Chinese Journal of Catalysis 42 (2021) 1593–1607

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.sciencedirect.com/journal/chinese-journal-of-catalysis

Article

Catalytic C2 prenylation of unprotected indoles: Late-stage diversification of peptides and two-step total synthesis of tryprostatin B

Yan-Cheng Hu [a,b,†], Ying Li [a,b,†], Ding-Wei Ji [a,b], Heng Liu [a,b], Hao Zheng [a,b], Gong Zhang [a,b], Qing-An Chen [a,b,*]

[a] *Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, Liaoning, China*
[b] *University of Chinese Academy of Sciences, Beijing 100049, China*

ARTICLE INFO

Article history:
Received 2 January 2021
Accepted 7 February 2021
Available online 5 May 2021

Keywords:
Indole prenylation
Step economy
Atom economy
Tryptophan
Peptide diversification
Total synthesis

ABSTRACT

C2 prenylated indoles are widespread in a variety of bioactive natural alkaloids. Therefore, the selective installation of prenyl group at C2 position of NH indoles is of great significance. However, the known protocols generally require a multi-step procedure and stoichiometric promoters. Herein we develop a one-step C2 prenylation of NH indole with cheap *tert*-prenyl alcohol enabled by acid catalysis. Salient features include good regioselectivity, step- and atom-economy, broad substrate scope, and simple catalytic system. The mechanistic investigations demonstrate that both C2 prenylation and C3 prenylation/migration pathways are engaged in the reaction. Notably, this practical strategy can be applied to the late-stage diversification of tryptophan-based peptides and concise synthesis of tryprostatin B.

1. Introduction

C2 prenylated indoles are fascinating frameworks embedded in a variety of natural alkaloids that usually display potent medicinal properties, because the presence of prenyl group can improve their interactions with the target proteins [1,2]. As exemplified in Fig. 1, tryprostatins A and B are two secondary metabolites of a marine strain BM939 featuring a prenyl group at C2 position of cyclodipeptide of *L*-tryptophan and -proline (cyclo-*L*-Trp-*L*-Pro). They have been demonstrated to be potent inhibitors of the mammalian cell cycle [3]. Besides, a diastereomer of tryprostatin B exhibits cytotoxic activity toward human cancer cell lines [4,5]. Terpeptin, produced by *Aspergillus terreus* 95F-1, is a C2 prenylated tryptamine-based noncyclic peptide and also shows cell cycle inhibitory activity [6,7]. Asterriquinone E is a marine natural product consisting of C2 prenylated tryptophol, which can inhibit the binding of adaptor proteins to tyrosine phosphorylated protein [8,9]. These intriguing properties render indole alkaloids promising lead structures for drug discovery [10–12].

Synthetically, the selective incorporation of prenyl group at C2 position of NH indole is of great significance. However, less attention has been paid to this area compared with the significant progress made in C3 prenylation [13–20]. In 1996, Danishefsky *et al.* [21,22] discovered that 3-Cl indolenine, *in situ* generated by reaction of ^{t}BuOCl and indole, could undergo

* Corresponding author. Tel: +86-411-84379260; Fax: +86-411-84379223; E-mail: qachen@dicp.ac.cn
† These authors contributed equally to this work.
This work was supported by the National Natural Science Foundation of China (21801239, 22071239).
DOI: 10.1016/S1872-2067(20)63780-9 | http://www.sciencedirect.com/journal/chinese-journal-of-catalysis | Chin. J. Catal., Vol. 42, No. 9, September 2021

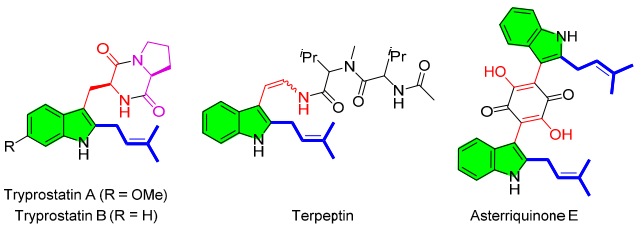


Fig. 1. Representative C2 prenylated indole alkaloids.

addition with prenyltin in the presence of BCl_3 to afford C2 prenylated indole (Fig. 2(a), (i)). A combination of *tert*-prenyl boronate and NCS could make the reaction conditions milder (Fig. 2(a), (i)) [23]. Alternatively, the prenyl group could be installed *via* an acid-promoted rearrangement of pre-formed *N*-prenylated indole (Fig. 2(a), ii) [24,25]. Another feasible protocol involving lithiation of Boc-protected indole was also reported (Fig. 2(a), iii) [26,27]. Besides, an elegant C–H activation strategy [28–30] consisting of pre-installation of a directing group on the nitrogen atom of indole and directed C2 prenylation was disclosed recently [31–37]. While these methodologies have great potential, they require a multi-step procedure and rely on the use of promoters. From the viewpoint of step- and atom-economy, developing a direct catalytic C2 prenylation of NH indole would be highly desirable yet challenging [38], likely because the nucleophilicity of C2 site is

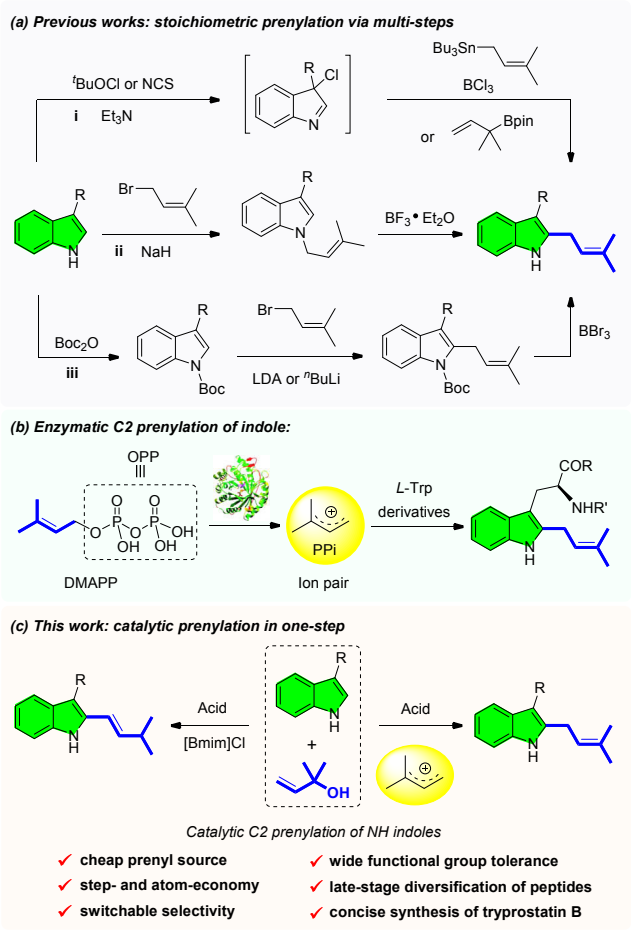


Fig. 2. An overview on C2 prenylation of NH indoles.

weaker than that of other two positions (N, C3) [39,40].

In nature, enzyme-catalyzed C2 prenylation of indole generally proceeds through a Friedel-Crafts S_N1-type alkylation with a prenyl cation-pyrophosphate ion (PPi) pair derived from dimethylallyl pyrophosphate (DMAPP) (Fig. 2(b)) [41,42]. Prompted by this mechanism and our long-standing interests in pentenylations [43–48], we envisioned that if a stable prenyl cation can be selectively formed via a chemical route, the expected indole prenylation might also occur. Indeed, by employing 2-methyl-3-buten-2-ol (*tert*-prenyl alcohol) as precursor and Lewis acid $AlCl_3$ as catalyst, various 3-substituted indoles, tryptophol and tryptamine derivatives in particular, can undergo C2 prenylation with high selectivity (Fig. 2(c)). This strategy also features good applications in peptide diversification and concise synthesis of natural indole alkaloid. Herein, we present these results.

2. Experimental

2.1. General information

Commercially available reagents were purchased from Aladdin, Innochem, TCI, Energy and J&K chemical companies, and were used as received. Before use, the solvents were treated according to the standard methods. Acid resins Amberlyst-15 and Nafion were purchased from Aladdin company and their acid amount was determined as 3.397 and 2.123 mmol/g by temperature-programmed desorption of ammonia (NH_3-TPD), respectively [49].

All reactions were performed under nitrogen atmosphere using standard Schlenk techniques or in a nitrogen-filled glove-box. NMR data was acquired on 400 or 700 MHz instrument using $CDCl_3$ or DMSO-d_6 as the solvent and tetramethylsilane (TMS) was chosen as the internal standard. All reactions were monitored by TLC or NMR analysis and were separated via column chromatography on silica gel (200-300 mesh). Petroleum ether (PE) and ethyl acetate (EtOAc) were used as the eluent. HRMS data was obtained with Micromass HPLC-Q-TOF mass spectrometer (ESI) or Agilent 6540 Accurate-MS spectrometer (Q-TOF). More experimental details are available in the Supporting Information.

2.2. General procedure for catalytic C2 prenylation of indole derivatives

In a sealed tube (4 mL), indole derivatives **1** (0.40 mmol) and $AlCl_3$ (10 mol%–30 mol%) were dissolved in 2-MeTHF (0.40 mL). For tryptamine derivatives, PhCl was used as solvent. Subsequently, 2-methyl-3-buten-2-ol **2** (3.0 equiv, 120 μL) was introduced. After stirring at 80 °C for 24 h, the expected C2-prenylated products **3** were furnished *via* column chromatography purification. Spectral data for products **3** are listed as following.

2-(2-Prenyl-3-indolyl)ethan-1-ol (3a): $AlCl_3$ (10 mol%, 5.4 mg), colorless oil, an inseparable mixture of **3a** and **3a'** (**3a**/**3a'** = 12/1), 62.5 mg, 68% yield, R_f = 0.75 (PE/EtOAc 2/1). NMR data for main isomer **3a** was provided. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.91 (s, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.26 (d, J = 7.7 Hz, 1H), 7.15–7.01 (m, 2H), 5.29 (t, J = 7.4 Hz, 1H), 3.82 (t, J = 6.5 Hz, 2H), 3.47 (d, J = 7.3 Hz, 2H), 2.98 (t, J = 6.5 Hz, 2H), 1.77 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.79, 135.38, 134.75, 128.89, 121.28, 120.47, 119.43, 118.19, 110.56, 106.92, 62.97, 27.78, 25.86, 25.22, 18.01. HRMS calculated for $C_{15}H_{20}NO$ $[M+H]^+$ 230.1539, found 230.1541.

2-(5-(Benzyloxy)-2-prenyl-3-indolyl)ethan-1-ol (3b): $AlCl_3$ (10 mol%, 5.4 mg), colorless oil, an inseparable mixture of **3b** and **3b'** (**3b**/**3b'** = 11/1), 69.5 mg, 52% yield, R_f = 0.70 (PE/EtOAc 2/1). NMR data for main isomer **3b** was provided. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.47 (d, J = 7.5 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.31 (d, J = 7.0 Hz, 1H), 7.17 (d, J = 8.7 Hz, 1H), 7.07 (s, 1H), 6.91–6.81 (m, 1H), 5.30 (t, J = 7.4 Hz, 1H), 5.09 (s, 2H), 3.81 (t, J = 6.4 Hz, 2H), 3.46 (d, J = 7.4 Hz, 2H), 2.94 (t, J = 6.5 Hz, 2H), 1.77 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.33, 137.85, 136.74, 134.88, 130.69, 129.40, 128.61, 127.87, 127.73, 120.38, 111.81, 111.20, 106.89, 102.38, 71.20, 62.94, 27.84, 25.90, 25.34, 18.03. HRMS calculated for $C_{22}H_{26}NO_2$ $[M+H]^+$ 336.1958, found 336.1959.

2-(5-Fluoro-2-prenyl-3-indolyl)ethan-1-ol (3c): $AlCl_3$ (10 mol%, 5.4 mg), colorless oil, an inseparable mixture of **3c** and **3c'** (**3c**/**3c'** = 12/1), 70.3 mg, 71% yield, R_f = 0.75 (PE/EtOAc 2/1). NMR data for main isomer **3c** was provided. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.22–7.11 (m, 2H), 6.94–6.76 (m, 1H), 5.30 (t, J = 7.3 Hz, 1H), 3.82 (q, J = 6.3 Hz, 2H), 3.48 (d, J = 7.3 Hz, 2H), 2.94 (t, J = 6.5 Hz, 2H), 1.78 (s, 3H), 1.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.98 (d, J = 234.1 Hz), 137.76, 135.25, 131.81, 129.41 (d, J = 9.4 Hz), 120.08, 111.07 (d, J = 9.7 Hz), 109.38 (d, J = 26.1 Hz), 107.41 (d, J = 4.5 Hz), 103.32 (d, J = 23.4 Hz), 62.87, 27.79, 25.91, 25.34, 18.05. HRMS calculated for $C_{15}H_{19}FNO$ $[M+H]^+$ 248.1445, found 248.1447.

2-(5-Chloro-2-prenyl-3-indolyl)ethan-1-ol (3d): $AlCl_3$ (10 mol%, 5.4 mg), colorless oil, an inseparable mixture of **3d** and **3d'** (**3d**/**3d'** = 24/1), 68.4 mg, 65% yield, R_f = 0.75 (PE/EtOAc 2/1). NMR data for main isomer **3d** was provided. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.47 (d, J = 1.9 Hz, 1H), 7.16 (d, J = 8.6 Hz, 1H), 7.05 (dd, J = 8.5, 2.0 Hz, 1H), 5.28 (t, J = 7.3 Hz, 1H), 3.80 (t, J = 6.5 Hz, 2H), 3.46 (d, J = 7.3 Hz, 2H), 2.92 (t, J = 6.5 Hz, 2H), 1.77 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.37, 135.27, 133.69, 130.09, 125.13, 121.43, 119.99, 117.73, 111.51, 106.98, 62.86, 27.66, 25.88, 25.25, 18.03. HRMS calculated for $C_{15}H_{19}ClNO$ $[M+H]^+$ 264.1150, found 264.1150.

