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One-pot synthesis of the naturally occurring dimeric carbazole alkaloid murranimbine and its analogue

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ABSTRACT

Murranimbine, a naturally occurring dimeric carbazole alkaloid, isolated from the root bark of *Murraya euchrestfolia* was synthesized in one step by the application of Lewis acid (BF_3–Et_2O) on its monomer girinimbine. A new dimer of koenidine was also synthesized following the same procedure. Structures of these dimeric carbazole alkaloids were determined by detailed spectral analysis.

The genus *Murraya* encompasses several carbazole alkaloids and has been shown to display numerous biological activities including anti-malarial[1], anti-oxidant[1] and anti-fungal.[1] A number of dimeric carbazole alkaloids were also isolated from different species under the genus *Murraya*.[2–9] Some of these dimeric carbazole alkaloids were reported to have important biological activities, for example, anti-microbial[2], anti-oxidative[10] and cytotoxic activity.[11] In recent times, synthesis of dimeric carbazole alkaloids is considered to be a challenging problem. The total synthesis of murrastifoline-A was reported by Kitawaki et al. utilizing palladium-catalyzed double N-arylation reaction.[12] The synthesis of the methylene-bridged binary carbazole alkaloids bis-murrayafoline-A and chrestifoline-A was described by Bringmann and Tasler.[13] As an interesting side product, a benzylically connected trimer was also identified.[13] Intermolecular coupling of pyranocarbazole alkaloids was also reported in the literature leading to biscarbazole alkaloids.[14] In the present communication, we would like to report the first one-pot synthesis of murranimbine **3**, which was previously isolated from *Murraya euchrestfolia*[15], from its monomer girinimbine **1**[16] and a new dimeric carbazole alkaloid **4** from koenidine[17] (Fig. 1). The structures of the dimers were determined by detailed 1D and 2D NMR spectral analysis.

Reaction of girinimbine **1** with BF_3–etherate[18] afforded an amorphous white solid **3,** the ^{1}H NMR (Table 1) spectrum of which displayed two aryl methyl groups and two sets of gem-dimethyls attached to oxygenated carbons which are characteristic peaks of pyranocarbazole alkaloids. There were two sets of four aromatic protons and two aromatic singlets which had long-range coupling and NOE responses with the aryl methyls. These data suggested that compound **3** contained two girinimbine units. In the HMBC spectrum of **3** the proton (H-12′, δ_H 6.11) of the benzylic methine attached to N atom was related to another benzylic methine carbon (C-12, δ_C 27.1) on upper unit and the proton at δ 2.15 (H-11′) was related to C-11 (δ_C 39.7) indicating C–C linkage between C-12 and C-11′. On the other hand, 1–3 correlations between the proton at C-12′ (δ_H 6.11, δ_C 50.4) and C-8a (δ_C 138.9) confirmed the presence as well as position of the C–N linkage. The relative stereochemistry was proposed by NOE correlations, which showed that H-12 (δ_H 3.10), H-12′ (δ_H 6.11) and H-11′ (δ_H 2.15) are in the same plane (Fig. 2). Finally the structure **3** was found to be identical with naturally occurring dimeric carbazole alkaloid murranimbine[15] by comparison of spectral data of the natural product and synthetic material. The probable mechanism of the formation of the dimer **3** may be initiated by the nucleophilic addition by the lone pair of NH group of one monomer to the electron-deficient centre at C-12′ of the second molecule with concomitant ring closure resulting in the formation of a new six-membered ring.

Koenidine **2** on treatment with BF_3–etherate[18] gave a new dimer **4**, the structure of which was also established by detailed analysis of spectral data (Table 2, Fig. 3). Interestingly the dimer **4** has exactly similar skeletal pattern as in **3**. Thus this simple reaction provides a rapid and efficient entry to naturally occurring dimeric carbazole alkaloids from simple pyranocarbazole precursors.

