of palladium did not lead to an improved yield (entries 2 and 3); rather the yield remained constant or decreased. With a weaker base the reaction was clean and delivered 54% of the isolated product with recovery of 36% of the starting material (entry 4). It was not possible, however, to improve the yield of isolated product upon increasing the reaction temperature (entry 5). A variation of solvent revealed, somewhat to our surprise, that DMA and DMF (entries 6−8) are better suited for the conversion of tryptophan **1** than the previously optimized solvent mixture (DMF/DMSO = 9/1) employed for the alkylation of TBS-protected tryptophol. In DMF, the yield increased to a satisfactory 72%. The choice of base was not restricted to K_2CO_3, and for example, Na_2CO_3 (entry 9) could also be employed. Too basic conditions, i.e., the use of Cs_2CO_3, were not compatible with the reaction, and *N*-alkylation at the indole nitrogen atom became the major reaction pathway. The importance of water for the success of the reaction seems to be due to its ability to solubilize the base. Air was found to be beneficial for alkylation reactions of 3-alkylindoles because it avoids reduction of palladium to Pd(0). In the absence of air, attempted alkylation reactions remained incomplete.[11b]

The enantiomeric purity of product **2a** obtained according to the optimized procedure (entry 8) was determined by chiral HPLC analysis (see the Supporting Information). A racemic sample was generated from racemic starting material *rac*-**1**, and complete separation of the enantiomers **2a** and *ent*-**2a** was possible. The product of the alkylation reaction showed an enantiomeric purity of ≥99% ee; i.e., the stereogenic center at the α-amino carbon atom of tryptophan esters **1** and **2a** is configurationally stable under the conditions of entry 8.

When the optimized procedure was applied to other alkyl bromides (Scheme 2), it was found that the method allows the

Scheme 2. Alkylation of Tryptophan Ester 1 with Various Alkyl Bromides



introduction of primary alkyl groups into the indole position C-2 of tryptophan also with alkyl bromides, which carry a functional group. Apart from the nonfunctionalized alkyl-substituted products **2a**, **2b**, **2e**, and **2g**, it was also possible to introduce alkyl groups with a phenyl group (product **2c**), a cyano group (product **2d**), an ether group (product **2f**), an acetal-protected aldehyde group (product **2h**), and a silyl-protected hydroxy group (product **2i**). In all cases, the alkyl bromide was employed in excess (4 equiv), and product yields varied from 60% to 80%.

Mechanistically, the reaction is believed to occur in a similar fashion as the above-mentioned indole alkylation reaction (scheme 1). Apparently, there is no detrimental interference with the catalytic system either by the tryptophan functional groups or by the functional groups of the alkyl bromide. The fact that the alkyl bromide is very likely to attack intermediates of type **A** in an oxidative addition step[14] limits the steric bulk tolerated around the electrophilic alkyl carbon atom. Branching

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in α-position (e.g., product **2g**) is tolerated, but further steric bulk, i.e., the use of secondary or tertiary alkyl bromides does not comply with the reaction conditions. An attempted alkylation reaction of tryptophan ester **1** with cyclohexyl iodide failed. It has further been shown in previous work[11a] that monosubstituted olefinic bromides are unsuited as alkylating reagents because side reactions at the double bond occur. A benzylation with benzyl bromide was feasible, but the respective benzylated product, which was formed in ca. 50% yield, could not be obtained in sufficiently pure form. Due to the additional electron-donating group at the indole core tryptohan derivatives **2** are not air- or light-stable if stored in pure form. However, DMSO solutions could be kept on the bench for at least one week without notable decomposition.

In summary, a yet unexplored route to 2-alkylated tryptophan derivatives has been described. Although the method is limited to an alkylation by primary alkyl bromides the operational simplicity and the synthetic brevity should make it very useful for the decoration of the indole core.