2-(7-Methyl-2-prenyl-3-indolyl)ethan-1-ol (3e): $AlCl_3$ (10 mol%, 5.4 mg), colorless oil, an inseparable mixture of **3e** and **3e'** (**3e**/**3e'** = 16/1), 65.7 mg, 68% yield, R_f = 0.70 (PE/EtOAc 2/1). NMR data for main isomer **3e** was provided. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.93 (d, J = 7.0 Hz, 1H), 5.31 (t, J = 7.1 Hz, 1H), 3.83 (t, J = 6.5 Hz, 2H), 3.50 (d, J = 7.2 Hz, 2H), 2.98 (t, J = 6.5 Hz, 2H), 2.46 (s, 3H), 1.77 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.55, 134.90, 134.66, 128.41, 122.07, 120.65, 119.75, 116.00, 107.58, 63.04, 27.95, 25.89, 25.34, 18.09, 16.73. HRMS calculated for $C_{16}H_{22}NO$ $[M+H]^+$ 244.1696, found 244.1698.

2-(7-Ethyl-2-prenyl-3-indolyl)ethan-1-ol (3f): $AlCl_3$ (10 mol%, 5.4 mg), colorless oil, an inseparable mixture of **3f** and **3f'** (**3f**/**3f'** = 10/1), 56.8 mg, 55% yield, R_f = 0.70 (PE/EtOAc 2/1). NMR data for main isomer **3f** was provided. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 7.3 Hz, 1H), 5.32 (t, J = 7.3 Hz, 1H), 3.84 (q, J = 6.2 Hz, 2H), 3.50 (d, J = 7.2 Hz, 2H), 2.99 (t, J = 6.4 Hz, 2H), 2.84 (q, J = 7.6 Hz, 2H), 1.77 (s, 6H), 1.36 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.46, 134.72, 134.19, 128.64, 125.96, 120.66, 120.05, 119.86, 116.05, 107.57, 63.05, 27.96, 25.89, 25.36, 24.07, 18.12, 13.94. HRMS calculated for $C_{17}H_{24}NO$ $[M+H]^+$ 258.1852, found 258.1853.

3-(2-Methoxyethyl)-1-methyl-2-prenyl-1*H*-indole (3g): $AlCl_3$ (20 mol%, 11.0 mg), colorless oil, 48.5 mg, 47% yield, R_f = 0.80 (PE/EtOAc 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.8 Hz, 1H), 7.23 (d, J = 8.2 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.07 (t, J = 7.4 Hz, 1H), 5.10 (t, J = 6.2 Hz, 1H), 3.61 (s, 3H), 3.53 (t, J = 7.7 Hz, 2H), 3.48 (d, J = 6.8 Hz, 2H), 3.36 (s, 3H), 3.02 (t, J = 7.7 Hz, 2H), 1.79 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.07, 136.82, 132.50, 127.91, 121.58, 120.82, 118.89, 118.19, 108.78, 107.25, 73.52, 58.73, 29.76, 25.78, 25.22, 24.10, 18.12. **HRMS** calculated for $C_{17}H_{24}NO$ $[M+H]^+$ 258.1852, found 258.1856.

1-Benzyl-3-(2-(benzyloxy)ethyl)-2-prenyl-1*H*-indole (3h): $AlCl_3$ (30 mol%, 16.0 mg), colorless oil, 95.7 mg, 58% yield, R_f = 0.80 (PE/EtOAc 5/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.49 (m, 1H), 7.40–7.04 (m, 11H), 6.89 (d, J = 7.2 Hz, 2H), 5.25 (s, 2H), 5.00 (t, J = 6.4 Hz, 1H), 4.53 (s, 2H), 3.68 (t, J = 7.6 Hz, 2H), 3.39 (d, J = 6.8 Hz, 2H), 3.11 (t, J = 7.7 Hz, 2H), 1.63 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.72, 138.35, 136.99, 136.72, 132.56, 128.69, 128.43, 128.21, 127.72, 127.56, 127.13, 125.94, 121.82, 121.12, 119.19, 118.33, 109.34, 108.21, 73.12, 71.13, 46.67, 25.60, 25.49, 24.18, 18.03. HRMS calculated for $C_{29}H_{32}NO$ $[M+H]^+$ 410.2478, found 410.2476.

2-(1-Benzyl-2-prenyl-3-indolyl)ethan-1-ol (3i): Amberlyst-15 (10 mol%, 12.0 mg), colorless oil, 52.8 mg, 41% yield, R_f = 0.30 (PE/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.54 (m, 1H), 7.28–7.15 (m, 4H), 7.14–7.06 (m, 2H), 6.96–6.86 (m, 2H), 5.29 (s, 2H), 5.02 (t, J = 6.6 Hz, 1H), 3.85 (t, J = 6.6 Hz, 2H), 3.42 (d, J = 6.3 Hz, 1H), 3.04 (t, J = 6.6 Hz, 1H), 1.66 (s, 3H), 1.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.22, 137.62, 136.89, 133.05, 128.75, 128.19, 127.23, 125.95, 121.59, 121.39, 119.42, 118.37, 109.48, 107.57, 63.27, 46.76, 28.24, 25.63, 24.16, 18.10. **HRMS** calculated for $C_{22}H_{26}NO$ $[M+H]^+$ 320.2009, found 320.2008.

4-Methyl-*N*-(2-(2-preny-3-indolyl)ethyl)benzenesulfonamide (3j): $AlCl_3$ (20 mol%, 11.0 mg), colorless oil, 66.8 mg, 44% yield, R_f = 0.75 (PE/EtOAc 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.34–7.24 (m, 2H), 7.20 (d, J = 7.9 Hz, 2H), 7.10 (t, J = 7.5 Hz, 1H), 7.01 (t, J = 7.4 Hz, 1H), 5.26 (t, J = 6.9 Hz, 1H), 4.33 (t, J = 5.9 Hz, 1H), 3.40 (d, J = 7.2 Hz, 2H), 3.21 (q, J = 6.5 Hz, 2H), 2.91 (t, J = 6.7 Hz, 2H), 2.38 (s, 3H), 1.78 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.31, 136.94, 135.80, 135.32, 135.18, 129.70, 128.34, 127.13, 121.46, 120.15, 119.61, 117.89, 110.63, 106.49, 43.35, 25.90, 25.19, 24.66, 21.63, 18.07. HRMS calculated for $C_{22}H_{27}N_2O_2S$ $[M+H]^+$ 383.1788, found 383.1787.

***N*-(2-(2-Prenyl-3-indolyl)ethyl) acetamide (3k):** $AlCl_3$

(20 mol%, 11.0 mg), colorless oil, 44.4 mg, 41% yield, R_f = 0.30 (PE/EtOAc 2/1). ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.50 (d, J = 7.8 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 7.4 Hz, 1H), 5.54 (s, 1H), 5.29 (t, J = 7.2 Hz, 1H), 3.51 (q, J = 6.4 Hz, 2H), 3.45 (d, J = 7.3 Hz, 2H), 2.93 (t, J = 6.6 Hz, 2H), 1.88 (s, 3H), 1.78 (s, 3H), 1.76 (s, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 170.16, 135.42, 135.38, 134.88, 128.78, 121.37, 120.41, 119.54, 118.06, 110.64, 107.92, 40.20, 25.92, 25.17, 24.16, 23.49, 18.05. HRMS calculated for $C_{17}H_{23}N_2O$ $[M+H]^+$ 271.1805, found 271.1808.

***N*-(2-(5-Methoxy-2-prenyl-3-indolyl)ethyl) acetamide (3l):** Nafion (5 mol%, 9.4 mg), colorless oil, 57.6 mg, 48% yield, R_f = 0.30 (PE/EtOAc 1/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.17 (d, J = 8.7 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 6.78 (dd, J = 8.7, 2.4 Hz, 1H), 5.58 (s, 1H), 5.28 (t, J = 7.3 Hz, 1H), 3.84 (s, 3H), 3.50 (q, J = 6.4 Hz, 2H), 3.43 (d, J = 7.3 Hz, 2H), 2.89 (t, J = 6.6 Hz, 2H), 1.90 (s, 3H), 1.77 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.14, 154.18, 136.29, 134.81, 130.46, 129.23, 120.38, 111.33, 111.08, 107.77, 100.35, 56.10, 40.10, 25.89, 25.27, 24.18, 23.49, 18.01. HRMS calculated for $C_{18}H_{25}N_2O_2$ $[M+H]^+$ 301.1911, found 301.1915.

***N*-(2-(2-Prenyl-3-indolyl)ethyl) benzamide (3m):** $AlCl_3$ (20 mol%, 11.0 mg), colorless oil, an inseparable mixture of **3m** and **3m'** (**3m**/**3m'** = 20/1), 77.2 mg, 58% yield, R_f = 0.50 (PE/EtOAc 4/1). NMR data for main isomer **3m** was provided. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.63 (d, J = 7.7 Hz, 2H), 7.56 (d, J = 7.7 Hz, 1H), 7.44 (t, J = 7.3 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.30 (d, J = 8.0 Hz, 1H), 7.18–7.04 (m, 2H), 6.21 (s, 1H), 5.23 (t, J = 7.1 Hz, 2H), 3.73 (q, J = 6.4 Hz, 2H), 3.44 (d, J = 7.2 Hz, 2H), 3.06 (t, J = 6.6 Hz, 2H), 1.70 (s, 3H), 1.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.53, 135.55, 135.42, 134.96, 134.79, 131.39, 128.77, 128.58, 126.98, 121.44, 120.27, 119.60, 118.14, 110.68, 107.89, 40.62, 25.83, 25.17, 24.14, 17.97. HRMS calculated for $C_{22}H_{25}N_2O$ $[M+H]^+$ 333.1961, found 333.1965.

***tert*-Butyl(2-(2-prenyl-3-indolyl)ethyl) carbamate (3n):** $AlCl_3$ (20 mol%, 11.0 mg), colorless oil, an inseparable mixture of **3n** and **3n'** (**3n**/**3n'** = 14/1), 52.4 mg, 40% yield, R_f = 0.65 (PE/EtOAc 2/1). NMR data for main isomer **3n** was provided. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.20 (d, J = 7.9 Hz, 1H), 7.09–6.95 (m, 2H), 5.23 (t, J = 7.1 Hz, 1H), 4.50 (s, 1H), 3.38 (d, J = 7.2 Hz, 2H), 3.33–3.16 (m, 2H), 2.83 (t, J = 6.3 Hz, 2H), 1.71 (s, 3H), 1.68 (s, 3H), 1.36 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.07, 135.36, 134.72, 128.75, 121.24, 120.56, 119.39, 118.20, 110.50, 108.03, 79.10, 41.10, 28.56, 25.90, 25.16, 24.67, 18.02. HRMS calculated for $C_{20}H_{29}N_2O_2$ $[M+H]^+$ 329.2224, found 329.2226.

2-(2-(2-Prenyl-3-indolyl)ethyl)isoindoline-1,3-dione (3o): $AlCl_3$ (20 mol%, 11.0 mg), light yellow oil, 90.6 mg, 63% yield, R_f = 0.80 (PE/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.83–7.77 (m, 2H), 7.71–7.62 (m, 3H), 7.24 (d, J = 7.2 Hz, 1H), 7.07 (p, J = 6.9 Hz, 2H), 5.27 (t, J = 6.8 Hz, 1H), 4.11–3.73 (m, 2H), 3.49 (d, J = 7.2 Hz, 2H), 3.13–3.02 (m, 2H), 1.74 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.41, 135.25, 135.23, 134.75, 133.91, 132.34, 128.77, 123.22, 121.22, 120.34, 119.50, 118.19, 110.46, 107.30, 38.54, 25.86, 25.14, 23.53, 17.96. HRMS calculated for $C_{23}H_{23}N_2O_2$ $[M+H]^+$ 359.1754, found 359.1757.

2-Prenyl-3-phenyl-1*H*-indole (3p): $AlCl_3$ (30 mol%, 16.0 mg), colorless oil, 56.8 mg, 54% yield, R_f = 0.80 (PE/EtOAc 10/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.6 Hz, 2H), 7.45 (t, J = 7.5 Hz, 2H), 7.36–7.27 (m, 2H), 7.16 (t, J = 7.5 Hz, 1H), 7.10 (t, J = 7.4 Hz, 1H), 5.36 (t, J = 7.1 Hz, 1H), 3.59 (d, J = 7.3 Hz, 2H), 1.79 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.48, 135.30, 135.08, 134.80, 129.68, 128.60, 128.10, 125.97, 121.67, 120.57, 120.06, 119.07, 114.09, 110.58, 25.94, 25.75, 18.07. HRMS calculated for $C_{19}H_{20}N$ $[M+H]^+$ 262.1590, found 262.1587.

1-Methyl-2-prenyl-3-phenyl-1*H*-indole (3q): $AlCl_3$ (30 mol%, 8.0 mg, 0.2 mmol scale), colorless oil, 32.1 mg, 58% yield, R_f = 0.85 (PE/EtOAc 6/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 7.9 Hz, 1H), 7.51–7.41 (m, 4H), 7.31 (t, J = 7.5 Hz, 2H), 7.22 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 7.4 Hz, 1H), 5.24 (t, J = 5.8 Hz, 1H), 3.72 (s, 3H), 3.57 (d, J = 6.4 Hz, 2H), 1.74 (s, 3H), 1.71 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.91, 136.79, 135.85, 133.12, 129.95, 128.56, 127.15, 125.88, 121.49, 121.39, 119.75, 119.10, 114.23, 108.90, 29.93, 25.82, 24.58, 18.13. HRMS calculated for $C_{20}H_{22}N$ $[M+H]^+$ 276.1747, found 276.1748.

1-(3-Methyl-2-prenyl-1*H*-indol-1-yl)ethan-1-one (3r): $AlCl_3$ (30 mol%, 16.0 mg), colorless oil, 53.1 mg, 55% yield, R_f = 0.80 (PE/EtOAc 6/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 1H), 7.55–7.37 (m, 1H), 7.33–7.09 (m, 2H), 5.17 (t, J = 5.5 Hz, 1H), 3.71 (d, J = 6.0 Hz, 2H), 2.72 (s, 3H), 2.21 (s, 3H), 1.74 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.22, 136.45, 135.87, 132.97, 131.32, 123.91, 122.87, 121.65, 118.48, 115.61, 114.98, 27.37, 26.43, 25.79, 18.21, 8.87. HRMS calculated for $C_{16}H_{20}NO$ $[M+H]^+$ 242.1539, found 242.1541.