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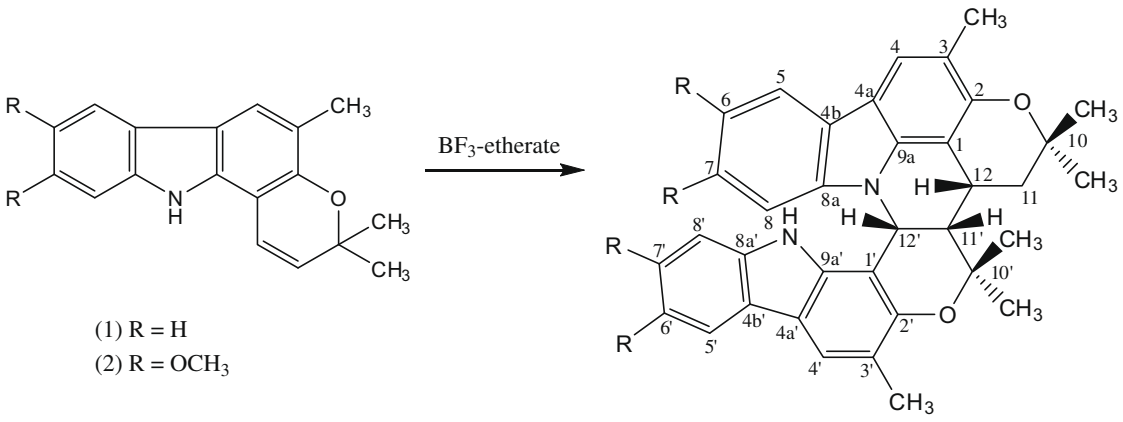

Figure 1. Dimerization reaction of girinimbine and koenidine with BF_3–etherate.

Table 1
NMR spectroscopic data (600 MHz, $CDCl_3$) for compound **3** assigned on the basis of HSQC and HMBC correlations

Position	δc, mult.	δ_H (*J* in Hz)	HMBC correlations
C-1	103.1, qC		27.1(C-12), 39.7(C-11)
C-2	150.3, qC		16.6(CH_3-3), 39.7(C-11), 120.1(C-4)
C-3	119.0, qC		16.6(CH_3-3)
C-4	120.1, CH	7.70, s	16.6 (CH_3-3), 124.5(C-4b), 136.2(C-9a), 150.3(C-2)
C-4a	118.8, qC		124.0(C-5)
C-4b	124.5, qC		120.1(C-4)
C-5	124.0, CH	7.07 dd (7.8, 1.2)	138.9(C-8a), 118.8(C-4a)
C-6	120.6, CH	8.10, d (7.8)	124.0(C-5)
C-7	118.7, CH	7.80, d (7.8)	138.9(C-8a), 124.0(C-5)
C-8	120.1, CH	7.33, t (7.2)	124.5(C-4b), 136.2(C-9a)
C-8a	138.9, qC		118.7(C-7), 124.0(C-5), 50.4(C-12′)
C-9a	136.2, qC		120.1(C-8)
C-10	75.0, qC		39.7(C-11), 30.6(CH_3-10), 25.1(CH_3-10)
C-11	39.7, CH_2	2.38, d (5.4), 1.63, m	27.1(C-12), 103.1(C-1), 25.1(CH_3-10), 30.6(CH_3-10), 75.0(C-10)
C-12	27.1, CH	3.10, m	39.7(C-11), 46.4(C-11′), 103.1(C-1), 50.4(C-12′)
CH_3-3	16.6, CH_3	2.29, s	120.1(C-4), 119.0(C-3), 150.3(C-2), 118.8(C-4a)
CH_3-10	30.6, CH_3	1.48, s	25.1(CH_3-10), 39.7(C-11), 75.0(C-10)
CH_3-10	25.1, CH_3	1.22, s	30.6 (CH_3-10), 39.7(C-11), 75.0(C-10)
C-1′	106.6, qC		50.4(C-12′), 46.4(C-11′)
C-2′	150.4, qC		50.4(C-12′), 39.7(C-11), 16.7(CH_3-3′)
C-3′	112.5, qC		120.7(C-4′)
C-4′	120.7, CH	7.76, s	16.7(CH_3-3′), 136.0(C-9a′), 150.4(C-2′)
C-4a′	117.6, qC		118.9(C-6′)
C-4b′	122.3, qC		120.7(C-4′), 118.9(C-6′), 110.2(C-8′)
C-5′	108.7, CH	7.51, d (8.4)	123.9(C-7′)
C-6′	118.9, CH	7.02, t (7.2)	110.2(C-8′)
C-7′	123.9, CH	7.42, t (7.2)	139.6(C-8a′), 118.9(C-6′)
C-8′	110.2, CH	6.65, d (7.8)	118.9(C-6′)
C-8a′	139.6, qC		123.9(C-7′)
C-9a′	136.0, qC		120.7(C-4′), 50.4(C-12′)
C-10′	78.9, qC		28.8(CH_3-10′)
C-11′	46.4, CH	2.15, m	106.6(C-1′), 28.8(CH_3-10′), 39.7(C-11), 27.1(C-12), 50.4(C-12′)
C-12′	50.4, CH	6.11, d (4.8)	138.9(C-8a), 27.1(C-12), 46.4(C-11′), 106.6(C-1′), 136.0(C-9a′), 150.4(C-2′), 78.9(C-10′)
CH_3-3′	16.7, CH_3	2.41, s	120.7(C-4′)
CH_3-10′	28.8, CH_3	1.71, s	28.8(CH_3-10′), 78.9(C-10′)
CH_3-10′	28.8, CH_3	1.71, s	28.8(CH_3-10′), 78.9(C-10′)

