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Stereoselective Synthesis of Piperamide Alkaloids by Modified Ramberg-Bäcklund Reaction

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Abstract: A convenient and rapid approach for the synthesis of piperamide alkaloids **1a** ~ **h** by the recently developed one-flask Ramberg-Bäcklund reaction was described. The synthesis of **1e** was reported for the first time.

Keywords: Piperamide alkaloids, Ramberg-Bäcklund reaction.

A large number of carboxyamides with more or less unsaturated chain residue linked to different carboxyl group moieties have been isolated from the plants of *Piper*. This important class of natural alkaloids show a variety of pharmacological activities, *e.g.* antifungal, antidiarrheal, antiinflammatory[1]. Some synthetic methods of piperamide alkaloids have been repored[1d, 2], but most of them involve low yield reactions, expensive starting materials and reagents or produce a mixture of *cis* and *trans* stereoisomer. Here we reported a simple approach for the synthesis of piperamide **1a** ~ **h** by our modified Ramberg-Bäcklund reaction[3].

The starting material was piperonal **2**. Reaction of **2** with $Ph_3P{=}CHCO_2Et$ afforded ester with good (*E*)-selectivity, followed by reduction of the ester moiety with $LiAlH_4/AlCl_3$ to furnish the alcohol **3**. The alcohol **3** was hydrogenated, oxidized with PCC($CrO_3{\cdot}C_5H_5N$), prolonged carbon chain with Wittig reaction, and reduced with $LiAlH_4/AlCl_3$ selectively to give alcohol **4**. On the other hand, reaction of **2** with $Ph_3P{=}CHCH{=}CHCO_2Et$, followed by reduction of the ester moiety with $LiAlH_4/AlCl_3$ to give alcohol **5**. Hydrogenation of **5** afforded the alcohol **6**. These alcohols **3**, **4**, **5** and **6** were transformed into the thiolacetates **7a** ~ **h** *via* the Mitsunobu reaction with HSAc in the presence of Ph_3P and DIAD[4]. *In situ* cleavage of acetyl moieties of **7a** ~ **h** with KOH in MeOH, followed by alkylation of the resulting thiols with 1-chloroacetylpiperidine and its analogues[5], provided the sulfides **8a** ~ **h** in good yields. These sulfides could be converted to the corresponding sulfones **9a** ~ **h** by oxone oxidation in $MeOH/H_2O$(1:1)[6]. As expected, stereochemistry of double bonds was remained during these transformation. Subjecting the sulfones **9a** ~ **h** to our previously described modified Ramberg-Bäcklund reaction protocol (CBr_2F_2, KOH-on-Al_2O_3, CH_2Cl_2) invariably gave the geometrically

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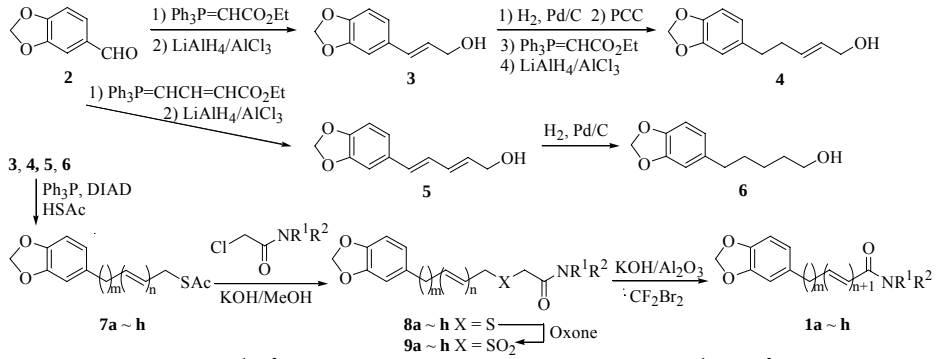

piperylin (**1a**) m = 0, n = 1, R^1, R^2 = $(CH_2)_4$ piperlonguminine (**1b**) m = 0, n = 1, R^1 = H, R^2 = $CH_2CH(CH_3)_2$
piperine (**1c**) m = 0, n = 1, R^1, R^2 = $(CH_2)_5$ pipercallosidine (**1d**) m = 4, n = 0, R^1 = H, R^2 = $CH_2CH(CH_3)_2$
piperine S (**1e**) m = 4, n = 0, R^1, R^2 = $(CH_2)_5$ chingchengenamide A (**1f**) m = 2, n = 1, R^1 = H, R^2 = $CH_2CH(CH_3)_2$
piperdardine (**1g**) m = 2, n = 1, R^1, R^2 = $(CH_2)_5$ piperettine (**1h**) m = 0, n = 2, R^1, R^2 = $(CH_2)_5$

