Alkaloid Synthesis

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Bio-Inspired Dimerization Reaction of Tryptophan Derivatives in Aqueous Acidic Media: Three-Step Syntheses of (+)-WIN 64821, (−)-Ditryptophenaline, and (+)-Naseseazine B**

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A large number of tryptophan-based dimeric diketopiperazine (DKP) alkaloids, which show fascinating biological activities, have been isolated from fungi[1] (Figure 1). For instance, (+)-WIN 64821 (**1**) and (−)-ditryptophenaline (**2**) were isolated from *Aspergillus* sp. and reported to be competitive substance P antagonists with respect to human neurokinin-1 and the cholecystokinin B receptor, respectively.[2] These tryptophan-based homodimeric alkaloids contain vicinal quaternary stereocenters joined through C3(sp^3)–C3(sp^3) bonds. In 2009, (+)-naseseazine B (**3**) possessing a C3(sp^3)–C7(sp^2) bridge was isolated from Fijian actinomycete *Streptomyces* sp.[3] and the stereochemistry of **3** was revised by Movassaghi and co-worker following total synthesis in 2011.[4] (+)-Pestalazine B (**4**) possessing a C3(sp^3)–N1 bridge was isolated from the plant pathogenic fungus *Pestalotiopsis theae* in 2008[5] and the structure was revised by de Lera and co-worker after total synthesis in 2010.[6] More recently, the anti-influenza active compound aspergilazine A, which possesses a unique C7(sp^2)–N1 bridge, was reported.[7] Tryptophan-based DKP alkaloids exhibit a unique architecture and a wide variety of interesting biological activities; therefore several total syntheses have been reported.[8] Recently, Movassaghi and co-workers developed an elegant Co^I-mediated radical coupling reaction using brominated pyrrolidinoindolines for the synthesis of C_2-symmetrically connected dimeric compounds such as (+)-WIN 64821 (**1**) and (−)-ditryptophenaline (**2**).[9] They also described a Friedel–Crafts-type biomimetic coupling reaction for the synthesis of nonsymmetric dimeric naseseazines.[4] In previously reported biomimetic syntheses, key dimerization reactions were carried out in organic solvents with fully protected substrates. In contrast, in a true biosynthesis, the key dimerization reactions should be carried out in aqueous media without special protective groups on the substrates.

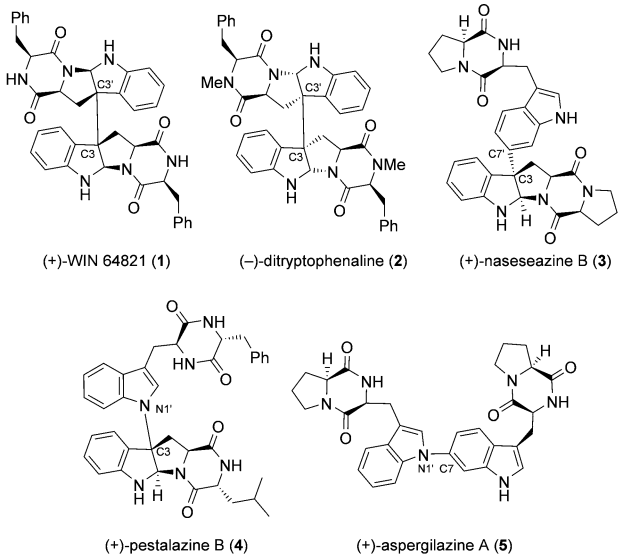

Figure 1. Natural tryptophan-based diketopiperazine alkaloids.

Conducting organic reactions in water is not trivial because common organic compounds are usually insoluble in water, and sometimes the water reacts with substrates or reagents. With alkaloids that contain basic amine portions in the molecule, such situations occur under neutral or basic conditions. In contrast, in acidic solution, basic alkaloids form water-soluble salts. In addition, salt formation possibly prevents side reactions arising from the nucleophilicity of the amine's unprotected lone pair. Thus, we expected acidic conditions would play an important role in aqueous biosynthesis of alkaloids. Recently, Boger and co-workers reported elegant biomimetic radical-mediated oxidative coupling reactions of vinca alkaloids in aqueous HCl and 2,2,2-trifluoroethanol.[10]

Our proposed biosynthetic pathway for dimeric DKP alkaloids is shown in Scheme 1. After the water-soluble salt of tryptophan is formed under acidic conditions, it undergoes selective one-electron oxidation on the indole core without undesired oxidation of the primary amine. The radical compounds generated have several resonance hybrids such