3-Prenylindolin-2-one (3s): $AlCl_3$ (30 mol%, 16.0 mg), colorless oil, 50.4 mg, 63% yield, R_f = 0.45 (PE/EtOAc 2/1). ^{1}H NMR (700 MHz, $CDCl_3$) δ 8.77 (s, 1H), 7.22 (d, J = 7.4 Hz, 1H), 7.20 (t, J = 7.7 Hz, 1H), 6.99 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 7.7 Hz, 1H), 5.14 (t, J = 7.2 Hz, 1H), 3.47 (dd, J = 8.0, 4.9 Hz, 1H), 2.80–2.65 (m, 1H), 2.63–2.50 (m, 1H), 1.67 (s, 3H), 1.58 (s, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 180.41, 141.68, 134.91, 129.90, 127.92, 124.45, 122.27, 119.74, 109.74, 46.32, 29.39, 25.91, 18.19. HRMS calculated for $C_{13}H_{16}NO$ $[M+H]^+$ 202.1226, found 202.1228.

2-(2-Prenyl-3-indolyl)acetonitrile (3t): $AlCl_3$ (30 mol%, 16.0 mg), colorless oil, 51.4 mg, 57% yield, R_f = 0.60 (PE/EtOAc 4/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.23–7.08 (m, 2H), 5.32 (t, J = 7.1 Hz, 1H), 3.76 (s, 2H), 3.50 (d, J = 7.2 Hz, 2H), 1.80 (s, 3H), 1.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.08, 135.86, 134.95, 127.63, 122.02, 120.23, 119.00, 118.22, 117.56, 110.84, 99.48, 25.89, 25.23, 18.08, 12.96. HRMS calculated for $C_{15}H_{17}N_2$ $[M+H]^+$ 225.1386, found 225.1388.

2.3. General procedure for catalytic late-stage prenylation of peptides

In a sealed tube (4 mL), (*L*)-Trp-based peptides (0.40 mmol) and $AlCl_3$ (30 mol%, 16.0 mg) were dissolved in PhCl (0.40 mL). Subsequently, 2-methyl-3-buten-2-ol **2** (3.0 equiv, 120 μL) was introduced. After stirring at 80 °C for 24 h, the target C2-prenylated peptides were obtained via column chromatog-

raphy purification. Spectral data for products 5 and 7 are listed as following.

(*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(2-prenyl-3-indolyl)propanoate (5a): colorless oil, 65.6 mg, 42% yield, R_f = 0.60 (PE/EtOAc 2/1). $[\alpha]^{20}_D$ = +40.3 (*c* 0.36, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.89 (brs, 1H), 7.44 (d, *J* = 7.4 Hz, 1H), 7.32–7.19 (m, 1H), 7.18–6.98 (m, 2H), 5.30 (t, *J* = 7.0 Hz, 1H), 5.08 (d, *J* = 7.8 Hz, 1H), 4.70–4.50 (m, 1H), 3.65 (s, 3H), 3.43 (d, *J* = 7.1 Hz, 2H), 3.24 (d, *J* = 5.2 Hz, 2H), 1.79 (s, 3H), 1.76 (s, 3H), 1.41 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.95, 155.22, 136.19, 135.26, 135.08, 129.04, 121.35, 120.36, 119.56, 118.27, 110.48, 105.25, 79.82, 54.26, 52.39, 28.44, 27.30, 25.92, 25.18, 18.04. **HRMS** calculated for $C_{22}H_{31}N_2O_4$ $[M+H]^+$ 387.2278, found 387.2277.

(*S*)-2-acetamido-3-(2-prenyl-3-indolyl)propanoate (5b): colorless oil, 67.4 mg, 51% yield, R_f = 0.40 (PE/EtOAc 1/1). $[\alpha]^{20}_D$ = +109.2 (*c* 1.01, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.92 (brs, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 6.6 Hz, 1H), 7.17–7.00 (m, 2H), 6.00 (d, *J* = 8.0 Hz, 1H), 5.28 (t, *J* = 6.8 Hz, 1H), 4.87 (q, *J* = 5.8 Hz, 1H), 4.28–4.10 (m, 1H), 4.10–3.91 (m, 1H), 3.42 (d, *J* = 7.1 Hz, 2H), 3.33–3.15 (m, 2H), 1.92 (s, 3H), 1.79 (s, 3H), 1.76 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 172.33, 169.72, 136.10, 135.29, 135.25, 129.24, 121.42, 120.24, 119.63, 118.10, 110.60, 105.26, 61.65, 53.18, 26.95, 25.91, 25.13, 23.36, 18.06, 14.09. HRMS calculated for $C_{20}H_{27}N_2O_3$ $[M+H]^+$ 343.2016, found 343.2015.

(*S*)-(1-hydroxy-3-(2-prenyl-3-indolyl)propan-2-yl)carbamate (5c): colorless oil, 76.0 mg, 53% yield, R_f = 0.40 (PE/EtOAc 2/1). $[\alpha]^{20}_D$ = −18.2 (*c* 0.77, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.88 (brs, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.29–7.24 (m, 1H), 7.16–7.03 (m, 2H), 5.31 (t, *J* = 7.2 Hz, 1H), 4.85 (d, *J* = 6.2 Hz, 1H), 4.00–3.86 (m, 1H), 3.72–3.61 (m, 1H), 3.59–3.51 (m, 1H), 3.48 (d, *J* = 7.2 Hz, 2H), 2.94 (d, *J* = 6.9 Hz, 2H), 2.52 (s, 1H), 1.79 (s, 3H), 1.77 (s, 3H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 156.43, 135.71, 135.32, 135.05, 129.10, 121.36, 120.37, 119.62, 118.34, 110.49, 106.90, 79.71, 64.87, 53.43, 28.50, 25.92, 25.25, 22.48, 18.06. HRMS calculated for $C_{21}H_{31}N_2O_3$ $[M+H]^+$ 359.2329, found 359.2281.

(*S*)-(2-((*tert*-butoxycarbonyl)amino)-3-(2-prenyl-3-indolyl)propanoyl) glycinate (5d): colorless oil, an inseparable mixture of **5d** and **5d'** (**5d**/**5d'** = 10/1), 46.7 mg, 51% yield (0.20 mmol scale), R_f = 0.50 (PE/EtOAc 2/1). $[\alpha]^{20}_D$ = −51.8 (*c* 0.65, DMA). NMR data for main isomer **5d** was provided. ^{1}H NMR (700 MHz, $CDCl_3$) *δ* 7.88 (brs, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.27 (s, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 6.14 (s, 1H), 5.33–5.25 (m, 1H), 5.19 (s, 1H), 4.43 (s, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 3.95–3.88 (m, 1H), 3.81–3.76 (m, 1H), 3.47 (d, *J* = 7.3 Hz, 1H), 3.34–3.22 (m, 1H), 3.19–3.09 (m, 1H), 1.79 (s, 3H), 1.76 (s, 3H), 1.41 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) *δ* 172.01, 169.37, 155.48, 136.24, 135.31, 135.18, 128.83, 121.49, 120.26, 119.76, 118.43, 110.52, 105.66, 80.10, 61.56, 55.09, 41.61, 28.43, 28.32, 25.95, 25.19, 18.08, 14.23. HRMS calculated for $C_{25}H_{36}N_3O_5$ $[M+H]^+$ 458.2649, found 458.2645. HPLC: Chiralpak IA column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 80/20, flow = 1.0 mL/min, retention time 5.6 min and 6.6 min (maj).

((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(2-prenyl-3-indolyl)propanoyl)-*L*-alaninate (5e): colorless oil, 70.9 mg, 50% yield (0.30 mmol scale), R_f = 0.35 (PE/EtOAc 2/1). $[\alpha]^{20}_D$ = +18.7 (*c* 0.55, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$) *δ* 7.88 (brs, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.16–7.01 (m, 2H), 6.24 (d, *J* = 7.0 Hz, 1H), 5.30 (t, *J* = 7.1 Hz, 1H), 5.20 (s, 1H), 4.36 (t, *J* = 7.1 Hz, 1H), 4.06 (q, *J* = 7.0 Hz, 2H), 3.47 (d, *J* = 7.3 Hz, 2H), 3.31–3.25 (m, 1H), 3.18–3.04 (m, 1H), 1.79 (s, 3H), 1.76 (s, 3H), 1.42 (s, 9H), 1.25 (d, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) *δ* 172.38, 171.28, 155.38, 136.17, 135.34, 135.14, 128.86, 121.42, 120.26, 119.71, 118.50, 110.42, 105.72, 80.02, 61.50, 55.12, 48.44, 28.45, 27.68, 25.95, 25.21, 18.75, 18.07, 14.19. HRMS calculated for $C_{26}H_{38}N_3O_5$ $[M+H]^+$ 472.2806, found 472.2810.

((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(2-prenyl-3-indolyl)propanoyl)-*L*-leucinate (5f): colorless oil, an inseparable mixture of **5f** and **5f'** (**5f**/**5f'** = 10/1), 81.5 mg, 41% yield, R_f = 0.60 (PE/EtOAc 2/1). $[\alpha]^{20}_D$ = -19.8 (*c* 0.27, DMA). NMR data for main isomer **5f** was provided. ^{1}H NMR (700 MHz, $CDCl_3$) *δ* 7.86 (brs, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 6.8 Hz, 1H), 7.10 (t, *J* = 7.2 Hz, 1H), 7.06 (t, *J* = 7.2 Hz, 1H), 6.07 (d, *J* = 7.9 Hz, 1H), 5.29 (t, *J* = 6.8 Hz, 1H), 5.18 (s, 1H), 4.53–4.43 (m, 1H), 4.37 (s, 1H), 3.59 (s, 3H), 3.51–3.42 (m, 2H), 3.32–3.19 (m, 1H), 3.17–3.07 (m, 1H), 1.79 (s, 3H), 1.76 (s, 3H), 1.49–1.35 (m, 12H), 0.85 (d, *J* = 6.2 Hz, 3H), 0.83 (d, *J* = 5.8 Hz, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) *δ* 172.75, 171.48, 155.49, 136.19, 135.36, 135.10, 128.80, 121.40, 120.30, 119.75, 118.46, 110.43, 105.75, 80.06, 55.14, 52.27, 50.93, 42.04, 28.42, 27.46, 25.95, 25.23, 24.73, 22.76, 22.22, 18.07. HRMS calculated for $C_{28}H_{42}N_3O_5$ $[M+H]^+$ 500.3119, found 500.3112.

((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(2-prenyl-3-indolyl)propanoyl)-*L*-phenylalaninate (5g): colorless oil, an inseparable mixture of **5g** and **5g'** (**5g**/**5g'** = 9/1), 78.9 mg, 36% yield, R_f = 0.70 (PE/EtOAc 3/1). $[\alpha]^{20}_D$ = +21.4 (*c* 1.25, $CHCl_3$). NMR data for main isomer **5g** was provided. ^{1}H NMR (700 MHz, $CDCl_3$) *δ* 7.87 (brs, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.30–7.24 (m, 1H), 7.18–7.02 (m, 5H), 6.82 (d, *J* = 6.9 Hz, 2H), 6.13 (d, *J* = 6.9 Hz, 1H), 5.28 (t, *J* = 7.3 Hz, 1H), 5.21–5.00 (m, 1H), 4.70–4.55 (m, 1H), 4.37 (s, 1H), 4.09–3.88 (m, 2H), 3.47 (d, *J* = 7.2 Hz, 2H), 3.38–3.20 (m, 1H), 3.15–3.03 (m, 1H), 2.93 (d, *J* = 5.7 Hz, 2H), 1.78 (s, 3H), 1.75 (s, 3H), 1.41 (s, 9H), 1.13 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) *δ* 171.34, 170.75, 155.38, 136.20, 135.83, 135.37, 135.14, 129.41, 128.84, 128.45, 127.03, 121.49, 120.26, 119.79, 118.49, 110.48, 105.71, 80.03, 61.43, 55.23, 53.52, 38.16, 28.42, 27.67, 25.93, 25.22, 18.07, 14.14. HRMS calculated for $C_{32}H_{42}N_3O_5$ $[M+H]^+$ 548.3119, found 548.3112.

((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(2-prenyl-3-indolyl)propanoyl)-*L*-methioninate (5h): colorless oil, 82.9 mg, 39% yield, R_f = 0.60 (PE/EtOAc 2/1). $[\alpha]^{20}_D$ = +22.5 (*c* 0.36, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$) *δ* 7.86 (brs, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 6.7 Hz, 1H), 7.20–6.95 (m, 2H), 6.30 (d, *J* = 7.3 Hz, 1H), 5.30 (t, *J* = 7.2 Hz, 1H), 5.19 (s, 1H), 4.57–4.42 (m, 1H), 4.42–4.32 (m, 1H), 4.06 (q, *J* = 6.9 Hz, 2H), 3.48 (d, *J* = 7.2 Hz, 2H), 3.36–3.21 (m, 1H), 3.19–3.03 (m, 1H), 2.37–2.16 (m, 2H), 2.10–1.94 (m, 4H), 1.89–1.82 (m, 1H), 1.79 (s, 3H), 1.77 (s, 3H), 1.43 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) *δ* 171.69, 171.18, 155.44, 136.19, 135.36, 135.17,

128.80, 121.47, 120.24, 119.77, 118.37, 110.48, 105.66, 80.15, 61.66, 55.33, 51.90, 32.02, 29.64, 28.45, 27.50, 25.95, 25.23, 18.09, 15.49, 14.20. HRMS calculated for $C_{28}H_{42}N_3O_5S$ $[M+H]^+$ 532.2840, found 532.2848.

(*S*)-3-(2-((*tert*-butoxycarbonyl)amino)-3-(2-prenyl-3-indolyl)propanamido) propanoate (5i): colorless oil, 65.1 mg, 46% yield (0.30 mmol scale), R_f = 0.40 (PE/EtOAc 2/1). $[\alpha]^{20}_D$ = +13.2 (*c* 0.40, $CHCl_3$). ^1H NMR (700 MHz, $CDCl_3$) δ 7.86 (brs, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.25 (d, *J* = 7.1 Hz, 1H), 7.15–7.02 (m, 2H), 6.02 (s, 1H), 5.29 (t, *J* = 7.8 Hz, 1H), 5.19 (s, 1H), 4.33 (s, 1H), 4.00 (q, *J* = 7.2 Hz, 2H), 3.54–3.41 (m, 2H), 3.38–3.19 (m, 3H), 3.19–3.00 (m, 1H), 2.37–2.20 (m, 1H), 2.19–2.03 (m, 1H), 1.79 (s, 3H), 1.77 (s, 3H), 1.42 (s, 9H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 172.14, 171.74, 155.38, 136.05, 135.27, 135.19, 128.80, 121.53, 120.21, 119.81, 118.51, 110.47, 105.86, 79.97, 60.71, 55.23, 34.83, 33.74, 28.45, 27.92, 25.95, 25.15, 18.08, 14.23. HRMS calculated for $C_{26}H_{38}N_3O_5$ $[M+H]^+$ 472.2806, found 472.2800.

