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Total synthesis and stereochemistry assignment of 15-membered peptide alkaloids abyssenine B and mucronine E

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Abstract—The total synthesis of 15-membered peptide alkaloids abyssenine B and mucronine E was accomplished via olefination of phenylalanine-embodied aldehydes followed by CuI/*N*,*N*-dimethylglycine-catalyzed coupling of vinyl iodides with amides and FDPP-mediated macrocyclization in the key steps. From the total synthesis the stereochemistry of these two natural products was tentatively assigned to be *S*,*S*,*S*.

Abyssenines A–C,[1] mucronines A–C,[2] and E–H[1] (Fig. 1) are 15-membered macrocycles that were isolated 30 years ago from the bark of *Zizyphus abyssinica* Hochst. Ex A. Rich, and the crude base of *Z. abyssinica* Willd, respectively. Some of these compounds were found to have significant antifungal (against *Pythium debaryanum* and *Trichoderma viride*) and antibacterial (against *Bacillus subtilis* and *Escherichia coli*) activities. Structurally, they belong to a growing family of cyclopeptide alkaloids including over 200 members.[3] During the past decades, considerable synthetic efforts have been devoted to these cyclopeptide alkaloids, mainly because of their unique structure and interesting biological properties.[3–11] Comparing to 13- and 14-membered cyclopeptide alkaloids, little attention has been directed to the synthesis of 15-membered cyclopeptides alkaloids,[3–10] which is evident from the fact that only the total synthesis of mucronine B has been reported to date.[11]

The major challenge in elaborating the cyclopeptide alkaloids, mentioned above, is the construction of their enamide moiety.[3–8,11] Different elimination reactions were employed to reach this goal (see Fig. 1 for an example).[3–8,11] Since the elimination was performed after the macrocyclization step, the tedious and low-yielding manipulations greatly decreased the synthetic efficiency. The recently developed Cu-catalyzed coupling of vinyl iodides and amides, which proceeds under mild conditions, may offer a solution to this problem.[12] Independently, the Evano group[9] and we[10] successfully applied this method in the total synthesis of 13-membered cyclopeptide alkaloids paliurine F and ziziphine N. In this report, we wish to disclose our studies toward the synthesis of 15-membered cyclopeptide alkaloids abyssenin B and mucromines E by using this strategy.

As depicted in Figure 1, we planned to elaborate 15-membered cyclopeptide alkaloids via a CuI-catalyzed cross-coupling of vinyl iodides **C** with a suitable amide and subsequent macrocyclization. The vinyl iodides **C** can be obtained via Wittig olefination[13] of the corresponding aldehydes **D**. Thus, the asymmetric synthesis of these polysubstituted phenylalanine derivatives became our first task. Another problem we faced in the total synthesis of these natural products is that their stereochemistry is still unknown. We assumed that the configuration at the three chiral centers is *S*,*S*,*S*, respectively, because mucronine B, a structurally related compound isolated from the same species, was synthesized by Schmidt and assigned to have *S*,*S*,*S* stereochemistry.[11]

Aldehyde **17**, required for the assembly of abyssenin B, was elaborated via an asymmetric Strecker reaction[14] as shown in Scheme 1. Treatment of aldehyde **11** with (*R*)-phenylglycinol and TMSCN in methanol at room temperature gave a mixture of diastereomeric aminonitriles in a ratio of 1:1. Upon heating this mixture in a sealed