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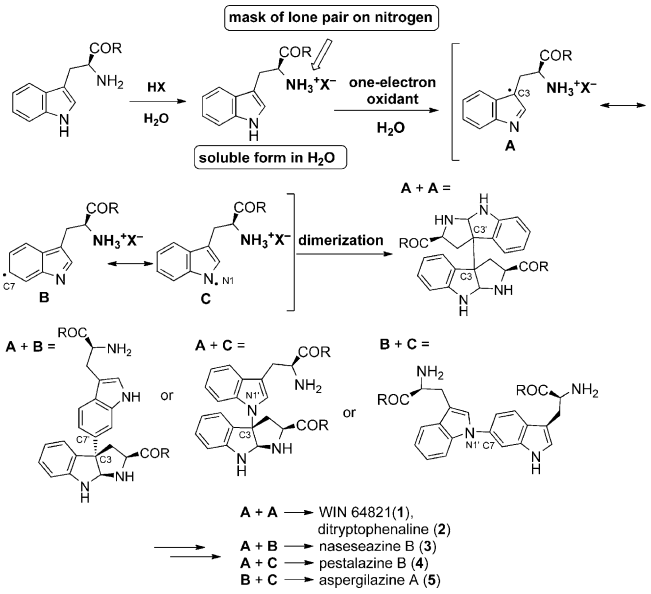
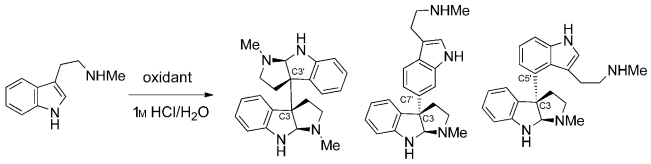


Scheme 1. Proposed biosynthetic pathway.

Table 1: The screening of oxidants for bio-inspired oxidative dimerization reaction.[a]



N_b-methyl triptamine (**6**) *rac*-chimonanthine (**7**) **8** **9**

Entry	Oxidant (equiv)	*T* [°C]	*t* [h]	Yield [%][b]			
				7	**8**	**9**	rec. **6**
1	$MoCl_5$ (2.0)	23	5	–	–	–	>90[c]
2	$[Cu(acac)_2]$ (1.5)	23–80	19	–	–	–	>90[c]
3	$CuBr_2$ (1.5)	23–80	19	–	–	–	>90[c]
4	$FeCl_3$ (2.0)	23–80	19	–	–	–	>90[c]
5	$Mn(OAc)_3$ (1.5)	0	2	7	37	9	trace
6	VOF_3 (1.5)	0	2	9	30	12	12
7	V_2O_5 (0.55)	0	12	8	50	–	19

[a] Reaction conditions: *N*-methyltryptamine (**6**) (0.5 mmol), 1 M HCl/H_2O (3 mL) in open flask. See the Supporting Information for details. [b] Yield of isolated compound. [c] Calculated from ^{1}H NMR spectrum of crude material.

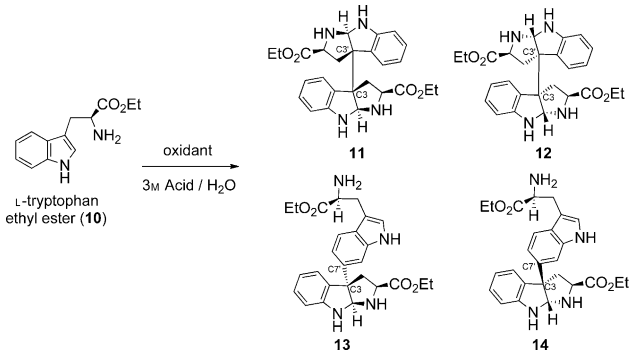
as active species with the radical on C3, C7, or N1 (**A**, **B**, or **C**). These intermediates dimerize to provide corresponding natural product scaffolds: **A** + **A** → **1** and **2**, **A** + **B** → **3**, **A** + **C** → **4**, and **B** + **C** → **5**.

Herein, we describe direct bio-inspired dimerization reactions along the lines of our proposed biosynthetic pathway using commercially available amine-free tryptophan derivatives in aqueous acidic media to provide C_2-symmetrical and nonsymmetrical dimeric compounds. We also report concise three-step, two-pot total syntheses of the naturally occurring alkaloids (+)-**1**, (−)-**2**, and (+)-**3** in overall yields of 20%, 13%, and 20%, respectively.