EXPERIMENTAL SECTION

General Methods. Thin-layer chromatography (TLC) was performed on silica-coated glass plates (silica gel 60 F 254). The TLC plates were visualized by either ultraviolet light or treatment with a ceric ammonium molybdate (CAM) stain followed by gentle heating. Purification of products was accomplished by flash column chromatography on silica gel (230−400 mesh). ^{1}H and ^{13}C NMR spectra were recorded at 298 K and calibrated to the residual solvent signals. $CDCl_3$: δ (^{1}H) = 7.26 ppm, δ (^{13}C) = 77.16 ppm, DMSO: δ (^{1}H) = 2.50 ppm, δ (^{13}C) = 39.52 ppm. Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm), peak shape (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets), coupling constant (Hz), and integration. ^{13}C NMR spectra are proton decoupled. Two rotamers are detectable by NMR spectroscopy. The NMR data of the major rotamer are given. HRMS data were recorded by electrospray ionization (ESI) on a linear ion trap analyzer. A 0.5 M solution of H_2O in DMF was prepared by adding a certain amount of deionized water to freshly distilled DMF and was stored in a tightly sealed bottle. Technical solvents (*n*-pentane, ethyl acetate, diethyl ether) employed for preparative column chromatography were purified by distillation prior to use. *N*-*tert*-Butyloxycarbonyl (Boc) (*S*)-tryptophan ethyl ester[13] and [(10-bromodecyl)oxy] (*tert*-butyl)dimethylsilane[15] were synthesized according to literature procedures. All other chemicals were used as received from commercial suppliers.

General Procedure for the C-2 Alkylation of Tryptophan Derivatives. To a mixture of *N*-Boc-(*S*)-tryptophan ethyl ester (166 mg, 0.50 mmol, 1.00 equiv), norbornene (94 mg, 1.00 mmol, 2.00 equiv), K_2CO_3 (276 mg, 2.00 mmol, 4.00 equiv), and $PdCl_2$ (8.9 mg, 0.05 mmol, 10 mol %) was added 2.5 mL of DMF (containing 0.5 M H_2O) and a primary alkyl bromide (2.00 mmol, 4.00 equiv). The resulting suspension was stirred at 60 °C for 24 h. After being cooled to room temperature, the reaction mixture was diluted with Et_2O (30 mL) and washed with water (50 mL). The aqueous layer was then extracted with Et_2O (2 × 50 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated. The crude product was purified by flash column chromatography on silica gel to afford the 2-alkyltryptophan product.

*(S)-2-[(tert-Butoxycarbonyl)amino]-3-(2-butyl-1H-indol-3-yl)-propanoic Acid Ethyl Ester (**2a**).* Compound **2a** was synthesized according to the general procedure using *N*-Boc-(*S*)-tryptophan ethyl ester (166 mg, 0.50 mmol, 1.00 equiv) and 1-bromobutane (215 μL, 2.00 mmol, 4.00 equiv). After 24 h, purification by column chromatography (*n*-pentane/EtOAc: 5/1) yielded product **2a** (140 mg, 72%) as a pale yellow oil. Two rotamers are detectable by NMR spectroscopy (ratio: 87/13). ^{1}H NMR (500 MHz, d_6-DMSO): (major rotamer) δ (ppm) = 10.70 (s, 1H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 6.98 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 6.92 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 4.10 (q, *J* = 7.8 Hz, 1H), 3.97 (q, *J* = 7.1 Hz, 2H), 3.07 (dd, *J* = 14.3, 6.3 Hz, 1H), 2.97 (dd, *J* = 14.3, 8.1 Hz, 1H), 2.66 (t, *J* = 7.6 Hz, 2H), 1.64−1.58 (m, 2H), 1.38−1.32 (m, 2H), 1.33 (s, 9H), 1.03 (t, *J* = 7.1 Hz, 3H), 0.92 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (126 MHz, d_6-DMSO): (major rotamer) δ (ppm) = 172.9, 155.8, 137.9, 135.8, 128.6, 120.5, 118.6, 117.9, 110.9, 106.0, 78.6, 60.7, 55.5, 32.1, 28.6, 28.2, 26.5, 25.5, 22.5, 14.3. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3343, 2970, 2931, 1697, 1464, 1375, 1305, 1160, 1129, 949, 819. $[\alpha]^{20}_{D}$ = +28.7 (*c* = 1.0, $CHCl_3$). HRMS (ESI): calcd for $C_{22}H_{33}N_2O_4^+$ [(M + H)$^+$] 389.2435, found 389.2435.