Table 1 Yield of sufides **8**, sulfones **9** and piperamide alkaloids **1** (%)

Entry	sufides **8** (X=S)	sulfones **9** (X=SO_2)	piperamide alkaloids **1**
a	68	90	85[1a, 2e]
b	68	94	84[1b, 2e]
c	85	92	82[1c, 2e, 2g]
d	73	86	68[1d]
e	75	88	65[1e]
f	65	95	78[1f, 2c]
g	82	86	80[1c, 2f]
h	78	87	83[1c, 2a, 2b]

defined piperamides **1a** ~ **h** in good yields. Examination of the ^{13}C NMR spectra of the products indicated the presence of only one isomer in each case[7]. Thus, the stereoselectivity of the reaction was >95%. The configurations of the newly formed double bond in **1a** ~ **h** were readily diagnosed by typical coupling constant of 14.1 ~ 15.0 Hz for *trans*-olefinic prontons in ^1H NMR spectrum. All of the compounds were characterized by IR, ^1H and ^{13}C NMR, and high resolution mass spectra. The natural

piperamide alkaloids **1a** ~ **h** were in agreement with those found in the literature[1,2]. It is noteworthy that if simply replacing CBr_2F_2 by CCl_4 in the Ramberg-Bäcklund reaction, **9a** ~ **c**, **f** ~ **h** bearing allylic sulfones can be uniformly converted to **1a** ~ **c**, **f** ~ **h**. To the best our knowledge, **1e** was synthesized for the first time.

We have presented a rapid route to stereochemically defined natural piperamide alkaloids. The yields were satisfactory and the reactions can be performed in molar scales. The synthesis and investigation of the biological activity of their analogues are in progress.

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7. Selected spectra data (The ^{1}H and ^{13}CNMR data were recorded on Mercury Plus–300, the chemical shifts are reported in δppm): **1a**, ^{1}HNMR: 1.86–2.05 (m, 4 H, 2 × CH_2), 3.45–3.55 (m, 4 H, 2 × CH_2N), 5.98 (s, 2 H, OCH_2O), 6.26 (d, 1 H, *J* 15.0 Hz, 2-CH=), 6.74 (d, 1 H, *J* 15.0 Hz, ArCH=), 6.75 (d, 1 H, *J* 8.1 Hz, ArH), 6.76–6.99 (m, 3 H, 2 × ArH, CH=), 7.43 (dd, 1 H, *J* 15.0, 9.0 Hz, CH=); ^{13}CNMR: 24.3, 26.1, 45.9, 46.4, 101.2, 105.6, 108.4, 121.4, 122.5, 125.1, 130.9, 138.6, 141.7, 148.1, 148.1, 164.9; EI-MS (*m/z*, %): 271 (M^+, 32), 201 (100), 173 (38), 121 (53), 115 (86). **1b**, ^{1}HNMR: 0.94 (d, 6 H, *J* 6.6 Hz, 2 × CH_3), 1.78–1.89 [m, 1 H, C*H*$(CH_3)_2$], 3.17–3.21 (m, 2 H, C*H*$_2$NH), 5.78 (br s, 1 H, NH), 5.95 (d, 1 H, *J* 14.4 Hz, 2-CH=), 5.98 (s, 2 H, OCH_2O), 6.67 (dd, 1 H, *J* 15.6, 10.5 Hz, CH=), 6.76 (d, 1 H, *J* 8.1 Hz, ArH), 6.77 (d, 1 H, *J* 15.6 Hz, ArCH=), 6.88 (d, 1 H, *J* 8.1 Hz, ArH), 6.96 (s, 1 H, ArH), 7.36 (dd, 1 H, *J* 14.4, 10.5 Hz, CH=); ^{13}CNMR: 20.1, 20.1, 28.6, 47.0, 101.3, 105.6, 108.4, 122.5, 123.2, 124.6, 130.8, 138.7, 140.9, 148.1, 148.1, 166.2; EI-MS (*m/z*, %): 273 (M^+, 37), 201 (100), 173 (71), 115 (97). **1c**, ^{1}HNMR:1.58–1.67 (m, 6 H, 3 × CH_2), 3.50–3.62 (m, 4 H, 2 × CH_2N), 5.97 (s, 2 H, OCH_2O), 6.44 (d, 1 H, *J* 14.1 Hz, 2-CH=), 6.70 (d, 1 H, *J* 15.9 Hz,