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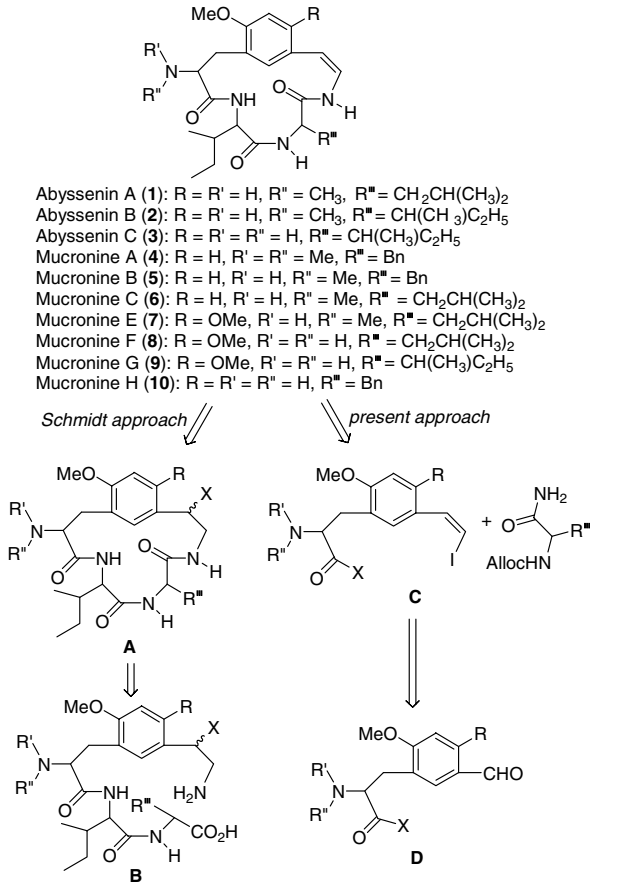
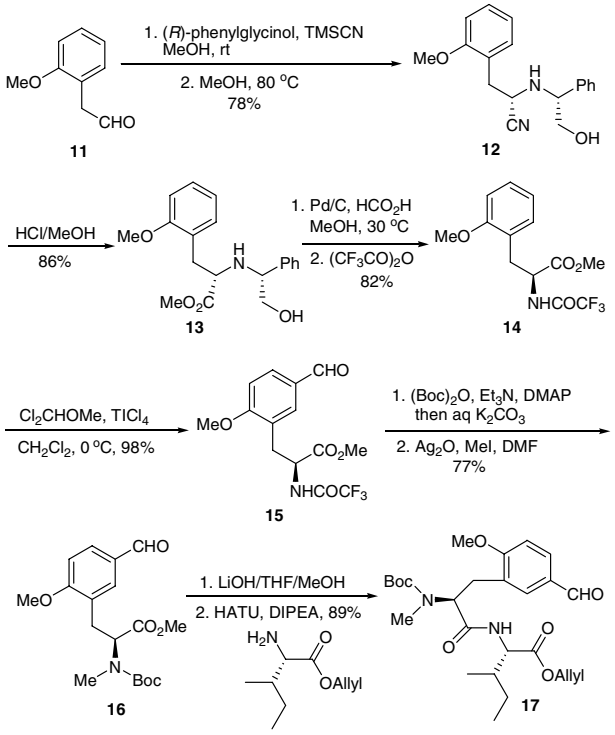


Figure 1. Structures of abyssenines A–C, mucronines A–C, and E–H, and their retrosynthetic analysis.



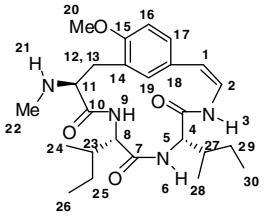
Scheme 1.

tube at 80 °C, the ratio of the desired diastereomer **12** was raised to 9:1.[14b] Aminonitrile **12** was isolated in 78% overall yield and exposed to methanolic hydrogen chloride to afford amino ester **13**. After hydrogenolysis of **13**, to remove the chiral auxiliary, the resulting amine was protected with trifluoroacetic anhydride to provide amide **14**. After initial attempts to perform a Vilsmeier formylation on **14** failed, we found that aldehyde **15** could be constructed by the treatment of **14** with Cl_2CHOMe and $TiCl_4$ in 98% yield.[15] Next, we decided to switch the N-protecting group to Boc in order to avoid possible racemization of the amino acid moiety during the CuI-catalyzed coupling step.[16] Direct cleavage of the trifluoroacetyl in **15** under both acidic and basic conditions was found to be difficult. Reaction of **15** with di-*tert*-butyl dicarbonate afforded a carbamate, which was treated with 1 N K_2CO_3 to remove the trifluoroacetyl group. The resulting Boc-protected amino ester was then methylated with Ag_2O/MeI to afford ester **16**. Hydrolysis of **16**, followed by condensation with L-isoleucine allyl ester furnished aldehyde **17**.