To achieve the proposed bio-inspired dimerization reaction in the flask, we began by screening the oxidants in aqueous HCl solution with simple *N_b*-methyltryptamine (**6**) as a model substrate (Table 1). Oxidants that promoted oxidative biaryl coupling reactions with electron-rich aromatics in organic solvents were examined.[11] Even though **6** dissolves completely in aqueous solution, $MoCl_5$, $[Cu(acac)_2]$ (acac = acetylacetonate), $CuBr_2$, and $FeCl_3$ are not reactive reagents for indoles (Table 1, entries 1–4). In addition, $MoCl_5$ immediately decomposed in aqueous acidic media (Table 1, entry 1). In contrast, $Mn(OAc)_3$ promoted the desired dimerization reaction without decomposition under aqueous acidic conditions (Table 1, entry 5). When treated with 1.5 equivalents of $Mn(OAc)_3$, naturally occurring chimonanthine (**7**),[12] which has a C_2-symmetrical C3(sp^3)–C3′(sp^3) bridge, naseseazine-type compound **8**,[13] which has a C3(sp^3)–C7′(sp^2) bridge, and the nonsymmetrical dimeric compound **9**, which has an unnatural C3(sp^3)–C5′(sp^2) bridge, were isolated in yield of 7%, 37%, and 9%, respectively. Isolated **7** was identified by comparison to spectral data of the natural product and the stereochemistry of **8** and **9** was determined by 2D NMR experiments including NOESY spectra (see the Supporting Information). Vanadium(V) oxidants such as VOF_3 and V_2O_5 also provided the desired dimeric compounds along with recovered starting material **6** (Table 1, entries 6 and 7). With both vanadium reagents (entries 6 and 7), compound **8** was the major product (30% and 50%, respectively). All successful reactions were carried out in open flasks.

After discovering suitable oxidants for these bio-inspired dimerization reactions under aqueous conditions, we moved to tryptophan derivatives as substrates. Commercially available L-tryptophan ethyl ester (**10**) was chosen as a substrate because the anticipated dimeric compounds can be quickly accessed as natural products (Table 2). When **10** was treated with 1.2 equiv of $Mn(OAc)_3$ in aqueous HCl solution, C_2-symmetrical and nonsymmetrical dimeric compounds **11**, **12**, **13**, and **14** were obtained in yields of 7%, 4%, 12%, and 9%, respectively, along with recovered starting material **10** (Table 2, entry 1). All isomers were easily separated by silica gel column chromatography. The stereochemistry of **11**, **12**,and **13** correspond to that of (+)-**1**, (−)-**2**, and (+)-**3**, respectively. Next, the acid effect was screened for optimization (see the Supporting Information for full details). Aqueous HCl, H_2SO_4, CH_3SO_3H, Cl_3CO_2H, and H_3PO_4 solutions ($pK_a = -8.0$ to 2.12 in H_2O) promoted the dimerization reaction effectively (Table 2, entries 2–5; −10°C, 40 min to 2 h). In particular, when the reaction was carried out in aqueous CH_3SO_3H solution, high conversions were observed. Thus, dimeric compounds **11**, **12**, **13**, and **14** were obtained in yields of 19%, 11%, 28%, and 21%, respectively (Table 2, entry 3; total yield of dimeric compounds, 79%; recovered **10**, 4%). In contrast, weaker acids such as HCO_2H and CH_3CO_2H did not form any products at ambient temperature for 24 h, even though the substrate was cleanly dissolved in aqueous solution. CH_3SO_3H was also a suitable acid for VOF_3 as oxidant, providing almost the same result as $Mn(OAc)_3$ (Table 2, entry 8). Interestingly, V_2O_5 in aqueous CH_3SO_3H solution was the most effective combination for forming C_2-symmetrical compounds. Thus, when **10** was

Table 2: The effect of aqueous acidic conditions on the oxidative dimerization reaction of **10**.[a]