*(S)-2-[(tert-Butoxycarbonyl)amino]-3-(2-octyl-1H-indol-3-yl)-propanoic Acid Ethyl Ester (**2b**).* Synthesized according to the general procedure using *N*-Boc-(*S*)-tryptophan ethyl ester (166 mg, 0.50 mmol, 1.00 equiv) and 1-bromooctane (0.35 mL, 2.00 mmol, 4.00 equiv). After 24 h, purification by column chromatography (*n*-pentane/EtOAc 5/1) yielded product **2b** (169 mg, 76%) as a pale yellow oil. Two rotamers are detectable by NMR spectroscopy (ratio: 87/13). ^{1}H NMR (500 MHz, d_6-DMSO): (major rotamer) δ (ppm) = 10.70 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 1H), 6.97 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.92 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 4.09 (q, *J* = 7.8 Hz, 1H), 3.97 (q, *J* = 7.1 Hz, 2H), 3.05 (dd, *J* = 14.4, 6.3 Hz, 1H), 2.96 (dd, *J* = 14.4, 8.0 Hz, 1H), 2.67−2.63 (m, 2H), 1.65−1.59 (m, 2H), 1.33 (s, 9H), 1.32−1.23 (m, 10H), 1.03 (t, *J* = 7.1 Hz, 3H), 0.85 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, d_6-DMSO): (major rotamer) δ (ppm) = 172.9, 155.8, 137.9, 135.8, 128.6, 120.5, 118.6, 117.9, 110.9, 106.0, 78.6, 60.7, 55.5, 31.8, 29.9, 29.4, 29.3, 29.2, 28.6, 26.5, 25.8, 22.6, 14.4, 14.3. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3369, 2917, 2850, 1756, 1694, 1531, 1460, 1345, 1270, 1175, 1062, 1024. $[\alpha]^{20}_{D}$ = +28.3 (*c* = 1.0, $CHCl_3$). HRMS (ESI): calcd for $C_{26}H_{41}N_2O_4^+$ [(M + H)$^+$] 445.3061, found 445.3060.

*(S)-2-[(tert-Butoxycarbonyl)amino]-3-[2-(3-phenylpropyl)-1H-indol-3-yl]propanoic Acid Ethyl Ester (**2c**).* Compound **2c** was synthesized according to the general procedure using *N*-Boc-(*S*)-tryptophan ethyl ester (166 mg, 0.50 mmol, 1.00 equiv) and 1-bromo-3-phenylpropane (0.30 mL, 2.00 mmol, 4.00 equiv). After 24 h, purification by column chromatography (*n*-pentane/EtOAc 5/1) yielded product **2c** (178 mg, 79%) as a pale yellow oil. Two rotamers are detectable by NMR spectroscopy (ratio: 86/14). ^{1}H NMR (500 MHz, d_6-DMSO): (major rotamer) δ (ppm) = 10.76 (s, 1H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.30−7.27 (m, 2H), 7.25−7.20 (m, 3H), 7.20−7.13 (m, 2H), 6.98 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.93 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 4.10 (q, *J* = 7.8 Hz, 1H), 3.96 (q, *J* = 7.1 Hz, 2H), 3.06 (dd, *J* = 14.4, 6.3 Hz, 1H), 2.97 (dd, *J* = 14.4, 8.2 Hz, 1H), 2.75−2.69 (m, 2H), 2.63 (t, *J* = 7.8 Hz, 2H), 2.00−1.90 (m, 2H), 1.30 (s, 9H), 1.02 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (90.6 MHz, d_6-DMSO): (major rotamer) δ (ppm) = 172.9, 155.8, 142.4, 137.5, 135.9, 128.7, 128.7, 128.6, 126.2, 120.6, 118.6, 117.9, 111.0, 106.3, 78.6, 60.7, 55.4, 35.5, 31.6, 28.6, 26.5, 25.7, 14.3. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3355, 2976, 2935, 1690, 1494, 1459, 1364, 1161, 1024, 741. $[\alpha]^{20}_{D}$ = +30.6 (*c* = 0.97, $CHCl_3$). HRMS (ESI): calcd for $C_{27}H_{35}N_2O_4^+$ [(M + H)$^+$] 451.2591, found 451.2591.