Wittig olefination[13] of **17** with $Ph_3P^+(CH_2I)I^-$/LiHMDS produced vinyl iodide **18** in 86% yield as a mixture of *Z*- and *E*-isomers in a ratio of 6:1. This mixture was inseparable by column chromatography and thus we decided to use it as is for the next step. To our delight, CuI/*N*,*N*-dimethylglycine-catalyzed coupling of **18** with *N*-alloxycarbonyl-L-isoleucine amide worked well in dioxane at 80 °C, affording separable enamide **19** (61% yield from **18**) and its *E*-isomer (~5% yield from **18**). After the removal of the allyl and alloxycarbonyl protecting groups with $Pd(PPh_3)_4$ and diethylamine, a strongly diluted solution of the liberated amino acid in DMF was treated with FDPP/DIPEA to afford macrolactam **20** in 27% yield. Finally, the removal of the Boc group in **20** with $ZnBr_2$ in methylene chloride afforded **2**. The optical rotation of synthetic **2** ($[\alpha]_D^{22}$ +161 (*c* 0.7, MeOH)) is in close proximity to that reported for natural abyssenin B ($[\alpha]_D^{20}$ +151 (*c* 0.17, MeOH)).[1] In addition, its ^1H NMR data was found to be indistinguishable from the literature reference, except for some additional peaks, which were recorded at δ 3.07–3.30 (m, 2H), 3.44 (dd, $J = 13.6$, 7.8 Hz, 1H), and 3.02 (d, $J = 13.8$ Hz, 1H) in our sample (see Table 1). These peaks apparently belong to the signals from H-5, H-8, H-12, and H-13 of abyssenin B and were not reported previously. These results offer additional support for the *S*,*S*,*S* configuration of abyssenin B (Scheme 2).

Our synthetic pathway toward mucronine E is outlined in Scheme 3. The known amino ester **21**, prepared from L-tyrosine in five steps,[17] was reported to amide **22** via Pd/C-catalyzed hydrogenolysis and subsequent protection of the liberated amine with $(CF_3CO)_2O$. Vilsmeier formylation worked well in this case, affording aldehyde **23** in 97% yield, after exposure of **22** to $POCl_3$/DMF. The higher nucleophilicity of **22** was accounted for the difference in reactivity compared to anisole **14**. After changing the N-protecting group to Boc, methylation with Ag_2O/MeI afforded amino ester **24b**. Hydrolysis of **24b** followed by coupling with L-isoleucine allyl ester

Table 1. ^{1}H NMR and ^{13}C NMR data and their assignment to abyssenin B **2**[a]