((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(2-prenyl-3-indolyl)propanoyl)-*L*-aspartate (5j): colorless oil, an inseparable mixture of **5j** and **5j'** (**5j**/**5j'** = 5/1), 84.8 mg, 39% yield, R_f = 0.65 (PE/EtOAc 3/1). $[\alpha]^{20}_D$ = –30.5 (*c* 0.40, DMA). NMR data for main isomer **5j** was provided. ^1H NMR (700 MHz, $CDCl_3$) δ 7.86 (brs, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 7.05 (t, *J* = 7.2 Hz, 1H), 6.66 (d, *J* = 7.3 Hz, 1H), 5.30 (t, *J* = 7.3 Hz, 1H), 5.12 (s, 1H), 4.60–4.64 (m, 1H), 4.41 (s, 1H), 4.11 (q, *J* = 6.7 Hz, 2H), 4.07–3.98 (m, 2H), 3.47 (d, *J* = 7.2 Hz, 2H), 3.34–3.23 (m, 1H), 3.20–3.11 (m, 1H), 2.88 (dd, *J* = 17.0, 4.2 Hz, 1H), 2.74 (dd, *J* = 17.0, 4.9 Hz, 1H), 1.79 (s, 3H), 1.77 (s, 3H), 1.58 (s, 9H), 1.22–1.17 (m, 6H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 171.76, 170.63, 170.18, 155.34, 136.18, 135.36, 135.12, 128.49, 121.41, 120.31, 119.68, 118.40, 110.44, 105.58, 80.04, 61.88, 60.99, 55.15, 49.00, 36.43, 28.41, 27.54, 25.94, 25.22, 18.07, 14.17, 14.14. HRMS calculated for $C_{29}H_{42}N_3O_7$ $[M+H]^+$ 544.3017, found 544.3020.

((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(2-prenyl-3-indolyl)propanoyl)-*L*-isoleucinate (5k): colorless oil, an inseparable mixture of **5k** and **5k'** (**5k**/**5k'** = 8/1), 84.2 mg, 41% yield, R_f = 0.50 (PE/EtOAc 3/1). $[\alpha]^{20}_D$ = +8.6 (*c* 0.63, $CHCl_3$). NMR data for main isomer **5k** was provided. ^1H NMR (700 MHz, $CDCl_3$) δ 7.84 (brs, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 6.2 Hz, 1H), 7.16–7.00 (m, 2H), 6.19 (d, *J* = 8.0 Hz, 1H), 5.30 (t, *J* = 6.3 Hz, 1H), 5.21 (s, 1H), 4.45–4.30 (m, 2H), 4.03 (q, *J* = 7.5 Hz, 2H), 3.47 (d, *J* = 7.1 Hz, 2H), 3.32–3.20 (m, 1H), 3.20–3.07 (m, 1H), 1.79 (s, 3H), 1.76 (s, 3H), 1.42 (s, 9H), 1.37–1.29 (m, 2H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.09–0.99 (m, 1H), 0.85 (t, *J* = 7.3 Hz, 3H), 0.73 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 171.43, 171.05, 155.51, 136.13, 135.35, 135.10, 128.83, 121.38, 120.32, 119.73, 118.42, 110.40, 105.80, 80.04, 61.16, 56.69, 55.32, 38.28, 28.45, 27.57, 25.95, 25.38, 25.24, 18.07, 15.12, 14.27, 11.74. HRMS calculated for $C_{29}H_{44}N_3O_5$ $[M+H]^+$ 514.3275, found 514.3282.

(*S*)-2-(2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino) acetamido)-3-(2-prenyl-3-indolyl) propanoate (5l): colorless oil, 97.3 mg, 43% yield, R_f = 0.50 (PE/EtOAc 2/1). $[\alpha]^{20}_D$ = +12.59 (*c* 1.85, $CHCl_3$). ^1H NMR (700 MHz, $CDCl_3$) δ 7.91 (brs, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 8.1 Hz, 2H), 7.44–7.35 (m, 3H), 7.34–7.27 (m, 2H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.10–6.99 (m, 2H), 6.43 (d, *J* = 7.7 Hz, 1H), 5.30 (s, 1H), 5.24 (t, *J* = 6.2 Hz, 1H), 4.89 (q, *J* = 6.3 Hz, 1H), 4.34 (d, *J* = 7.2 Hz, 2H), 4.18 (t, *J* = 7.3 Hz, 1H), 3.79 (d, *J* = 5.6 Hz, 1H), 3.67 (s, 3H), 3.45–3.32 (m, 2H), 3.32–3.19 (m, 2H), 1.76 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 172.33, 168.58, 156.41, 143.91, 141.40, 141.39, 136.24, 135.34, 135.25, 129.02, 127.84, 127.20, 125.21, 121.53, 120.11, 120.08, 119.75, 117.82, 110.76, 104.84, 67.30, 53.13, 52.64, 47.16, 44.38, 26.82, 25.87, 25.05, 18.05. HRMS calculated for $C_{34}H_{36}N_3O_5$ $[M+H]^+$ 566.2649, found 566.2654. HPLC: Chiralpak IA column, 254 nm, 30 °C, *n*-hexane/*i*-propanol = 80/20, flow = 1.0 mL/min, retention time 11.8 min and 16.7 min (maj).

(*S*)-2-((*S*)-2-((((9*H*-fluoren-9-yl)methoxy)carbonyl)amino) propanamido)-3-(2-prenyl-3-indolyl) propanoate (5m): colorless oil, 111.3 mg, 48% yield, R_f = 0.40 (PE/EtOAc 2/1). $[\alpha]^{20}_D$ = +36.9 (*c* 0.23, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (brs, 1H), 7.76 (d, *J* = 7.6 Hz, 2H), 7.62–7.51 (m, 2H), 7.40 (t, *J* = 7.7 Hz, 3H), 7.31 (t, *J* = 7.3 Hz, 2H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.13–6.99 (m, 2H), 6.42 (d, *J* = 8.0 Hz, 1H), 5.24 (t, *J* = 7.7 Hz, 2H), 4.94–4.76 (m, 1H), 4.43–4.25 (m, 2H), 4.24–4.09 (m, 2H), 3.66 (s, 3H), 3.45–3.34 (m, 2H), 3.35–3.19 (m, 2H), 1.76 (s, 3H), 1.72 (s, 3H), 1.27 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.29, 171.83, 155.77, 143.94, 141.41, 136.20, 135.34, 135.23, 129.08, 127.84, 127.20, 125.22, 121.53, 120.10, 119.72, 117.96, 110.74, 104.95, 67.08, 53.17, 52.58, 50.51, 47.23, 26.94, 25.86, 25.07, 19.02, 18.04. HRMS calculated for $C_{35}H_{38}N_3O_5$ $[M+H]^+$ 580.2806, found 580.2807.

(*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-methylbutanamido)-3-(2-prenyl-3-indolyl) propanoate (5n): colorless oil, an inseparable mixture of **5n** and **5n'** (**5n**/**5n'** = 6/1), 89.4 mg, 46% yield, R_f = 0.50 (PE/EtOAc 2/1). $[\alpha]^{20}_D$ = +13.9 (*c* 1.52, $CHCl_3$). NMR data for main isomer **5n** was provided. ^1H NMR (700 MHz, $CDCl_3$) δ 7.90 (brs, 1H), 7.45 (d, *J* = 7.0 Hz, 1H), 7.27 (d, *J* = 6.3 Hz, 1H), 7.14–7.07 (m, 2H), 6.31 (d, *J* = 7.8 Hz, 1H), 5.28 (t, *J* = 7.1 Hz, 1H), 5.00 (d, *J* = 8.2 Hz, 1H), 4.84 (q, *J* = 6.2 Hz, 1H), 3.91 (t, *J* = 7.3 Hz, 1H), 3.64 (s, 3H), 3.47–3.39 (m, 2H), 3.32–3.22 (m, 2H), 2.10–2.01 (m, 1H), 1.79 (s, 3H), 1.76 (s, 3H), 1.43 (s, 9H), 0.88 (d, *J* = 6.9 Hz, 3H), 0.77 (d, *J* = 6.2 Hz, 3H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 172.41, 171.23, 155.74, 136.17, 135.36, 135.27, 129.01, 121.57, 120.08, 119.84, 117.98, 110.69, 109.84, 105.00, 79.82, 59.69, 53.13, 52.51, 31.33, 28.42, 27.11, 25.91, 25.10, 19.15, 18.09, 17.48. HRMS calculated for $C_{27}H_{40}N_3O_5$ $[M+H]^+$ 486.2962, found 486.2956.

(*S*)-2-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-phenylpropanamido)-3-(2-prenyl-3-indolyl) propanoate (5o): colorless oil, an inseparable mixture of **5o** and **5o'** (**5o**/**5o'** = 6/1), 86.3 mg, 40% yield, R_f = 0.70 (PE/EtOAc 1/1). $[\alpha]^{20}_D$ = +9.5 (*c* 0.99, $CHCl_3$). NMR data for main isomer **5o** was provided. ^1H NMR (700 MHz, $CDCl_3$) δ 7.86 (brs, 1H), 7.27–7.23 (m, 4H), 7.20 (d, *J* = 7.3 Hz, 1H), 7.17–7.12 (m, 2H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.05–6.98 (m, 1H), 6.33–6.23 (m, 1H), 5.24 (t, *J* = 7.5 Hz, 1H), 4.93–4.75 (m, 2H), 4.30 (s, 1H), 3.61 (s, 3H), 3.40–3.30 (m, 2H), 3.24–3.12 (m, 2H), 3.05–2.93 (m, 1H), 2.88 (s, 1H), 1.78 (s, 3H), 1.74 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 172.06, 170.79, 155.22, 136.77, 136.08, 135.30, 135.20, 129.52, 129.07, 128.68, 127.00, 121.49, 120.08, 119.71, 117.95, 110.70, 105.00, 80.08, 55.82, 53.19, 52.47, 38.67, 28.32, 27.14, 25.91, 25.03,

18.07. HRMS calculated for $C_{31}H_{40}N_3O_5$ $[M+H]^+$ 534.2962, found 534.2970.

(3*S*,8a*S*)-3-((2-Prenyl-3-indolyl)methyl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (7l): white solid, m.p. 87–89 °C, 23.1 mg, 33% yield, R_f = 0.50 (EtOAc). $[\alpha]^{20}_D$ = +12.0 (*c* 0.41, DMA). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (brs, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.20–7.12 (m, 1H), 7.12–7.06 (m, 1H), 5.64 (s, 1H), 5.31 (td, *J* = 7.2, 3.8 Hz, 1H), 4.46–4.30 (m, 1H), 4.05 (t, *J* = 8.0 Hz, 1H), 3.74–3.63 (m, 2H), 3.63–3.54 (m, 1H), 3.54–3.39 (m, 2H), 2.95 (dd, *J* = 15.1, 11.4 Hz, 1H), 2.40–2.26 (m, 1H), 2.10–1.95 (m, 2H), 1.95–1.86 (m, 1H), 1.78 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.47, 165.94, 136.57, 135.59, 135.57, 128.11, 121.97, 120.02, 119.86, 117.86, 110.92, 104.74, 59.40, 54.73, 45.55, 28.48, 25.87, 25.76, 25.26, 22.77, 18.11. HRMS calculated for $C_{21}H_{26}N_3O_2$ $[M+H]^+$ 352.2020, found 352.2015.

(3*S*,6*S*)-3-Methyl-6-((2-prenyl-3-indolyl)methyl) piperazine-2,5-dione (7m): white solid, m.p. 250–251 °C, 55.8 mg, 86% yield, R_f = 0.30 (PE/EtOAc 1/2). $[\alpha]^{20}_D$ = –9.7 (*c* 0.16, DMSO). ^{1}H NMR (700 MHz, DMSO-d_6) δ 10.60 (s, 1H), 7.96 (d, *J* = 2.7 Hz, 1H), 7.90 (d, *J* = 2.7 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 6.94 (t, *J* = 7.4 Hz, 1H), 6.87 (t, *J* = 7.4 Hz, 1H), 5.31 (t, *J* = 7.2 Hz, 1H), 4.10–3.95 (m, 1H), 3.52 (qd, *J* = 7.1, 2.4 Hz, 1H), 3.41 (d, *J* = 7.4 Hz, 2H), 3.22 (dd, *J* = 14.6, 4.2 Hz, 1H), 2.96 (dd, *J* = 14.6, 4.7 Hz, 1H), 1.72 (s, 3H), 1.70 (s, 3H), 0.31 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (175 MHz, DMSO-d_6) δ 167.39, 166.79, 137.26, 135.24, 132.10, 128.83, 121.53, 120.05, 118.50, 118.32, 110.33, 103.95, 55.82, 49.99, 28.80, 25.61, 24.83, 19.82, 17.81. HRMS calculated for $C_{19}H_{24}N_3O_2$ $[M+H]^+$ 326.1863, found 326.1838.

2.4. General procedure for one-step prenylation-isomerization of tryptophols/tryptamines

To a sealed tube (2 mL) was added tryptophol or tryptamine **1** (0.40 mmol), Nafion (5 mol%, 9.4 mg), [Bmim]Cl (0.50 g) and 2-methyl-3-buten-2-ol **2** (6.0 equiv, 0.24 mL) successively. After stirring at 120 °C for 24 h, water was added and the solution was extracted with ethyl acetate for three times. The combined organic layer was dried over sodium sulfate and concentrated in vacuo. The desired products **9** were isolated via column chromatography purification. Spectral data for products 9 was listed as following.