*(S)-2-[(tert-Butoxycarbonyl)amino]-3-[2-(3-cyanopropyl)-1H-indol-3-yl]propanoic Acid Ethyl Ester (**2d**).* Compound **2d** was synthesized according to the general procedure using *N*-Boc-(*S*)-tryptophan ethyl ester (166 mg, 0.50 mmol, 1.00 equiv) and 4-bromobutanenitrile (0.20 mL, 2.00 mmol, 4.00 equiv). After 24 h, purification by column chromatography (*n*-pentane/EtOAc 5/1) yielded product **2d** (130 mg, 65%) as a pale yellow oil. Two rotamers are detectable by NMR spectroscopy (ratio: 86/14). ^{1}H NMR (500 MHz, d_6-DMSO): (major rotamer) δ (ppm) = 10.80 (s, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.01 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 6.95 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 4.14−4.08 (m, 1H), 4.00 (q, *J* = 7.1 Hz, 2H), 3.08 (dd, *J* = 14.5, 5.8 Hz, 1H), 2.95 (dd, *J* = 14.5, 8.7 Hz, 1H), 2.81−2.74 (m, 2H), 2.53−2.49 (m, 2H), 1.99−1.85 (m, 2H), 1.32 (s, 9H), 1.06 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, d_6-DMSO): (major rotamer) δ (ppm) = 172.9, 155.8, 136.0, 135.9, 128.4, 120.9, 120.9, 118.8, 118.0, 111.1, 107.0, 78.6, 60.8, 55.3, 28.6, 26.4, 25.7, 24.8, 16.3, 14.3. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3358, 2977, 2931, 1697, 1507, 1460, 1369, 1164, 1026.

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$[\alpha]^{20}_D$ = +20.6 (c = 0.51, $CHCl_3$). HRMS (ESI): calcd for $C_{22}H_{30}N_3O_4^+$ [(M + H)$^+$] 400.2230, found 400.2231.

*(S)-2-[(tert-Butoxycarbonyl)amino]-3-(2-isopentyl-1H-indol-3-yl)-propanoic Acid Ethyl Ester (**2e**).* Compound **2e** was synthesized according to the general procedure using *N*-Boc-(*S*)-tryptophan ethyl ester (166 mg, 0.50 mmol, 1.00 equiv) and 1-bromo-3-methylbutane (0.24 mL, 2.00 mmol, 4.00 equiv). After 24 h, purification by column chromatography (*n*-pentane/Et_2O 2/1) yielded product **2e** (122 mg, 60%) as a colorless oil. Two rotamers are detectable by NMR spectroscopy (ratio: 86/14). ^{1}H NMR (500 MHz, d_6-DMSO): (major rotamer) δ (ppm) = 10.71 (s, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.13 (d, J = 7.8 Hz, 1H), 6.98 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 6.92 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 4.10 (q, J = 7.8 Hz, 1H), 3.98 (q, J = 7.1 Hz, 2H), 3.06 (dd, J = 14.4, 6.3 Hz, 1H), 2.98 (dd, J = 14.4, 8.0 Hz, 1H), 2.70−2.63 (m, 2H), 1.63−1.45 (m, 3H), 1.33 (s, 9H), 1.04 (t, J = 7.1 Hz, 3H), 0.94 (d, J = 6.4 Hz, 6H). ^{13}C NMR (90.6 MHz, d_6-DMSO): (major rotamer) δ (ppm) = 172.8, 155.7, 138.1, 135.8, 128.6, 120.4, 118.5, 117.9, 110.9, 105.9, 78.6, 60.7, 55.5, 28.6, 27.9, 26.6, 23.8, 22.9, 22.8, 14.3. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3358, 2956, 2928, 2867, 1694, 1499, 1460, 1366, 1164, 1030. $[\alpha]^{20}_D$ = +27.2 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd for $C_{23}H_{35}N_2O_4^+$ [(M + H)$^+$] 403.2591, found 403.2592.