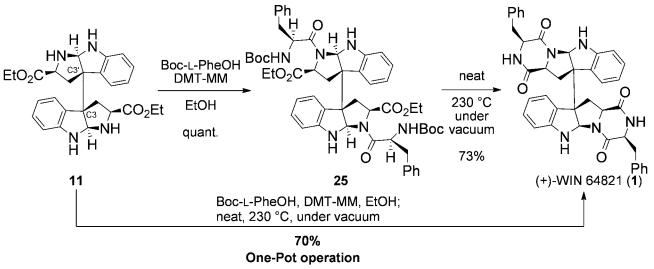
Entry	Oxidant (equiv)	Acid	*T* [°C]	*t*	Yield [%][c]				
					11	**12**	**13**	**14**	rec. **10**
1	$Mn(OAc)_3$ (1.2)	HCl	0	40 min	7	4	12	9	37
2		H_2SO_4	0	40 min	15	8	23	20	9
3		$MeSO_3H$	0	40 min	19	11	28	21	4
4		Cl_3CO_2H	0	2 h	12	9	27	20	14
5		H_3PO_4	0	2 h	12	8	21	17	14
6		HCO_2H	0–23	24 h	–	–	–	–	>90[d]
7		AcOH	0–23	24 h	–	–	–	–	>90[d]
8	VOF_3 (1.1)	$MeSO_3H$	−10	30 min	19	11	28	21	8
9	V_2O_5 (0.65)	$MeSO_3H$[b]	−15	129 h	28	28	14	10	0
10[e]		$MeSO_3H$	−15	192 h	26	27	9	10	0

[a] Reaction conditions: L-tryptophan ethyl ester (**10**) (0.5 mmol), 3 M acid in H_2O (3 mL) in open flask. See the Supporting Information for details. [b] 10 mL of 3 M CH_3SO_3H in H_2O was used. [c] Yield of isolated compound. [d] Calculated from ^1H NMR spectra of crude material. [e] L-tryptophan ethyl ester (**10**) (6.0 g, 25.8 mmol), 3 M $MeSO_3H$ in H_2O (517 mL) in open flask. See the Supporting Information for details.

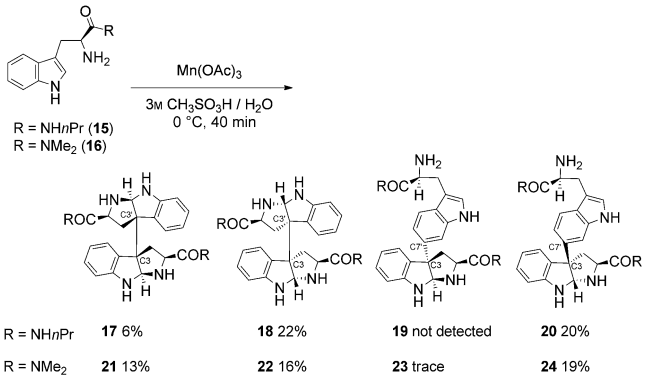
treated with 0.65 equiv of V_2O_5 at −15 °C for 129 h, **11** and **12** were obtained, each in 28% yield (Table 2, entry 9; total yield of dimeric compounds, 81%). The dimerization reaction supplied the desired dimeric compounds in multigram amounts by a one-step procedure (Table 2, entry 10).

Our method could also be applied to amide derivatives inspired by the *N*-terminus of peptides (Scheme 2). Thus, treatment of dissolved L-tryptophan *n*-propyl amide (**15**) in aqueous 3 M CH_3SO_3H solution with 1.2 equiv of $Mn(OAc)_3$ provided the corresponding dimeric compounds. Surprisingly, compounds **18** and **20** were major dimeric compounds (**18,** 22% yield; **20**, 20% yield); thus, obvious selectivity was observed and we are currently investigating the origin of this selectivity. In contrast, the dimerization reaction with L-tryptophan dimethyl amide (**16**) gave **21** (13%), **22** (16%), **24** (19%) with trace amounts of **23**. The absolute stereochemistry of dimeric amide derivatives was determined by its CD spectrum (see the Supporting Information for details).

With large amounts of these key dimeric intermediates of proposed biosyntheses in hand, our focus moved to the concise syntheses of (+)-**1**, (−)-**2**, and (+)-**3**. For the dehydration condensation reaction required for the synthesis of (+)-**1**, 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM), developed by Kunishima and co-workers, was employed because it can be used in environmentally friendly alcohol solvents without any additives such as bases.[14] Thus, treatment of **11** in ethanol with 2.1 equiv of *N*-Boc-phenylalanine in the presence of 2.2 equiv of DMT-MM (0 °C, 4 h) in an open flask cleanly provided **25** in superb conversion (quantitative yield) (Scheme 3). Initial attempts to convert **25** directly to **1** by removing the Boc group and forming the diketopiperazine unit in a single step provided (+)-**1** in 59% yield under an argon atmosphere at 230 °C and in the absence of solvent. Further improvement of conversion was accomplished under vacuum, because the reaction side



Scheme 3. Synthesis of (+)-WIN 64821 (**1**).