(*E*)-2-(2-(3-Methyl-1-butenyl)-3-indolyl)ethan-1-ol (9a): colorless oil, 50.6 mg, 55% yield, R_f = 0.70 (PE/EtOAc 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (brs, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.26 (t, *J* = 7.7 Hz, 1H), 7.20–7.13 (m, 1H), 7.11–7.04 (m, 1H), 6.49 (dd, *J* = 16.1, 1.4 Hz, 1H), 5.97 (dd, *J* = 16.1, 6.9 Hz, 1H), 3.85 (t, *J* = 6.6 Hz, 2H), 3.04 (t, *J* = 6.4 Hz, 2H), 2.62–2.42 (m, 1H), 1.51 (brs, 1H), 1.11 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.84, 136.27, 133.86, 129.12, 122.72, 119.70, 118.73, 116.01, 110.55, 110.10, 63.11, 31.92, 27.65, 22.63. HRMS calculated for $C_{15}H_{20}NO$ $[M+H]^+$ 230.1539, found 230.1542.

(*E*)-2-(5-Fluoro-2-(3-methyl-1-butenyl)-3-indolyl)ethan-1-ol (9b): colorless oil, 56.8 mg, 57% yield, R_f = 0.70 (PE/EtOAc 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (brs, 1H), 7.23–7.09 (m, 2H), 7.02–6.80 (m, 1H), 6.47 (dd, *J* = 16.1, 1.4 Hz, 1H), 5.98 (dd, *J* = 16.2, 6.9 Hz, 1H), 3.83 (t, *J* = 6.5 Hz, 2H), 2.99 (t, *J* = 6.5 Hz, 2H), 2.58–2.42 (m, 1H), 1.51 (brs, 1H), 1.11 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.97 (d, *J* = 234.5 Hz), 137.55, 135.62, 132.69, 129.58 (d, *J* = 9.5 Hz), 115.89, 111.08 (d, *J* = 9.5 Hz), 110.77 (d, *J* = 26.2 Hz), 110.28 (d, *J* = 4.7 Hz), 103.74 (d, *J* = 23.6 Hz), 62.96, 31.92, 27.64, 22.57. HRMS calculated for $C_{15}H_{19}FNO$ $[M+H]^+$ 248.1445, found 248.1444.

(*E*)-2-(5-Chloro-2-(3-methyl-1-butenyl)-3-indolyl)ethan-1-ol (9c): colorless oil, 49.1 mg, 47% yield, R_f = 0.70 (PE/EtOAc 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (brs, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 7.09 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.47 (dd, *J* = 16.2, 1.4 Hz, 1H), 5.99 (dd, *J* = 16.2, 6.9 Hz, 1H), 3.83 (t, *J* = 6.5 Hz, 2H), 2.99 (t, *J* = 6.5 Hz, 2H), 2.61–2.41 (m, 1H), 1.47 (brs, 1H), 1.11 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.78, 135.20, 134.57, 130.30, 125.36, 122.84, 118.22, 115.78, 111.50, 109.87, 62.99, 31.94, 27.55, 22.56. HRMS calculated for $C_{15}H_{19}ClNO$ $[M+H]^+$ 264.1150, found 264.1152.

(*E*)-2-(7-Methyl-2-(3-methyl-1-butenyl)-3-indolyl)ethan-1-ol (9d): colorless oil, 42.7 mg, 44% yield, R_f = 0.70 (PE/EtOAc 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (brs, 1H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.06–6.90 (m, 2H), 6.51 (dd, *J* = 16.2, 1.4 Hz, 1H), 6.01 (dd, *J* = 16.2, 6.9 Hz, 1H), 3.85 (q, *J* = 6.4 Hz, 2H), 3.05 (t, *J* = 6.4 Hz, 2H), 2.64–2.50 (m, 1H), 2.49 (s, 3H), 1.41 (t, *J* = 6.3 Hz, 1H), 1.14 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.60, 135.72, 133.58, 128.68, 123.43, 119.99, 119.79, 116.52, 116.16, 110.76, 63.16, 31.98, 27.81, 22.69, 16.76. HRMS calculated for $C_{16}H_{22}NO$ $[M+H]^+$ 244.1696, found 244.1698.

(*E*)-2-(7-Ethyl-2-(3-methyl-1-butenyl)-3-indolyl)ethan-1-ol (9e): colorless oil, 48.4 mg, 47% yield, R_f = 0.70 (PE/EtOAc 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (brs, 1H), 7.40 (d, *J* = 7.3 Hz, 1H), 7.14–6.95 (m, 2H), 6.51 (d, *J* = 16.2 Hz, 1H), 6.00 (dd, *J* = 16.2, 6.9 Hz, 1H), 3.86 (q, *J* = 6.3 Hz, 2H), 3.05 (t, *J* = 6.4 Hz, 2H), 2.87 (q, *J* = 7.6 Hz, 2H), 2.65–2.46 (m, 1H), 1.45–1.40 (m, 1H), 1.38 (t, *J* = 7.6 Hz, 3H), 1.14 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.54, 134.99, 133.49, 128.90, 126.02, 121.43, 120.09, 116.53, 116.19, 110.75, 63.15, 31.98, 27.80, 24.06, 22.69, 14.03. HRMS calculated for $C_{17}H_{24}NO$ $[M+H]^+$ 258.1852, found 252.1860.

(*E*)-*N*-(2-(2-(3-Methyl-1-butenyl)-3-indolyl) ethyl)benzamide (9f): colorless oil, 67.4 mg, 51% yield, R_f = 0.65 (PE/EtOAc 2/1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (brs, 1H), 7.63 (d, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.36 (d, *J* = 7.7 Hz, 2H), 7.33–7.28 (m, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.45 (d, *J* = 16.1 Hz, 1H), 6.14 (s, 1H), 5.97 (dd, *J* = 16.1, 6.9 Hz, 1H), 3.74 (q, *J* = 6.2 Hz, 2H), 3.12 (t, *J* = 6.3 Hz, 2H), 2.48–2.34 (m, 1H), 1.01 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.46, 137.03, 136.35, 134.74, 133.67, 131.39, 128.85, 128.54, 126.99, 122.87, 119.83, 118.60, 115.83, 111.05, 110.66, 40.49, 31.88, 23.91, 22.50. HRMS calculated for $C_{22}H_{25}N_2O$ $[M+H]^+$ 333.1961, found 333.1963.

(*E*)-2-(2-(2-(3-Methyl-1-butenyl)-3-indolyl) ethyl)isoindoline-1,3-dione (9g): colorless oil, an inseparable mixture of **9g** and **3o** (**9g**/**3o** = 4/1), 87.5 mg, 61% yield, R_f = 0.70 (PE/EtOAc 4/1). NMR data for main isomer **9g** was

provided. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (brs, 1H), 7.87–7.81 (m, 2H), 7.74–7.66 (m, 3H), 7.28–7.24 (m, 1H), 7.18–7.12 (m, 1H), 7.11–7.05 (m, 1H), 6.46 (dd, J = 16.2, 1.4 Hz, 1H), 5.91 (dd, J = 16.1, 6.8 Hz, 1H), 4.02–3.84 (m, 2H), 3.19–3.03 (m, 2H), 2.56–2.34 (m, 1H), 1.05 (d, J = 6.7 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.41, 136.79, 136.14, 133.94, 133.38, 132.38, 128.96, 123.28, 122.68, 119.79, 118.67, 115.72, 110.49, 110.37, 38.57, 31.82, 23.35, 22.51. HRMS calculated for $C_{23}H_{23}N_2O_2$ $[M+H]^+$ 359.1754, found 359.1759.

3. Results and discussion

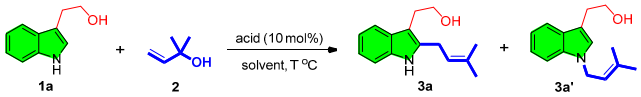
3.1. Establishing catalytic C2 prenylation of NH indoles

We initially set out to investigate the feasibility of C2 prenylation of tryptophol **1a** (Table 1). Commercially available and cheap *tert*-prenyl alcohol **2** was chosen as the prenyl donor, since it would probably be easier to generate a stable carbocation at the tertiary allylic position under acidic conditions. To our delight, treatment of a solution of **1a** and **2** in DCE with Brønsted acid CSA at 70 °C furnished the target product **3a** in 39% yield, albeit with an observation of *N*-prenylated product **3a'** (Table 1, entry 1). The stronger protic acid Tf_2NH gave an inferior result (Table 1, entry 2). An array of Lewis acids were further evaluated. Both $AlCl_3$ and $FeCl_3$ could promote the reaction and the former led to a better yield (Table 1, entries 3, 4). The stronger Lewis acids including $Bi(OTf)_3$, $Sc(OTf)_3$, $BF_3{\cdot}Et_2O$ and $Al(OTf)_3$ delivered a complex mixture (Table 1, entries 5–7, 16). In comparison, $Cu(OTf)_2$, $Zn(OTf)_2$, $Mg(ClO_4)_2$ and $AlMe_3$ showed poor catalytic activities (Table 1, entries 17–20) [50,51]. The prenylation did not occur in the presence of $Al(O^iPr)_3$ (Table 1, entry 21), while a combination of $Al(O^iPr)_3$ and HCl (Table 1, entry 22) gave similar result to sole HCl catalyst (Fig. 6(f)), revealing that $Al(O^iPr)_3$ had no positive effect on the selectivity. Although acid resins Amberlyst-15 and Nafion were suitable catalysts as well, the selectivity of **3a** was moderate (Table 1, entries 8, 9). A survey of solvents revealed that C2 prenylation in ethers resulted in comparable yields and selectivities, while strong polar solvent NMP totally suppressed the process (Table 1, entries 10–14). 2-MeTHF, a renewable feedstock derived from biomass [52], was selected as the optimal solvent. An elevated temperature led to an increase of the yield while maintaining good selectivity (Table 1, entry 15).

3.2. Substrate scope

With the optimized conditions in hand, the generality of this protocol was subsequently scrutinized (Fig. 3). Both electron-rich and -deficient substituents on the phenyl ring of tryptophol were well tolerated, delivering C2 prenylated products **3b**–**3d** in good selectivities. 7-Me and 7-Et tryptophols were suitable substrates as well (**3e**, **3f**). This method was also applicable to Me and Bn protected tryptophols (**3g**, **3h**). It is worth noting that acid resin Amberlyst-15 proved to be a better catalyst for C2 prenylation of *N*-Bn tryptophol (**3i**). The reactions between tryptophol **1a** and branched phenyl-substituted allylic alcohols proceeded well, providing the target products in satisfactory yields (SI, **3aa**, **3ab**). However, simple allylic alcohol and cinnamyl alcohol proved to be unsuccessful. A treatment of *N*-Ts tryptamine **1j** with the standard conditions mainly yielded cyclized C3 prenylated product (SI, **3j-I**). When varying the solvent to DCE, both C3 and *N*-prenylation took place at 100 °C (SI, **3j-II**). In contrast, the reaction in PhCl gave the desired C2 prenylated product **3j** in an acceptable yield. Hence, for tryptamine derivatives, PhCl was selected as an optimal solvent. The protecting groups including Ac, Bz, Boc and phthalimide on the amine had no significant impact on the reactions (**3k**–**3o**). Unprotected and *N*-Me tryptamines, which can form salts with $AlCl_3$, could not participate in the process. Melatonin is an important natural tryptamine produced mainly in the pineal gland and has anti-inflammatory and -oxidant effects [53]. Its modification took place readily with acid resin Nafion as catalyst (**3l**). 3-Ph and -Me indoles all underwent the transformation smoothly, regardless of whether NH was protected (**3p**–**3r**). In most cases, migration of the 3-alkyl substituents were not observed. Surprisingly, subjecting 3-acetoxyindole to the optimized conditions produced 3-prenyl indolinone **3s** in 63% yield, presumably because acyloxy group

Table 1
Optimization of C2 prenylation of tryptophol. [a]



Entry	Acid	Solvent	T (°C)	Yield [b] (%)	**3a**:**3a'** [c]
1	CSA	DCE	70	39	3:1
2	Tf_2NH	DCE	70	22	4:1
3	$AlCl_3$	DCE	70	46	5:1
4	$FeCl_3$	DCE	70	29	10:1
5	$Bi(OTf)_3$	DCE	70	Mixture	—
6	$Sc(OTf)_3$	DCE	70	Mixture	—
7	$BF_3{\cdot}Et_2O$	DCE	70	Mixture	—
8	Amberlyst-15 [d]	DCE	70	57	4:1
9	Nafion [e]	DCE	70	54	3:1
10	$AlCl_3$	PhCl	70	56	10:1
11	$AlCl_3$	NMP	70	N.R.	—
12	$AlCl_3$	dioxane	70	69	12:1
13	$AlCl_3$	THF	70	66	10:1
14	$AlCl_3$	2-MeTHF	70	67	12:1
15	**$AlCl_3$**	**2-MeTHF**	**80**	**75**	**12:1**
16	$Al(OTf)_3$	2-MeTHF	80	Mixture	—
17	$AlMe_3$	2-MeTHF	80	N.R.	—
18	$Cu(OTf)_2$	2-MeTHF	80	N.R.	—
19	$Zn(OTf)_2$	2-MeTHF	80	19	5:1
20	$Mg(ClO_4)_2$	2-MeTHF	80	N.R.	—
21	$Al(O^iPr)_3$	2-MeTHF	80	N.R.	—
22	$Al(O^iPr)_3$/HCl [f]	2-MeTHF	80	46	6:1

[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.60 mmol), acid (10 mol%), solvent (0.20 mL), T °C, 24 h. [b] Total yield, determined by HPLC with naphthalene as the internal standard. [c] Determined by ^{1}H NMR of crude reaction mixture. [d] Amberlyst-15 (acid amount 3.397 mmol/g, 6.0 mg). [e] Nafion (acid amount 2.123 mmol/g, 9.4 mg). [f] HCl (4.0 M in dioxane, 30 mol%). CSA = Camphorsulfonic acid. DCE = Dichloroethane. NMP = *N*-Methyl pyrrolidone. 2-MeTHF = 2-Methyltetrahydrofuran. N.R. = No reaction.