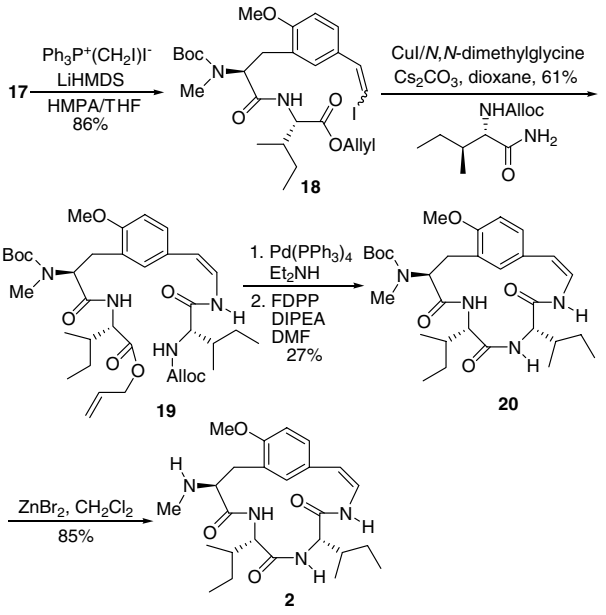
2

$\delta(^{1}H)$ [ppm]	Multiplicity	No. of H atoms	Assignment	J [Hz]	$\delta(^{13}C)$ [ppm]	Assignment
9.60	d	1H	H_9	8.0	176.1	C_7
8.48	d	1H	H_3	11.0	172.7	C_{10}
8.25	d	1H	H_6	8.0	169.1	C_4
7.09	d	1H	H_{19}	1.8	156.2	C_{15}
6.99	dd	1H	H_{17}	8.7, 2.4	129.8	C_{17}
6.89	dd	1H	H_{16}	8.7, 2.9	129.0	C_{19}
6.81	d	1H	H_2	9.6	128.9	C_{14}
5.61	d	1H	H_1	9.6	125.1	C_{18}
4.42	dd	1H	H_{11}	8.2, 3.2	120.3	C_2
3.85	s	3H	H_{20}		111.6	C_{16}
3.44	dd	1H	$H_{12,13}$	13.6, 7.8	109.5	C_1
3.07–3.30	m	2H	$H_{5,8}$		66.2	$C_{5,8}$
3.02	d	1H	$H_{12,13}$	13.8	66.0	$C_{5,8}$
2.54–2.59	m	1H	H_{23}		59.2	C_{11}
2.48	s	3H	H_{22}		55.7	C_{20}
2.34–2.43	m	1H	H_{27}		36.8	C_{27}
2.25	br	1H	H_{21}		36.5	C_{22}
1.52–1.56	m	1H	H_{29}		33.3	C_{23}
1.45–1.51	m	1H	H_{25}		31.2	$C_{12,13}$
1.29–1.39	m	1H	H_{29}		25.8	C_{29}
1.08–1.18	m	1H	H_{25}		24.2	C_{25}
1.04	d	3H	H_{28}	6.9	16.7	C_{28}
0.99	t	3H	H_{30}	7.3	15.5	C_{24}
0.91	d	3H	H_{24}	6.8	12.2	C_{30}
0.87	t	3H	H_{26}	7.4	9.7	C_{26}

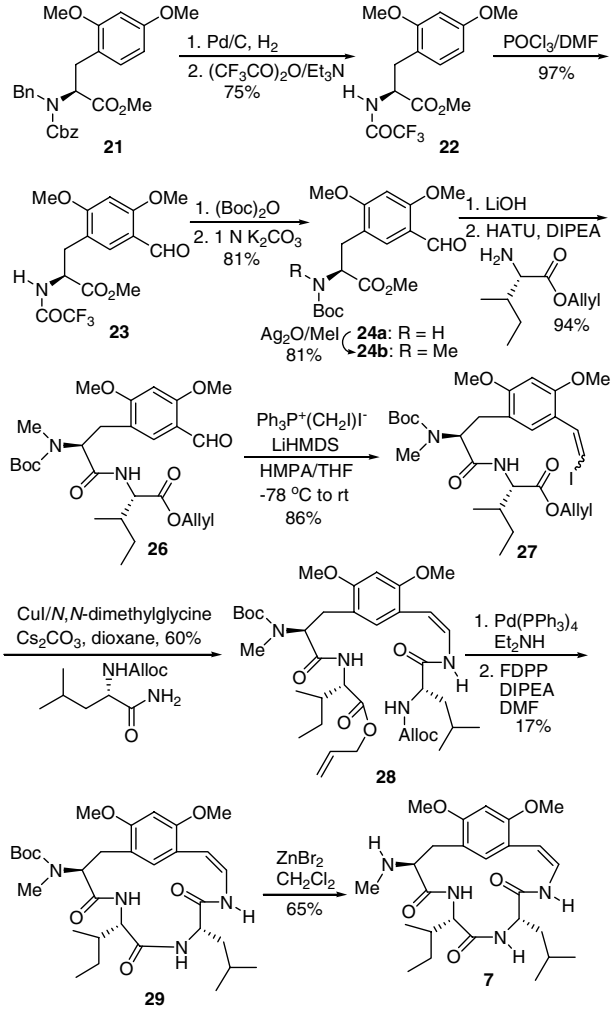
[a] All assignments were based on the COSY, NOSEY, HMBC, and HMQC studies of **2**.