*(S)-2-[(tert-Butoxycarbonyl)amino]-3-[2-(3-phenoxypropyl)-1H-indol-3-yl]propanoic Acid Ethyl Ester (**2f**).* Compound **2f** was synthesized according to the general procedure using *N*-Boc-(*S*)-tryptophan ethyl ester (166 mg, 0.50 mmol, 1.00 equiv) and 1-bromo-3-phenoxypropane (0.32 mL, 2.00 mmol, 4.00 equiv). After 24 h, purification by column chromatography (*n*-pentane/EtOAc 5/1) yielded product **2f** (168 mg, 72%) as a pale yellow oil. Two rotamers are detectable by NMR spectroscopy (ratio: 86/14). ^{1}H NMR (500 MHz, d_6-DMSO): (major rotamer) δ (ppm) = 10.82 (s, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.32−7.22 (m, 3H), 7.17 (d, J = 8.1 Hz, 1H), 7.00 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 6.96−6.91 (m, 4H), 4.13 (q, J = 7.8 Hz, 1H), 4.01−3.98 (m, 2H), 3.98 (q, J = 7.1 Hz, 2H), 3.08 (dd, J = 14.4, 6.3 Hz, 1H), 2.98 (dd, J = 14.4, 8.3 Hz, 1H), 2.85 (t, J = 7.7 Hz, 2H), 2.17−1.98 (m, 2H), 1.31 (s, 9H), 1.02 (t, J = 7.1 Hz, 3H). ^{13}C NMR (90.6 MHz, d_6-DMSO): (major rotamer) δ (ppm) = 172.8, 159.0, 155.7, 137.0, 135.9, 129.9, 128.5, 120.9, 120.7, 118.7, 118.0, 114.9, 111.0, 106.5, 78.6, 67.2, 60.7, 55.4, 29.4, 28.5, 26.5, 22.3, 14.3. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3354, 2977, 2931, 1697, 1598, 1496, 1460, 1366, 1242, 1168, 1037. $[\alpha]^{20}_D$ = +20.5 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd for $C_{27}H_{35}N_2O_5^+$ [(M + H)$^+$] 467.2541, found 467.2540.

*(S)-2-[(tert-Butoxycarbonyl)amino]-3-[2-(cyclopropylmethyl)-1H-indol-3-yl]propanoic Acid Ethyl Ester (**2g**).* Compound **2g** was synthesized according to the general procedure using *N*-Boc-(*S*)-tryptophan ethyl ester (166 mg, 0.50 mmol, 1.00 equiv) and (bromomethyl)cyclopropane (0.19 mL, 2.00 mmol, 4.00 equiv). After 24 h, purification by column chromatography (*n*-pentane/EtOAc: 5/1) yielded product **2g** (145 mg, 75%) as an off-white solid. Two rotamers are detectable by NMR spectroscopy (ratio: 85/15). ^{1}H NMR (360 MHz, $CDCl_3$): (major rotamer) δ (ppm) = 8.21 (s, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 7.12 (dd, J = 7.4, 7.2 Hz, 1H), 7.08 (dd, J = 7.4, 7.2 Hz, 1H), 5.07 (d, J = 8.2 Hz, 1H), 4.57 (dt, J = 7.5, 5.8 Hz, 1H), 4.18−3.97 (m, 2H), 3.23 (d, J = 5.8 Hz, 2H), 2.65 (d, J = 7.5 Hz, 2H), 1.42 (s, 9H), 1.17 (t, J = 7.1, 3H), 1.07−0.94 (m, 1H), 0.67−0.61 (m, 2H), 0.34−0.27 (m, 2H). ^{13}C NMR (90.6 MHz, $CDCl_3$): (major rotamer) δ (ppm) = 172.4, 155.1, 136.9, 135.2, 128.7, 121.3, 119.4, 118.2, 110.3, 105.4, 79.6, 61.3, 54.2, 30.7, 28.3, 27.2, 13.9, 10.2, 4.7, 4.6. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3341, 2977, 1725, 1686, 1524, 1457, 1369, 1277, 1158, 1020, 738. $[\alpha]^{20}_D$ = +34.5 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd for $C_{22}H_{31}N_2O_4^+$ [(M + H)$^+$] 387.2278, found 387.2278.