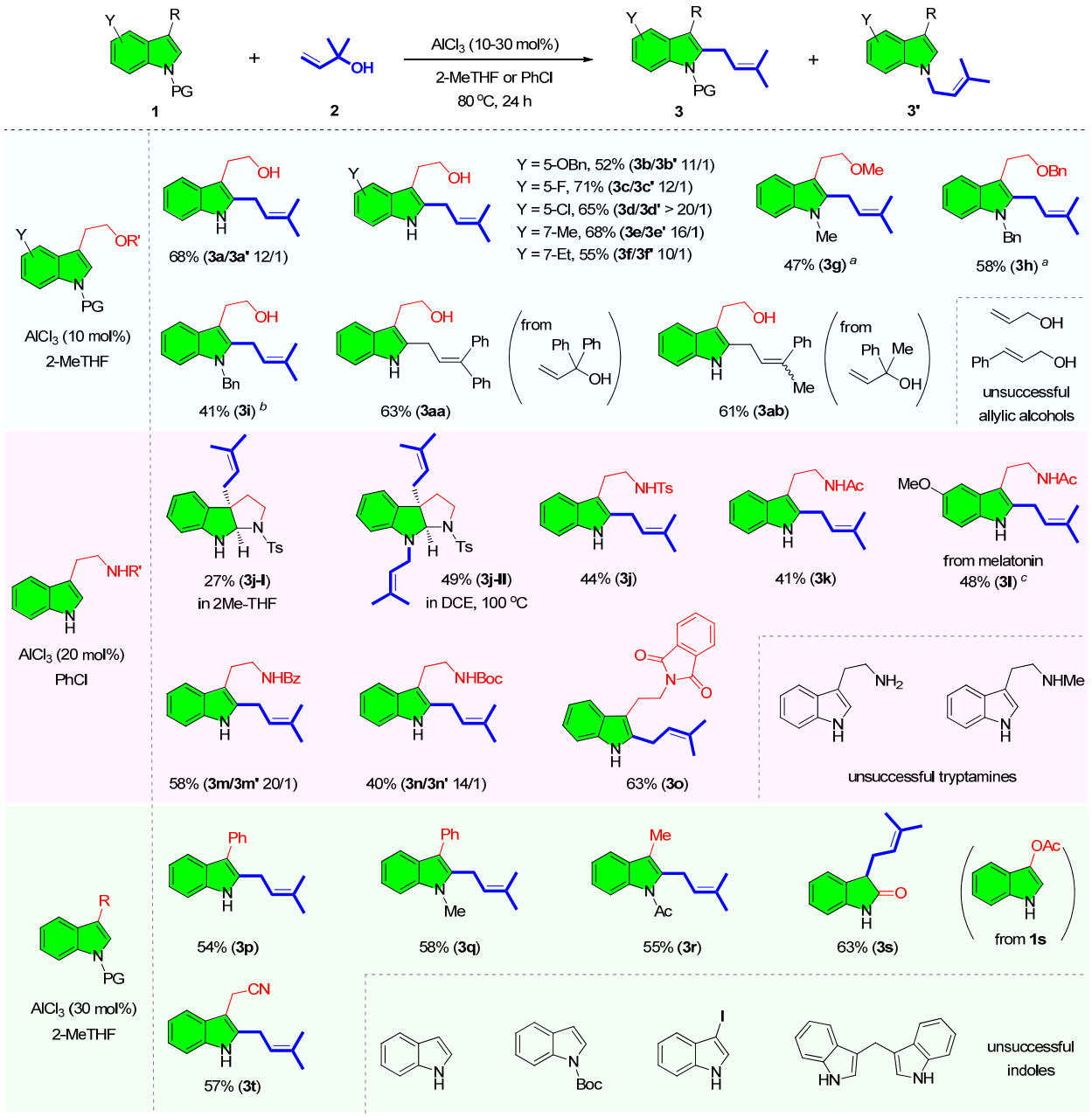


Fig. 3. Catalytic C2 prenylation of 3-substituted indoles. Reaction conditions: **1** (0.40 mmol), **2** (1.20 mmol), $AlCl_3$ (10 mol%–30 mol%), 2-MeTHF or PhCl (0.40 mL), 80 °C, 24 h. Isolated yields were given. The ratio (**3**/**3'**) was determined by ^1H NMR, unless otherwise stated, the ratio was > 20:1. [a] $AlCl_3$ (30 mol%). [b] Amberlyst-15 (12.0 mg), 100 °C for 24 h. [c] Nafion (9.4 mg).

is favourable to migrate via a five-membered ring (SI). In addition, 3-indoleacetonitrile was also compatible with the process (**3t**). Unsubstituted and *N*-Boc indoles, as well as 3-iodoindole and bisindole all afforded complex unidentified mixtures under the standard conditions.

3.3. *Late-stage peptide diversification*

Unnatural peptides cannot be recognized by protease, leading to their improved resistance toward biodegradation in living organisms. As such, they have found extensive applications in various aspects, including diagnostics, proteomics, and drug discovery [54,55]. In this context, tremendous efforts have been devoted to their synthesis over the past decades [56]. Among the known methods, late-stage diversification of the existed peptides is arguably the simplest strategy [57–65]. Given that tryptophan plays a critical role in protein biosynthesis, we attempted direct modification of tryptophan-containing skeletons using the developed protocol (Fig. 4). Gratifyingly, with $AlCl_3$ catalyst, C2 prenylation of *N*-Boc and -Ac tryptophanates also occurred, giving rise to the desired products **5a** and **5b** in acceptable yields. Boc-*L*-tryptophanol was converted to **5c** in 53% yield under the investigated conditions. Remarkably, a set of peptides derived from Boc-*L*-tryptophan and diverse amino acid esters including Gly, Ala, Leu, Phe, Met, β-Ala, Asp, and Ile, were all amenable to this catalytic process

(**5d**–**5k**). In addition, the peptides consisting of methyl *L*-tryptophanate and Fmoc/Boc protected amino acids (Gly, Ala, Val, Phe) could participate in the C2 prenylation as well (**5l**–**5o**). Most of the cases gave moderate yields because the starting peptides could not be totally consumed. It is noted that peptides might undergo racemization in an acidic milieu via an enolate intermediate [66]. In light of this, products **5d** and **5l** were selected as the representatives to study the issue. The complete retention of chirality showed no detectable racemization in the process.

3.4. *Total synthesis of tryprostatin B*

Tryprostatin B is a prominent C2 prenylated natural indole alkaloid. The groups of Danishefsky [21,22], Cook [26], Lobo and Prabhakar [24,25], Fukuyama [67,68], Ruijter [23], and Hossain [27] have contributed to its total synthesis. In their works, C2 prenyl decoration was accomplished at the early-stage. In contrast, the biosynthesis of tryprostatin B involves a final prenyl transfer from DMAPP to C2 position of brevianamide F [69,70]. In terms of the synthetic efficiency, the late-stage prenyl installation is undoubtedly more appealing. Then we wondered whether this step could be realized via our strategy. Pleasingly, brevianamide F **6l** [71] reacted with *tert*-prenyl alcohol smoothly to yield tryprostatin B **7l** in the presence of $AlCl_3$ (Fig. 5, top). Therefore, a two-step concise synthesis of tryprostatin B has been established starting from commercially available Boc-*L*-tryptophan and methyl *L*-prolinate.

In comparison, cyclodipeptide **6m** derived from methyl *L*-tryptophanate and Fmoc-*L*-alanine remained intact under the same conditions, due to its poor solubility in PhCl (Fig. 5, bottom). However, its precursor **4m** was a viable substrate, which could be readily transformed into the desired product **5m** (0.98 g) even in a gram scale. Subsequently, a piperidine-mediated deprotection of **5m** resulted in the formation of C2 prenylated cyclodipeptide **7m** in 86% yield. Moreover, following this three-step process, tryprostatin B could also be synthesized in an overall 38% yield starting from methyl *L*-tryptophanate and Fmoc *L*-proline (SI).

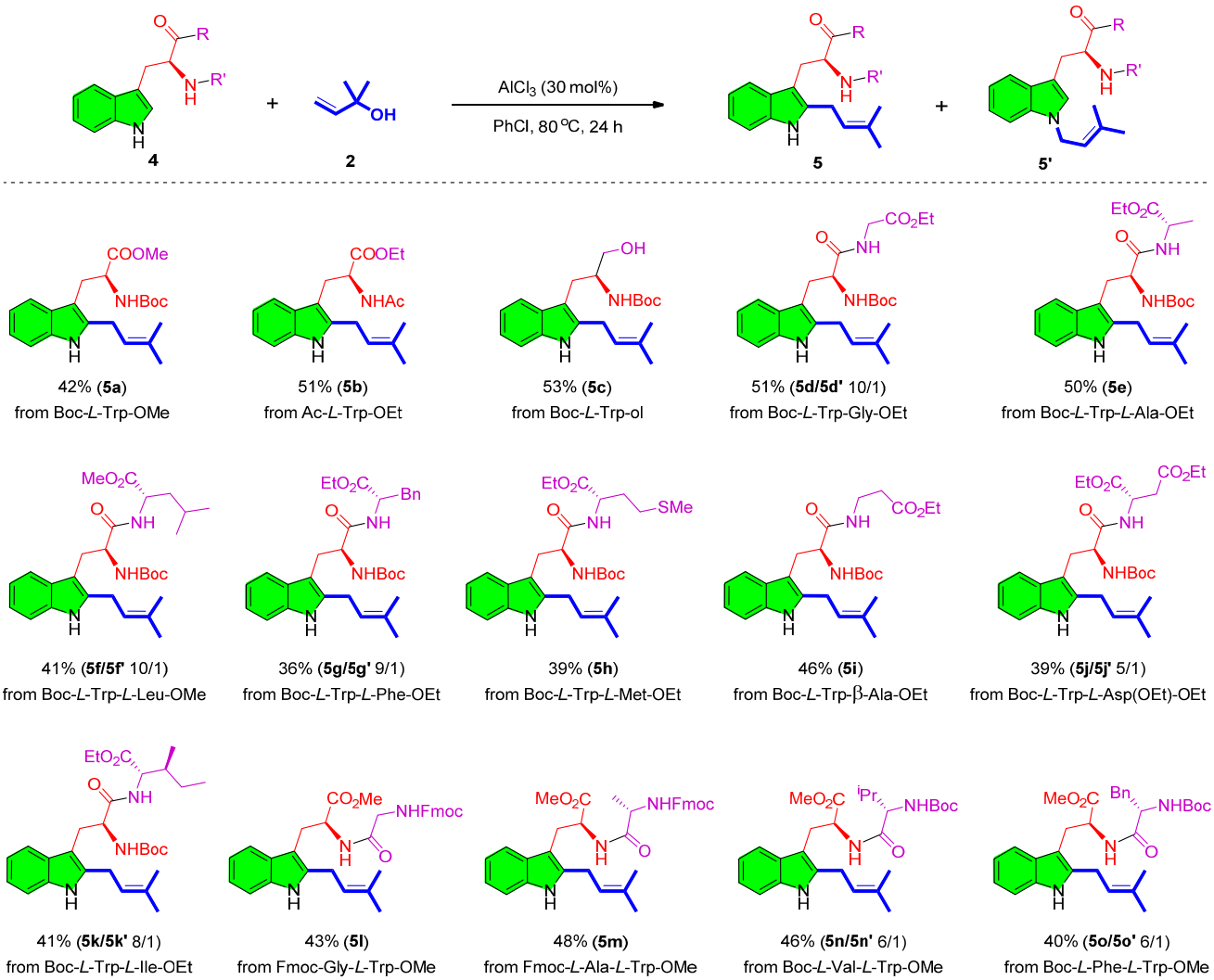


Fig. 4. Late-stage prenylation of tryptophanate and peptide. Reaction conditions: **4** (0.40 mmol), **2** (1.20 mmol), $AlCl_3$ (30 mol%), PhCl (0.40 mL), 80 °C, 24 h. Isolated yields were given. The ratio (**5**/**5'**) was determined by ^1H NMR, unless otherwise stated, the ratio was > 20:1.

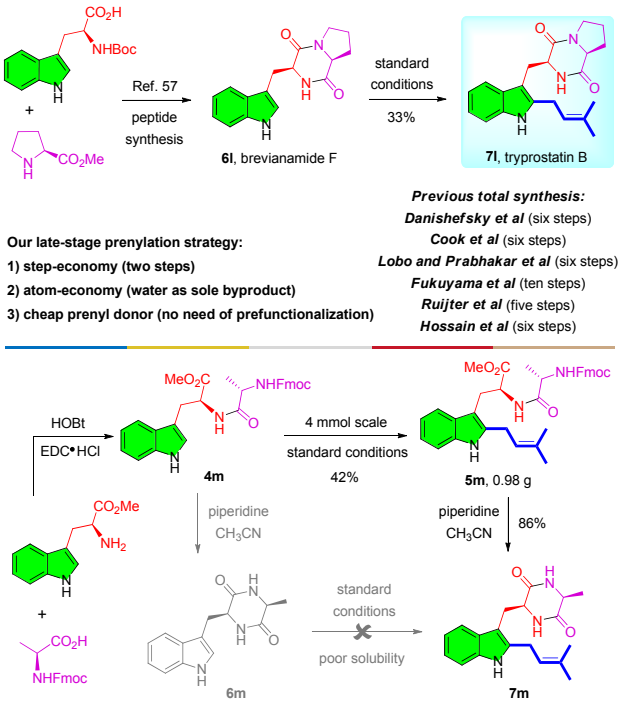
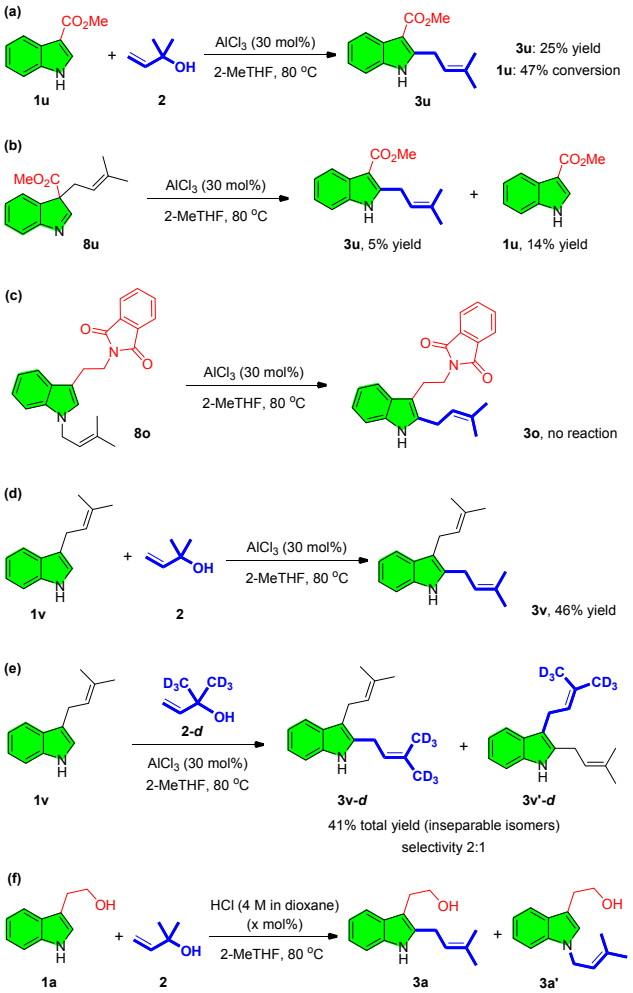


Fig. 5. Concise synthesis of tryprostatin B and cyclodipeptide.