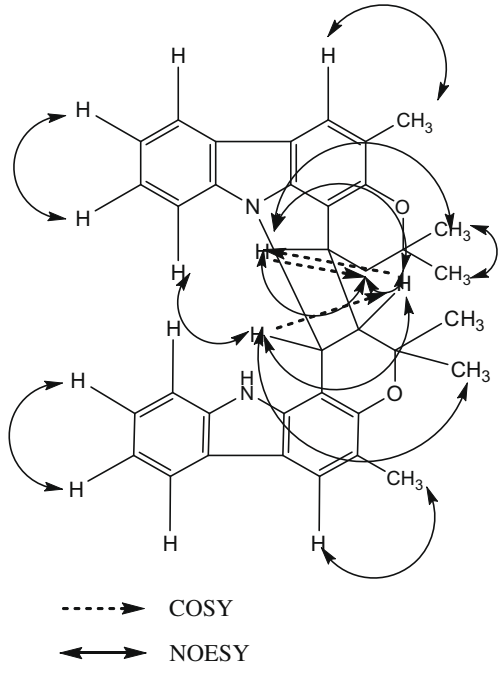

Figure 2. Some important COSY and NOESY correlations of compound **3**.

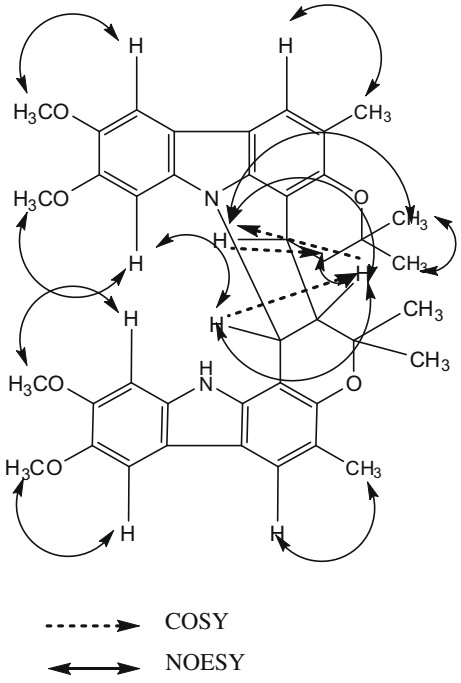

Figure 3. Some important COSY and NOESY correlations of compound **4**.

Table 2
NMR spectroscopic data (600 MHz, $CDCl_3$) for compound **4** assigned on the basis of HSQC and HMBC correlations