*(S)-2-[(tert-Butoxycarbonyl)amino]-3-[2-[2-(1,3-dioxolan-2-yl)-ethyl]-1H-indol-3-yl]propanoic Acid Ethyl Ester (**2h**).* Compound **2h** was synthesized according to the general procedure using *N*-Boc-(*S*)-tryptophan ethyl ester (166 mg, 0.50 mmol, 1.00 equiv) and 2-(2-bromoethyl)-1,3-dioxolane (0.23 mL, 2.00 mmol, 4.00 equiv). After 24 h, purification by column chromatography (*n*-pentane/Et_2O: 1/1 → Et_2O) yielded product **2h** (134 mg, 62%) as a colorless oil. Two rotamers are detectable by NMR spectroscopy (ratio: 86/14). ^{1}H NMR (500 MHz, d_6-DMSO): (major rotamer) δ (ppm) = 10.79 (s, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 7.7 Hz, 1H), 6.99 (ddd, J = 8.2, 7.2, 1.2 Hz, 1H), 6.92 (ddd, J = 8.2, 7.2, 1.2 Hz, 1H), 4.82 (dd, J = 5.6, 4.7 Hz, 1H), 4.10 (q, J = 7.7 Hz, 1H), 4.00−3.88 (m, 4H), 3.83−3.75 (m, 2H), 3.06 (dd, J = 14.3, 6.7 Hz, 1H), 2.96 (dd, J = 14.3, 8.0 Hz, 1H), 2.85−2.69 (m, 2H), 1.94−1.89 (m, 2H), 1.33 (s, 9H), 1.00 (t, J = 7.1 Hz, 3H). ^{13}C NMR (90.6 MHz, d_6-DMSO): (major rotamer) δ (ppm) = 172.8, 155.7, 136.9, 135.9, 128.5, 120.6, 118.6, 118.0, 111.0, 106.1, 103.5, 78.6, 64.7, 60.6, 55.3, 33.9, 28.6, 26.5, 20.6, 14.3. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3354, 2977, 2931, 1715, 1697, 1507, 1464, 1366, 1164, 1030. $[\alpha]^{20}_D$ = +22.4 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd for $C_{23}H_{33}N_2O_6^+$ [(M + H)$^+$] 433.2333, found 433.2332.

*(S)-2-[(tert-Butoxycarbonyl)amino]-3-[2-[11-((tert-butyldimethyl-silyl)oxy)undecyl]-1H-indol-3-yl]propanoic Acid Ethyl Ester (**2i**).* Compound **2i** was synthesized according to the general procedure using *N*-Boc-(*S*)-tryptophan ethyl ester (166 mg, 0.50 mmol, 1.00 equiv) and [(10-bromodecyl)oxy](*tert*-butyl)dimethylsilane[13] (0.572 g, 2.00 mmol, 4.00 equiv). After 24 h, purification by column chromatography (*n*-pentane/EtOAc: 5/1) yielded product **2i** (246 mg, 80%) as a pale yellow oil. Two rotamers are detectable by NMR spectroscopy (ratio: 85/15). ^{1}H NMR (500 MHz, d_6-DMSO): (major rotamer) δ (ppm) = 10.69 (s, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 6.97 (ddd, J = 8.2, 7.2, 1.2 Hz, 1H), 6.91 (ddd, J = 8.2, 7.2, 1.2 Hz, 1H), 4.09 (q, J = 7.8 Hz, 1H), 3.97 (q, J = 7.1 Hz, 2H), 3.55 (t, J = 6.3 Hz, 2H), 3.06 (dd, J = 14.4, 6.3 Hz, 1H), 2.97 (dd, J = 14.4, 8.0 Hz, 1H), 2.69−2.61 (m, 2H), 1.65−1.59 (m, 2H), 1.45−1.40 (m, 2H), 1.33 (s, 9H), 1.32−1.21 (m, 14H), 1.03 (t, J = 7.1 Hz, 3H), 0.85 (s, 9H), 0.01 (s, 6H). ^{13}C NMR (126 MHz, d_6-DMSO): (major rotamer) δ (ppm) = 172.8, 155.7, 137.9, 135.8, 128.6, 120.5, 118.5, 117.9, 110.9, 106.0, 78.5, 62.9, 60.6, 55.5, 32.7, 29.9, 29.5, 29.5, 29.5, 29.4, 29.2, 28.6, 28.2, 26.5, 26.2, 25.8, 25.7, 18.4, 14.3, −4.9. IR (ATR): $\tilde{\nu}$ (cm^{-1}) = 3358, 2928, 2854, 1697, 1499, 1460, 1366, 1249, 1168, 1098, 833. $[\alpha]^{20}_D$ = +13.3 (c = 1.0, $CHCl_3$). HRMS (ESI): calcd for $C_{35}H_{61}N_2O_5Si^+$ [(M + H)$^+$] 617.4344, found 617.4345.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Complete set of conditions for the reaction optimization, ^{1}H and ^{13}C NMR spectra of compounds **2**, and HPLC traces for *rac*-**2a** and **2a**. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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