3.5. Mechanistic investigation

To gain deeper insights into the reaction mechanism, some control experiments were performed (Fig. 6). Indole-3-carboxylate **1u** proved to be a suitable substrate. The electron-deficient 3-ester substituent can reduce the nucleophilicity of C2 site, thus giving the target product in a slightly decreased yield (**3u**, 25%, Fig. 6(a)). The same product **3u** could also be obtained from the rearrangement of 3-prenyl 3*H*-indole-3-carboxylate **8u** under the standard conditions (Fig. 6(b)). This result reveals that C3 prenylation/migration pathway is likely involved in the process but direct C2 prenylation dominates the process. Subjecting pre-synthesized *N*-prenylated phthalimide-protected tryptamine **8o** to the standard conditions did not generate C2-prenylated product **3o**, thus excluding the possible *N*-prenylation/migration pathway (Fig. 6(c)). This protocol was also able to facilitate the prenylation of 3-prenyl indole **1v** with *tert*-prenol **2** to deliver 2,3-diprenyl indole **3v** in 45% yield (Fig. 6(d)). Interestingly, when deuterated *tert*-prenol **2-*d*** was employed, a mixture of **3v-*d*** and **3v'-*d*** was obtained, thus explicitly demonstrating that both C2 prenylation and C3 prenylation/migration pathways are engaged in the reaction (Fig. 6(e)). In addition, this C2 prenylation process might be promoted by in situ generated acid HCl from the reaction of $AlCl_3$ with byproduct H_2O. To investigate this possibility, HCl was directly used as the additive in the absence of $AlCl_3$. With 10, 30 and 100 mol% of HCl, the prenylation indeed took place but the selectivity of C2- and *N*-prenylated products (**3a**, **3a'**) maintained 6:1 (Fig. 6(f)). In comparison, $AlCl_3$ could increase the selectivity to 12:1 (Table 1, entry 15), suggesting that the main contributor Al^{3+} likely coordinates with NH of indole to increase the C2 selectivity and



HCl (x mol%)	Yield (**3a**+**3a'**)	Selectivity (**3a**/**3a'**)
10	14%	7:1
30	32%	6:1
100	27%	7:1

Fig. 6. Mechanistic investigation.

its interaction with OH of *tert*-prenol presumably facilitates the formation of prenyl cation to improve the catalytic efficiency, but the HCl mediated pathway cannot be ruled out.

3.6. Prenyl isomerization

The synthetic utility of C2 prenylated tryptophol **3a** was further studied (Fig. 7). It was found that **3a** could be isomerized to **9a** at 120 °C in ionic liquid [Bmim]Cl using acid resin Nafion as catalyst. As Nafion could also promote the prenylation, we reasoned that it might be feasible to combine both processes into one-step. Just as anticipated, direct treatment of tryptophol with the same conditions furnished **9a** in 55% yield. This cascade reaction was also applicable to 5-F, -Cl, 7-Me and -Et tryptophols (**9b**–**9e**). Bz and phthalimide protected tryptamines were tolerated as well, delivering the isomerized products in acceptable yields (**9f**, **9g**). It should be noted that further intramolecular cyclization can lead to the formation of natural

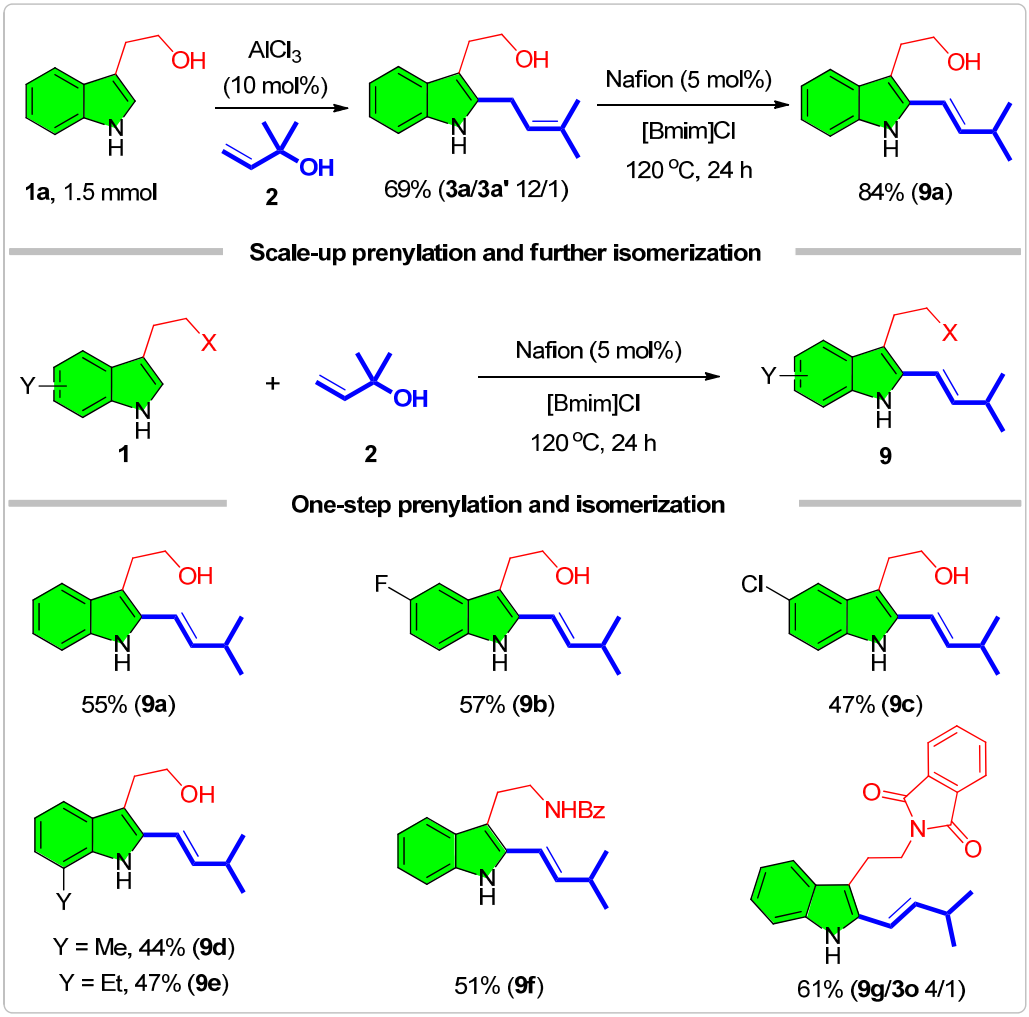


Fig. 7. Isomerization of prenyl group. Reaction conditions for one-step procedure: **1** (0.40 mmol), **2** (2.40 mmol), Nafion (9.4 mg), [Bmim]Cl (0.50 g), 120 °C, 24 h. [Bmim]Cl = 1-*Butyl*-3-methylimidazolium chloride.

alkaloids tetrahydro-β-carbolines [72–74].

4. Conclusions

In conclusion, we have realized a chemical catalytic C2 prenylation of NH indoles with cheap *tert*-prenyl alcohol. The main advantages include simple system, good regioselectivity, step- and atom-economy, and wide functional group tolerance. Notably, the versatility and practicability of this methodology were demonstrated in the late-stage diversification of tryptophan-based peptides and concise synthesis of tryprostatin B. Moreover, a one-step prenylation and isomerization cascade was accomplished by using ionic liquid [Bmim]Cl as solvent. Further applications of this protocol in the total synthesis of other natural indole alkaloids are currently underway in our laboratory.

Acknowledgement

We thank Prof. Yong-Gui Zhou (DICP) and Prof. Martin Oestreich (TU Berlin) for helpful discussion and paper revisions.

References

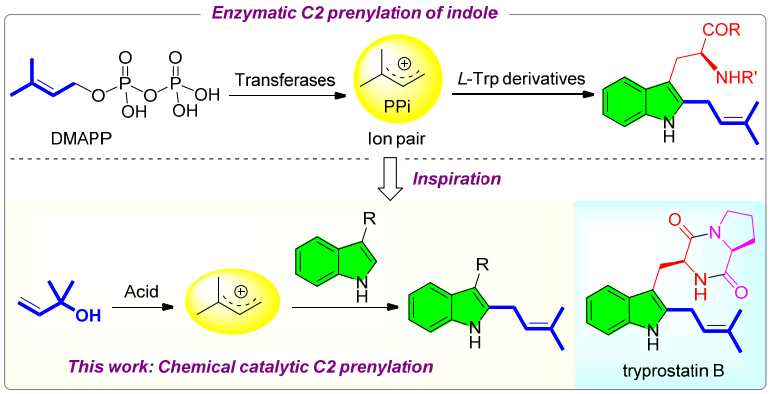
[1] S.-M. Li, *Nat. Prod. Rep.*, **2010**, 27, 57–78.
[2] L. P. Robertson, S. Duffy, Y. Wang, D. Wang, V. M. Avery, A. R. Carroll, *J. Nat. Prod.*, **2017**, 80, 3211–3217.
[3] C. B. Cui, H. Kakeya, G. Okada, R. Onose, H. Osada, *J. Antibiot.*, **1996**, 49, 527–533.
[4] S. Zhao, K. S. Smith, A. M. Deveau, C. M. Dieckhaus, M. A. Johnson, T. L. Macdonald, J. M. Cook, *J. Med. Chem.*, **2002**, 45, 1559–1562.
[5] H. D. Jain, C. Zhang, S. Zhou, H. Zhou, J. Ma, X. Liu, X. Liao, A. M. Deveau, C. M. Dieckhaus, M. A. Johnson, K. S. Smith, T. L. Macdonald, H. Kakeya, H. Osada, J. M. Cook, *Bioorg. Med. Chem.*, **2008**, 16, 4626–4651.
[6] T. Kagamizono, N. Sakai, K. Arai, K. Kobinata, H. Osada, *Tetrahedron Lett.*, **1997**, 38, 1223–1226.
[7] S. Su, H. Kakeya, H. Osada, J. A. Porco, *Tetrahedron*, **2003**, 59, 8931–8946.
[8] U. Mocek, L. Schultz, T. Buchan, C. Baek, L. Fretto, J. Nzerem, L. Sehl, U. Sinha, *J. Antibiot.*, **1996**, 49, 854–859.
[9] K. A. Alvi, H. Pu, M. Luche, A. Rice, H. App, G. McMahon, H. Dare, B. Margolis, *J. Antibiot.*, **1999**, 52, 215–223.
[10] A. J. Kochanowska-Karamyan, M. T. Hamann, *Chem. Rev.*, **2010**, 110, 4489–4497.

Graphical Abstract

Chin. J. Catal., 2021, 42: 1593–1607 doi: 10.1016/S1872-2067(20)63780-9

Catalytic C2 prenylation of unprotected indoles: Late-stage diversification of peptides and two-step total synthesis of tryprostatin B

Yan-Cheng Hu, Ying Li, Ding-Wei Ji, Heng Liu, Hao Zheng, Gong Zhang, Qing-An Chen *
Dalian Institute of Chemical Physics, Chinese Academy of Sciences; University of Chinese Academy of Sciences



Since C2 prenylated indoles are widespread in nature, the selective installation of prenyl group at C2 position of NH indoles is of great significance. However, the known protocols generally require a multi-step procedure and stoichiometric promoters. Herein a chemical catalytic C2 prenylation of NH indoles is developed, which can be applied to late-stage diversification of peptides and concise synthesis of tryprostatin B.