Position	δc, mult.	δ_H (*J* in Hz)	HMBC correlations
C-1	103.3, qC		119.1(C-4), 39.6(C-11), 112.7(C-3)
C-2	149.2, qC		16.5(CH_3-3), 119.1(C-4), 27.1(C-12)
C-3	112.7, qC		103.3(C-1), 119.1(C-4)
C-4	119.1, CH	7.62, s	103.3(C-1), 149.2(C-2), 112.7(C-3), 135.6(C-9a)
C-4a	118.5, qC		16.5(CH_3-3), 101.4(C-5)
C-4b	114.3, qC		119.1(C-4), 94.3(C-8)
C-5	101.4, CH	7.30, s	118.5(C-4a), 133.8(C-8a), 144.4(C-7)
C-6	148.2, qC		56.1(OCH_3-6), 101.4(C-5), 94.3(C-8)
C-7	144.4, qC		56.6 (OCH_3-7), 101.4(C-5), 94.3(C-8)
C-8	94.3, CH	6.26, s	114.3(C-4b), 133.8(C-8a), 144.4(C-7), 148.2(C-6)
C-8a	133.8, qC		94.3(C-8), 101.4(C-5), 50.8(C-12′)
C-9a	135.6, qC		119.1(C-4)
C-10	74.8, qC		39.6(C-11), 30.6(CH_3-10), 25.0(CH_3-10)
C-11	39.6, CH_2	2.32, 1.57, m	27.1(C-12), 25.0(CH_3-10), 30.6(CH_3-10), 47.8(C-11′), 103.3(C-1)
C-12	27.1, CH	3.02, m	103.3(C-1), 39.6(C-11), 47.8(C-11′), 149.2(C-2), 31.4(CH_3-10′), 50.8(C-12′)
CH_3-3	16.5, CH_3	2.29, s	119.1(C-4)
OCH_3-6	56.1, CH_3	3.78, s	148.2(C-6)
OCH_3-7	56.6, CH_3	4.08, s	144.4(C-7)
CH_3-10	30.6, CH_3	1.47, s	25.0(CH_3-10), 39.6(C-11), 74.8(C-10)
CH_3-10	25.0, CH_3	1.19, s	30.6 (CH_3-10), 39.6(C-11), 74.8(C-10)
C-1′	107.9, qC		47.8(C-11′), 119.4(C-4′), 50.8(C-12′)
C-2′	149.3,qC		119.4(C-4′), 16.6(CH_3-3′), 50.8(C-12′)
C-3′	118.5, qC		16.6(CH_3-3′)
C-4′	119.4, CH	7.66, s	149.3(C-2′)
C-4a′	116.4, qC		119.4(C-4′), 92.9(C-5′)
C-4b′	119.0, qC		134.2(9a′)
C-5′	92.9, CH	6.98, s	116.4(C-4a′), 144.1(C-7′)
C-6′	147.9, qC		56.4(OCH_3-6′)
C-7′	144.1, qC		56.5(OCH_3-7′)
C-8′	103.4, CH	7.61, s	134.2(C-9a′), 147.9(C-6′)
C-8a′	135.9, qC		103.4(C-8′)
C-9a′	134.2, qC		119.4(C-4′), 50.8(C-12′)
C-10′	79.4, qC		31.4, 28.0(CH_3-10′), 50.8(C-12′), 47.8(C-11′)
C-11′	47.8, CH	2.21, m	27.1(C-12), 50.8(C-12′), 107.9(C-1′), 31.4(CH_3-10′), 28.0(CH_3-10′), 39.6(C-11)
C-12′	50.8, CH	5.96, d (4.8)	133.8(C-8a), 118.5(C-3′), 149.3(C-2′), 107.9(C-1′), 47.8(C-11′), 27.1(C-12), 79.4(C-10′)
CH_3-3′	16.6, CH_3	2.43, s	119.4(C-4′), 149.3(C-2′)
OCH_3-6′	56.4, CH_3	3.86, s	147.9(C-6′)
OCH_3-7′	56.5, CH_3	3.91, s	144.1(C-7′)
CH_3-10′	28.0, CH_3	1.65, s	31.4(CH_3-10′), 47.8(C-11′), 79.4(C-10′)
CH_3-10′	31.4, CH_3	1.73, s	28.0(CH_3-10′), 47.8(C-11′), 79.4(C-10′)

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.030.

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17. Narasimhan, N. S.; Paradhkar, M. V.; Kelkar, S. L. *Indian J. Chem.* **1970**, *8*, 473–474.
18. General method of preparation: Freshly distilled BF_3–etherate (0.5 ml) was added to girinimbine **1** (50 mg) dissolved in 10 ml of dry and distilled benzene and the colour of the reaction mixture became dark blue. It was stirred at room temperature for 10 min and the progress of the reaction was monitored by TLC. After removal of benzene under reduced pressure, the reaction mixture was neutralized by adding 10% aqueous $NaHCO_3$ solution, when the dark blue colour disappeared. Then it was extracted with $CHCl_3$, washed with water and concentrated under reduced pressure. The major product **3** (30 mg) was purified by preparative TLC using petroleum ether/benzene = 4:1 as solvent system. ^1H and ^{13}C NMR data, see Table 1; HRESIMS *m/z* 527.2520 $(M+H)^+$ (calcd for $C_{36}H_{35}N_2O_2$, 527.2620). Dimer of koenidine **4** was prepared following the same procedure as described above. The major product (33 mg) was purified by preparative TLC using petroleum ether/benzene = 6:1 as solvent system. ^1H and ^{13}C NMR data, see Table 2; HRESIMS *m/z* 647.3742 $(M+H)^+$ (calcd for $C_{40}H_{43}N_2O_6$, 647.3043).