ArCH=), 6.71–6.76 (m, 1 H, CH=), 6.78 (d, 1 H, *J* 8.1 Hz, ArH), 6.90 (d, 1 H, *J* 8.1 Hz, ArH), 6.99 (s, 1 H, ArH), 7.41 (dd, 1 H, *J* 14.1, 10.2 Hz, CH=); ^{13}CNMR: 24.6, 25.6, 26.7, 43.2, 46.9, 101.3, 105.6, 108.5, 120.0, 122.5, 125.3, 130.9, 138.2, 142.5, 148.1, 148.1, 165.4; EI-MS (*m/z*, %): 285 (M^+, 36), 201 (100), 173 (38), 115 (92), 84 (42). **1d**, ^{1}HNMR: 0.92 (d, 6 H, *J* 6.3 Hz, 2 × CH_3), 1.44–1.59 (m, 4 H, 2 × CH_2), 1.75–1.84 [m, 1 H, C*H*$(CH_3)_2$], 2.16 (dd, 2 H, *J* 7.5, 6.0 Hz, C*H*$_2$CH=), 2.53 (t, 2 H, *J* 7.5 Hz, ArCH_2), 3.15 (t, 2 H, *J* 6.2 Hz, C*H*$_2$NH), 5.48 (br s, 1 H, NH), 5.74 (d, 1 H, *J* 15.0 Hz, 2-CH=), 5.92 (s, 2 H, OCH_2O), 6.61 (d, 1 H, *J* 8.1 Hz, ArH), 6.66 (d, 1 H, *J* 1.5 Hz, ArH), 6.72 (d, 1 H, *J* 8.1 Hz, ArH), 6.82 (dt, 1 H, *J* 15.0, 7.5 Hz, CH=); ^{13}CNMR: 20.1, 20.1, 27.6, 28.6, 31.0, 31.9, 35.4, 46.8, 100.7, 108.0, 108.8, 121.0, 123.7, 136.2, 144.4, 145.5, 147.5, 166.0; EI-MS (*m/z*, %): 303 (M^+, 7), 203 (9), 168 (11), 135 (100). **1e**, ^{1}HNMR: 1.59–1.61 (m, 10 H, 5 × CH_2), 2.21 (dd, 2 H, *J* 7.4, 6.4 Hz, C*H*$_2$CH=), 2.54 (t, 2 H, *J* 7.3 Hz, ArCH_2), 3.49–3.59 (m, 4 H, 2 × CH_2N), 5.92 (s, 2 H, OCH_2O), 6.23 (d, 1 H, *J* 15.0 Hz, 2-CH=), 6.64 (d, 1 H, *J* 8.0 Hz, ArH), 6.57 (s, 1 H, ArH) 6.72 (d, 1 H, *J* 8.0 Hz, ArH), 6.82 (dt, 1 H, *J* 15.0, 7.4 Hz, CH=); ^{13}CNMR: 24.6, 25.6, 26.6, 27.9, 31.3, 32.4, 35.5, 43.1, 46.8, 100.7, 108.0, 108.8, 120.4, 121.0, 136.2, 145.5, 145.6, 147.4, 165.5; EI-MS (*m/z*, %): 315 (M^+, 13), 202 (16), 180 (30), 166 (74), 135 (100). **1f**, ^{1}HNMR: 0.92 (d, 6 H, *J* 6.6 Hz, 2 × CH_3), 1.76–1.84 [m, 1 H, C*H*$(CH_3)_2$], 2.42 (dd, 2 H, *J* 7.2, 6.9 Hz, C*H*$_2$CH=), 2.65 (t, 2 H, *J* 7.2 Hz, ArCH_2), 3.14–3.18 (m, 2 H, C*H*$_2$NH), 5.54 (br s, 1 