[11] R. Montaser, H. Luesch, *Future Med. Chem.*, **2011**, 3, 1475–1489.
[12] R. Yi, L. Qian, B. Wan, *Chin. J. Catal.*, **2019**, 40, 177–183.
[13] M. Kimura, M. Futamata, R. Mukai, Y. Tamaru, *J. Am. Chem. Soc.*, **2005**, 127, 4592–4593.
[14] B. M. Trost, J. Quancard, *J. Am. Chem. Soc.*, **2006**, 128, 6314–6315.
[15] B. M. Trost, S. Malhotra, W. H. Chan, *J. Am. Chem. Soc.*, **2011**, 133, 7328–7331.
[16] J. Ruchti, E. M. Carreira, *J. Am. Chem. Soc.*, **2014**, 136, 16756–16759.
[17] J. M. Mueller, C. B. W. Stark, *Angew. Chem. Int. Ed.*, **2016**, 55, 4798–4802.
[18] B. M. Trost, W. H. Chan, S. Malhotra, *Chem. Eur. J.*, **2017**, 23, 4405–4414.
[19] B. M. Trost, W.-J. Bai, C. Hohn, Y. Bai, J. J. Cregg, *J. Am. Chem. Soc.*, **2018**, 140, 6710–6717.
[20] H.-F. Tu, X. Zhang, C. Zheng, M. Zhu, S.-L. You, *Nat. Catal.*, **2018**, 1, 601–608.
[21] K. M. Depew, S. J. Danishefsky, N. Rosen, L. SeppLorenzino, *J. Am. Chem. Soc.*, **1996**, 118, 12463–12464.
[22] J. M. Schkeryantz, J. C. G. Woo, P. Siliphaivanh, K. M. Depew, S. J. Danishefsky, *J. Am. Chem. Soc.*, **1999**, 121, 11964–11975.
[23] J. M. Saya, E. D. H. van Wordragen, R. V. A. Orru, E. Ruijter, *Eur. J. Org. Chem.*, **2019**, 2019, 5156–5160.
[24] A. S. Cardoso, A. M. Lobo, S. Prabhakar, *Tetrahedron Lett.*, **2000**, 41, 3611–3613.
[25] A. S. P. Cardoso, M. M. B. Marques, N. Srinivasan, S. Prabhakar, A. M. Lobo, H. S. Rzepa, *Org. Biomol. Chem.*, **2006**, 4, 3966–3972.
[26] S. Zhao, T. Gan, P. Yu, J. M. Cook, *Tetrahedron Lett.*, **1998**, 39, 7009–7012.
[27] M. Huisman, M. Rahaman, S. Asad, S. Oehm, S. Novin, A. L. Rheingold, M. M. Hossain, *Org. Lett.*, **2019**, 21, 134–137.
[28] Y. Yang, Z. Shi, *Chem. Commun.*, **2018**, 54, 1676–1685.
[29] J. Lv, X. Chen, X.-S. Xue, B. Zhao, Y. Liang, M. Wang, L. Jin, Y. Yuan, Y. Han, Y. Zhao, Y. Lu, J. Zhao, W.-Y. Sun, K. N. Houk, Z. Shi, *Nature*, **2019**, 575, 336–340.
[30] J. Lv, B. Zhao, Y. Yuan, Y. Han, Z. Shi, *Nat. Commun.*, **2020**, 11, 1316.
[31] H. Wang, N. Schröder, F. Glorius, *Angew. Chem. Int. Ed.*, **2013**, 52, 5386–5389.
[32] M. Kim, S. Sharma, N. K. Mishra, S. Han, J. Park, M. Kim, Y. Shin, J. H. Kwak, S. H. Han, I. S. Kim, *Chem. Commun.*, **2014**, 50, 11303–11306.
[33] Y. Suzuki, B. Sun, K. Sakata, T. Yoshino, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.*, **2015**, 54, 9944–9947.
[34] Y. Bunno, N. Murakami, Y. Suzuki, M. Kanai, T. Yoshino, S. Matsunaga, *Org. Lett.*, **2016**, 18, 2216–2219.
[35] G. S. Kumar, M. Kapur, *Org. Lett.*, **2016**, 18, 1112–1115.
[36] W. Liu, S. C. Richter, Y. Zhang, L. Ackermann, *Angew. Chem. Int. Ed.*, **2016**, 55, 7747–7750.
[37] X. Wu, H. Ji, *Org. Biomol. Chem.*, **2018**, 16, 5691–5698.
[38] J. A. Rossi-Ashton, A. K. Clarke, J. R. Donald, C. Zheng, R. J. K. Taylor, W. P. Unsworth, S.-L. You, *Angew. Chem. Int. Ed.*, **2020**, 59, 7598–7604..
[39] M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed.*, **2009**, 48, 9608–9644.
[40] X. Fang, Q. Li, R. Shi, H. Yao, A. Lin, *Org. Lett.*, **2018**, 20, 6084–6088.
[41] N. Mahmoodi, M. E. Tanner, *ChemBioChem*, **2013**, 14, 2029–2037.
[42] M. E. Tanner, *Nat. Prod. Rep.*, **2015**, 32, 88–101.
[43] W.-S. Zhang, Y.-C. Hu, Q.-A. Chen, *Synlett*, **2020**, 31, 1649–1655.
[44] Y.-C. Hu, D.-W. Ji, C.-Y. Zhao, H. Zheng, Q.-A. Chen, *Angew. Chem. Int. Ed.*, **2019**, 58, 5438–5442.
[45] Y. Li, Y.-C. Hu, H. Zheng, D.-W. Ji, Y.-F. Cong, Q.-A. Chen, *Eur. J. Org.*

Chem., **2019**, 2019, 6510–6514.
[46] J. Yang, D.-W. Ji, Y.-C. Hu, X.-T. Min, X. Zhou, Q.-A. Chen, *Chem. Sci.*, **2019**, 10, 9560–9564.
[47] Y. Li, Y.-C. Hu, D.-W. Ji, W.-S. Zhang, G.-C. He, Y.-F. Cong, Q.-A. Chen, *Chin. J. Catal.*, **2020**, 41, 1401–1409.
[48] C.-S. Kuai, D.-W. Ji, C.-Y. Zhao, H. Liu, Y.-C. Hu, Q.-A. Chen, *Angew. Chem. Int. Ed.*, **2020**, 59, 19115–19120.
[49] Y. Hu, L. Yuan, X. Zhang, H. Zhou, P. Wang, G. Li, A. Wang, Y. Cong, T. Zhang, X. Liang, W. Li, N. Li, *ACS Sustainable Chem. Eng.*, **2019**, 7, 2980–2988.
[50] B.-B. Huang, L. Wu, R.-R. Liu, L.-L. Xing, R.-X. Liang, Y.-X. Jia, *Org. Chem. Front.*, **2018**, 5, 929–932.
[51] X.-S. Hu, J.-X. He, S.-Z. Dong, Q.-H. Zhao, J.-S. Yu, J. Zhou, *Nat. Commun.*, **2020**, 11, 5500.
[52] V. Pace, P. Hoyos, L. Castoldi, P. Dominguez de Maria, A. R. Alcantara, *ChemSusChem*, **2012**, 5, 1369–1379.
[53] J. L. Mauriz, P. S. Collado, C. Veneroso, R. J. Reiter, J. Gonzalez-Gallego, *J. Pineal Res.*, **2013**, 54, 1–14.
[54] K. Fosgerau, T. Hoffmann, *Drug Discov. Today*, **2015**, 20, 122–128.
[55] N. Qvit, S. J. S. Rubin, T. J. Urban, D. Mochly-Rosen, E. R. Gross, *Drug Discov. Today*, **2017**, 22, 454–462.
[56] D. J. Ager, in: *Amino Acids, Peptides and Proteins in Organic Chemistry*, A. B. Hughes, eds., Wiley-VCH, Weinheim, **2010**, 495–526.
[57] L. R. Malins, *Curr. Opin. Chem. Biol.*, **2018**, 46, 25–32.
[58] W. Wang, M. M. Lorion, J. Shah, A. R. Kapdi, L. Ackermann, *Angew. Chem. Int. Ed.*, **2018**, 57, 14700–14717.
[59] H.-R. Tong, B. Li, G. Li, G. He, G. Chen, *CCS Chem.*, **2020**, 2, 1797–1820.
[60] X. Zhang, G. Lu, M. Sun, M. Mahankali, Y. Ma, M. Zhang, W. Hua, Y. Hu, Q. Wang, J. Chen, G. He, X. Qi, W. Shen, P. Liu, G. Chen, *Nat. Chem.*, **2018**, 10, 540–548.
[61] K. Chen, B.-F. Shi, *Sci. Bull.*, **2018**, 63, 1238–1240.
[62] N. Kaplaneris, T. Rogge, R. Yin, H. Wang, G. Sirvinskaite, L. Ackermann, *Angew. Chem. Int. Ed.*, **2019**, 58, 3476–3480.
[63] M. M. Lorion, N. Kaplaneris, J. Son, R. Kuniyil, L. Ackermann, *Angew. Chem. Int. Ed.*, **2019**, 58, 1684–1688.
[64] X. Chen, F. Ye, X. Luo, X. Liu, J. Zhao, S. Wang, Q. Zhou, G. Chen, P. Wang, *J. Am. Chem. Soc.*, **2019**, 141, 18230–18237.
[65] Q. Wang, Y. Fu, W. Zhu, S. An, Q. Zhou, S.-F. Zhu, G. He, P. Liu, G. Chen, *CCS Chem.*, **2020**, 2, 1729–1736.
[66] Y. Yang, in: *Side Reactions in Peptide Synthesis*, Y. Yang Eds., Elsevier, Beijing, **2015**, 257–292.
[67] T. Yamakawa, E. Ideue, J. Shimokawa, T. Fukuyama, *Angew. Chem. Int. Ed.*, **2010**, 49, 9262–9265.
[68] T. Yamakawa, E. Ideue, Y. Iwaki, A. Sato, H. Tokuyama, J. Shimokawa, T. Fukuyama, *Tetrahedron*, **2011**, 67, 6547–6560.
[69] A. Grundmann, S.-M. Li, *Microbiology*, **2005**, 151, 2199–2207.
[70] B. Wollinsky, L. Ludwig, X. Xie, S.-M. Li, *Org. Biomol. Chem.*, **2012**, 10, 9262–9270.
[71] M. E. Kieffer, K. V. Chuang, S. E. Reisman, *J. Am. Chem. Soc.*, **2013**, 135, 5557–5560.
[72] H. Song, Y. Liu, Y. Liu, L. Wang, Q. Wang, *J. Agric. Food. Chem.*, **2014**, 62, 1010–1018.
[73] S. Lancianesi, A. Palmieri, M. Petrini, *Chem. Rev.*, **2014**, 114, 7108–7149.
[74] P. Maity, D. Adhikari, A. K. Jana, *Tetrahedron*, **2019**, 75, 965–1028.

催化NH吲哚的C2异戊烯基化反应：肽后期多样化和两步全合成tryprostatin B

呼延成[a,b,†], 李　莹[a,b,†], 季定纬[a,b], 刘　恒[a,b], 郑　浩[a,b], 张　功[a,b], 陈庆安[a,b,*]
[a]中国科学院大连化学物理研究所, 辽宁大连116023
[b]中国科学院大学, 北京100049

摘要: 异戊烯基化吲哚生物碱是一类同时具有吲哚环和类异戊二烯基团的天然产物, 主要来源于各种真菌中. 异戊烯基的存在可以增强化合物的亲脂性, 使其能够更容易地穿过脂溶性的细胞膜与靶蛋白相结合, 因此, 这类天然产物往往表现出优异的生物活性. 例如, 从烟曲霉中分离的吲哚生物碱tryprostatins A和B是由*L*-色氨酸和*L*-脯氨酸组合而成, 在吲哚骨架C2位连有异戊烯基, 具有高效的抗肿瘤活性. 在已知的全合成中, 关键步骤C2位异戊烯基的引入, 均是通过多步当量反应实现的. 从原子和步骤经济性角度出发, 发展高效催化方法实现NH吲哚C2位直接异戊烯基化反应具有重要的意义. 但是由于吲哚的氮原子和C3位亲核性都较强, 使得挑战很大.

在生物体中, 吲哚生物碱C2位异戊烯基的引入是通过酶催化实现的. 二甲基烯丙基焦磷酸(DMAPP)先在酶作用下, 生成异戊烯基碳正离子, 然后与吲哚C2位进行傅克反应, 引入异戊烯基. 受这一生物过程启发, 设想通过化学方法能够生成稳定的异戊烯基碳正离子, 也可能实现吲哚C2异戊烯基化反应. 本文采用廉价易得的1,1-二甲基烯丙醇为异戊烯基前体, 对该想法进行了尝试. 首先, 以色醇为模板底物, 对酸催化剂、溶剂及反应温度进行了筛选. 在1,2-二氯乙烷(DCE)溶剂中, 布朗斯特酸、路易斯酸和固体酸都能促进反应的进行, 但会得到吲哚N和C2异戊烯基化两种产物, 其中三氯化铝有较好的收率和选择性. 通过对不同溶剂考察发现, 2-甲基四氢呋喃是最佳溶剂, 在80 °C下反应, 目标产物收率为75%, 产物选择性可达到12:1. 随后, 对不同类型的3-取代吲哚进行了普适性考察. 对于色醇类底物, 吲哚苯环上的取代基以及N上的保护基对反应影响不大, 都能很顺利地参与反应. 在标准条件下, 色胺的异戊烯基化反应会发生在C3位, 而以氯苯为溶剂时, 可以提高C2位选择性, 通过该方法可在抗衰老分子褪黑素(melatonin)的C2位引入异戊烯基. 3-苯基和烷基取代的吲哚也是合适的底物.

肽的后期修饰在生物医药中有着很重要的用途, 因此, 本文也将该异戊烯基化反应尝试用于修饰色氨酸类衍生物. 保护的*L*-色氨酸酯以及色氨醇都能够顺利发生转化, 以中等收率得到目标产物. *L*-色氨酸与其它各类氨基酸如甘氨酸、丙氨酸、亮氨酸、异亮氨酸、苯丙氨酸、甲硫氨酸、天冬氨酸等形成的肽也可进行C2异戊烯基化反应. 此外, 该转化过程中, 可以完全保持手性, 不会发生消旋化. 特别是, *L*-色氨酸与*L*-脯氨酸酯形成的环二肽brevianamide F, 在该条件下, 也能发生C2

位异戊烯基化反应, 快速合成天然吲哚生物碱tryprostatin B.

该反应有两种可能的路径, 一种是吲哚C2位直接异戊烯基化, 另一种是吲哚C3位先异戊烯基化, 然后再重排到C2位. 为进一步探索机理, 对其进行了研究. 首先, 在标准条件下, 3-酯基吲哚可以发生反应, C2位异戊烯基化产物收率为25%. 然后, 预先将异戊烯基引入C3位, 合成了3-酯基-3-异戊烯基-3*H*吲哚, 同样反应条件下, 也能检测到目标产物, 但收率只有5%. 其次, 以氘代1,1-二甲基烯丙醇为原料时, 3-异戊烯基吲哚也能与其发生反应, 并且在C3和C2位都观察到了氘代异戊烯基, 两种产物比例为1:2, 结果表明两种反应路径都是存在的, 但吲哚C2位直接异戊烯基化是主要路径.

此外, 以固体酸Nafion为催化剂, 离子液体[Bmim]Cl为反应介质, 在120 °C时, 3-取代吲哚与1,1-二甲基烯丙醇的反应选择性会发生改变, 得到C2位异戊烯基异构化的产物.

总之, 以商业可得的1,1-二甲基烯丙醇为前体, 首次实现了化学催化NH吲哚C2位直接异戊烯基化反应, 获得较好的区域和化学选择性. 该方法能够兼容各类官能团, 底物适用性广, 且可以用于褪黑素以及色氨酸衍生各种肽类化合物的后期修饰. 基于该催化方法, 可以两步全合成天然吲哚生物碱tryprostatin B, 极大提高了合成效率, 有助于实现放大生产. 在固体酸/离子液体催化体系中, 还实现了反应选择性的改变, 丰富了产物类型.

关键词: 吲哚异戊烯基化; 步骤经济性; 原子经济性; 色氨酸; 肽多样化; 全合成

收稿日期: 2021-01-02. 接受日期: 2021-02-07. 上网时间: 2021-05-05.

*通讯联系人. 电话: (0411)84379260; 传真: (0411)84379223; 电子信箱: qachen@dicp.ac.cn

†共同第一作者

基金来源: 国家自然科学基金(21801239, 22071239).

本文的电子版全文由Elsevier出版社在ScienceDirect上出版(http://www.sciencedirect.com/journal/chinese-journal-of-catalysis).