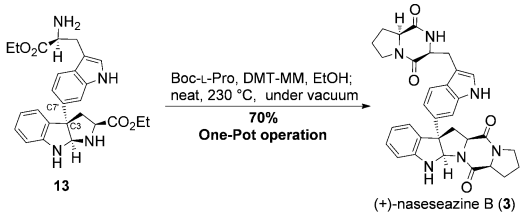


Scheme 2. Bio-inspired oxidative dimerization reactions of amide derivatives.

products such as isobutene, carbon dioxide, and ethanol could be removed immediately from the reaction vessel (1 mbar, 30 min, 73%). Furthermore, the diketopiperazine formation could be conducted simultaneously as a one-pot operation. Thus, after the condensation of dimeric compound **11** with *N*-Boc-phenylalanine (2 equiv) in the presence of DMT-MM (2 equiv, EtOH, 0 °C, 4 h) was complete, the solvent was removed under reduced pressure at ambient temperature. The reaction flask was directly heated to 230 °C under vacuum (1 mbar, 25 min) to provide (+)-**1** in superb yield (70%). To summarize the synthesis of **1**: It was accomplished by only two one-pot operations from commercially available **6** in an overall yield of 20%; the key step was the bio-inspired dimerization with V_2O_5 in aqueous CH_3SO_3H solution (Table 2, entry 9). This synthesis used only water and environ-

mentally friendly ethanol as reaction media. In addition, the sequence is simple and is not affected by air or water.

After completing the synthesis of (+)-**1**, we applied the same procedure to the synthesis of (+)-**3** (Scheme 4). Thus, the dehydration condensation reaction with **13** (1 equiv) and *N*-Boc-L-proline (2 equiv) in the presence of DMT-MM



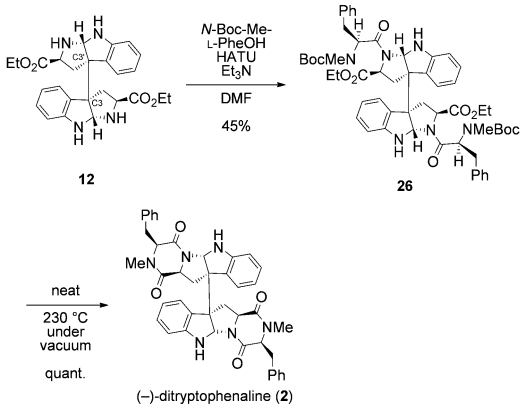
Scheme 4. Synthesis of (+)-naseseazine B (**3**).

(2 equiv, EtOH, 0 °C, 4 h) was followed by diketopiperazine formation (neat, 230 °C, 15 min, 1 mbar) to provide (+)-**3** in superb yield (70 %). To summarize the synthesis of **3**: It was accomplished in two one-pot operations from **6** in an overall yield of 20 % by $Mn(OAc)_3$ or VOF_3 oxidation in aqueous CH_3SO_3H solution (Table 2, entries 3 and 8).

Surprisingly, DMT-MM was not an effective coupling reagent for **12** in the synthesis of (−)-**2**. When the established reaction conditions were applied to **12** with *N*-Boc-methyl-L-phenylalanine, the starting material was completely recovered. In addition, *N*-Boc-methyl-L-phenylalanine ethyl ester was obtained as the only isolable product. After several attempts to convert **12** to **26**, we found that *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU, 2.4 equiv) and Et_3N (5.9 equiv) in combination gave the desired coupling reaction in moderate yield (45 %, Scheme 5). Deprotection and diketopiperazine formation of **26** (neat, 230 °C, 30 min, 1 mbar) then furnished (−)-**2** (quantitative yield). To summarize the synthesis of **2**: It was accomplished in three steps from **6** in an overall yield of 13 % by V_2O_5 oxidation in aqueous CH_3SO_3H solution (Table 2, entry 9).

In conclusion, we have developed direct bio-inspired dimerization reactions along the lines of our proposed biosynthetic pathway from commercially available amine-free tryptophan derivatives in aqueous acidic media to provide C_2-symmetrical and nonsymmetrical dimeric compounds. Then, concise syntheses of naturally occurring dimeric diketopiperazine alkaloids (+)-WIN 64821 (**1**), (−)-ditryptophenaline (**2**), and (+)-naseseazine B (**3**) were accomplished in overall yields of 20 %, 13 %, and 20 %, respectively. These overall yields are satisfactory compared to those of previous reported syntheses.

Further applications and mechanistic studies of these bio-inspired dimerization reactions and the synthesis of bioactive DKP alkaloids are currently underway.



Scheme 5. Synthesis of (−)-ditryptophenaline (**2**).

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