under the action of HATU provided dipeptide **26**. Olefination of **26** with $Ph_3P^+(CH_2I)I^-$/LiHMDS led to vinyl iodide **27** as a mixture of *Z*- and *E*-isomers in a ratio of 6:1. This mixture was also inseparable by column chromatography. However, its coupling products with *N*-alloxycarbonyl-L-leucine amide were easily separated to deliver the desired enamide **28** (60% yield from **27**) and its *E*-isomer (~5% yield from **27**). Next, the treatment of enamide **28** with $Pd(PPh_3)_4/Et_2NH$ to remove both allyl and alloxycarbonyl groups afforded a cyclization precursor, which was subjected to FDPP-mediated macrocyclization to furnish lactam **29**. Finally, the cleavage of the Boc group in **29** with $ZnBr_2$ yielded the target molecule **7.**

Synthetic **7** ($[\alpha]_D^{22}$ −86.5 (*c* 0.34, MeOH)) showed almost identical optical rotation to that reported for mucronine E ($[\alpha]_D^{20}$ −89 (*c* 0.084, MeOH)).[1] Its ^{1}H NMR data was found to be indistinguishable from that reported in the

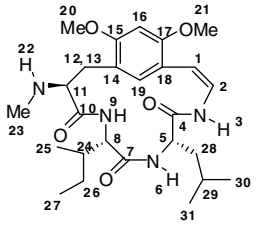


Scheme 2.



Scheme 3.

Table 2. ^{1}H NMR and ^{13}C NMR data and their assignment to mucronine E **7**[a]



7

$\delta(^{1}H)$ [ppm]	Multiplicity	No. of H atoms	Assignment	J [Hz]	$\delta(^{13}C)$ [ppm]	Assignment
9.34	d	1H	H_9	9.3	172.3	$C_{7,10}$
8.40	d	1H	H_3	11.4	169.8	C_4
8.12	d	1H	H_6	7.2	157.3	C_{17}
7.03	s	1H	H_{19}		157.1	C_{15}
6.83	dd	1H	H_2	9.6, 9.9	130.0	C_{19}
6.47	s	1H	H_{16}		120.2	C_2
5.76	d	1H	H_1	9.9	117.5	C_{14}
4.44	m	1H	H_{11}		116.3	C_{18}
3.88	s	3H	$H_{20,21}$		104.7	C_1
3.83	s	3H	$H_{20,21}$		95.9	C_{16}
3.25	dd	1H	$H_{12,13}$	14.6, 3.0	66.2	$C_{5,8}$
3.18	m	2H	$H_{5,8}$		65.3	$C_{5,8}$
2.92	dd	1H	$H_{12,13}$	14.6, 1.2	55.8	$C_{20,21}$
2.54	m	1H	H_{24}		52.4	C_{11}
2.47	s	3H	H_{23}		40.9	C_{28}
2.25	br	1H	H_{22}		36.2	C_{23}
1.87–1.94	m	1H	H_{28}		33.6	C_{24}
1.64–1.72	m	2H	$H_{28,29}$		31.1	$C_{12,13}$
1.41–1.46	m	1H	H_{26}		25.7	C_{26}
1.04–1.08	m	1H	H_{26}		25.0	C_{29}
0.93	d	3H	H_{31}	6.4	23.4	C_{30}
0.89	d	3H	H_{30}	6.4	21.1	C_{31}
0.82	d	3H	H_{25}	6.8	15.1	C_{25}
0.77	t	3H	H_{27}	7.4	9.7	C_{27}

[a] All assignments were based on the COSY, NOSEY, HMBC, and HMQC studies of **7**.

literature, except for some additional peaks, which were recorded at δ 3.25 (dd, $J = 14.6$, 3.0 Hz, 1H), 3.18 (m, 2H), and 2.92 (dd, $J = 14.6$, 1.2 Hz, 1H) in our experiment (Table 2). These peaks belong to the signals from H-5, H-8, H-12, and H-13 of mucronine E and were not reported previously. Therefore we could tentatively assign the configuration of mucronine E as *S*,*S*,*S*.

In conclusion, the total synthesis of abyssenin B and mucromine E with the *S*,*S*,*S*-configuration was achieved using a CuI/*N*,*N*-dimethylglycine-catalyzed coupling reaction of vinyl iodides with amides in the key step. Through this study, we could tentatively determine the stereochemistry of natural abyssenin B and mucromine E to be *S*,*S*,*S*. Since there is no more data for comparison, the synthesis of other isomers of these cyclopeptide alkaloids would be helpful to unambiguously determine the stereochemistry of these natural products.

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