H, NH), 5.76 (d, 1 H, *J* 15.0 Hz, 2-CH=), 5.92 (s, 2 H, OCH_2O), 6.06 (dt, 1 H, *J* 15.3, 6.9 Hz, CH=), 6.14 (dd, 1 H, *J* 15.3, 10.0 Hz, CH=), 6.61 (d, 1 H, *J* 8.1 Hz, ArH), 6.66 (s, 1 H, ArH), 6.72 (d, 1 H, *J* 8.1 Hz, ArH), 7.18 (dd, 1 H, *J* 15.0, 10.0 Hz, CH=); ^{13}CNMR: 20.1, 20.1, 28.6, 34.9, 34.9, 46.9, 100.7, 108.1, 108.8, 121.1, 122.2, 128.8, 135.0, 141.0, 141.5, 145.7, 147.5, 166.3; EI-MS (*m/z*, %): 301 (M^+, 2), 229 (1), 201 (1), 161 (1), 135 (100). **1g**, ^{1}HNMR: 1.56–1.65 (m, 6 H, 3 × CH_2), 2.42 (dd, 2 H, *J* 7.5, 6.9 Hz, C*H*$_2$CH=), 2.66 (t, 2 H, *J* 7.5 Hz, ArCH_2), 3.49–3.62 (m, 4 H, 2 × CH_2N), 5.92 (s, 2 H, OCH_2O), 6.05 (dt, 1 H, *J* 15.0, 6.9 Hz, CH=), 6.19 (dd, 1 H, *J* 15.0, 10.2 Hz, CH=), 6.26 (d, 1 H, *J* 15.0 Hz, 2-CH=), 6.60 (dd, 1 H, *J* 7.8, 1.8 Hz, ArH), 6.66 (d, 1 H, *J* 1.8 Hz, ArH), 6.72 (d, 1 H, *J* 7.8 Hz, ArH), 7.22 (dd, 1 H, *J* 15.0, 10.2 Hz, CH=); ^{13}CNMR: 24.6, 25.6 (br), 26.6 (br), 35.0, 35.0, 43.1 (br), 46.9 (br), 100.8, 108.1, 108.8, 119.1, 121.1, 129.5, 135.1, 140.8, 142.4, 145.7, 147.5, 165.5; EI-MS (*m/z*, %): 313 (M^+, 2), 201 (1), 178 (2), 164 (2), 135 (100). **1h**, ^{1}HNMR: 1.58–1.75 (m, 6 H, 3 × CH_2), 3.50–3.60 (m, 4 H, 2 × CH_2N), 5.97 (s, 2 H, OCH_2O), 6.38 (d, 1 H, *J* 14.7 Hz, 2-CH=), 6.41 (dd, 1 H, *J* 14.7, 11.4 Hz, CH=), 6.57–6.71 (m, 3 H, 3 × CH=), 6.77 (d, 1 H, *J* 8.1 Hz, ArH), 6.86 (dd, 1 H, *J* 8.1, 1.5 Hz, ArH), 6.96 (d, 1 H, *J* 1.5 Hz, ArH), 7.35 (dd, 1 H, *J* 14.7, 11.4 Hz, 3-CH=); ^{13}CNMR: 24.6, 25.6 (br), 26.6 (br), 43.2 (br), 46.9(br), 101.2, 105.5, 108.5, 120.0, 122.0, 126.7, 130.4, 131.5, 135.3, 139.1, 142.4, 147.8, 148.2, 165.5; EI-MS (*m/z*, %): 311 (M^+, 17), 226 (17), 199 (17), 135 (24), 112 (100).

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