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Bioinspired total synthesis and structural revision of yuremamine, an alkaloid from the entheogenic plant *Mimosa tenuiflora*†

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Guided by a biosynthetic hypothesis, a serendipitous total synthesis of yuremamine has resulted in its structural revision from the putative pyrroloindole (1) to the flavonoidal indole (2), which was initially proposed as a biosynthetic intermediate.

The root bark of the entheogenic plant *Mimosa tenuiflora* is used by the indigenous population of Northeastern Brazil to prepare *yurema*, a psychoactive beverage consumed for medico-religious purposes.[1] The bark contains the psychedelic serotonin agonist *N*,*N*-dimethyltryptamine (DMT),[2] which itself is not orally active due to rapid metabolism by monoamine oxidase (MAO).[3] As no MAO inhibitors have been detected in *Mimosa tenuiflora*, there is ongoing interest into how *yurema* exerts its visionary effects.[1–4] It has been suggested that yuremamine (**1**; Fig. 1), isolated from the stem bark of *Mimosa tenuiflora* in 2005,[4] possesses an intramolecular hydrogen bond that protects it from degradation by MAO, causing inhibition of the enzyme and thus facilitating the oral activity of DMT in *yurema*.

The inferred bioactivity and unique molecular architecture of yuremamine has led to significant interest in the synthesis of this alkaloid and in particular, the pyrrolo[1,2-*a*]indole core.[5,6] However, a total synthesis of **1** has remained elusive and none of the aforementioned studies have investigated a biomimetic approach to **1**. We propose that yuremamine is a flavoalkaloid[7] due to the presence of pyrogallol and resorcinol rings in the natural product and the documented abundance of flavonoids[8] in *Mimosa tenuiflora*. A credible biosynthesis is shown in Scheme 1, which commences with a diastereoselective coupling between DMT[2] and the flavanol leucorobinetinidin[9,10] to form the flavonoidal indole **2**. In a process known to occur photochemically in flavan-3-ols,[11] C–O bond scission in **2** gives the quinone methide **3** which is trapped by the indole nitrogen to provide yuremamine.

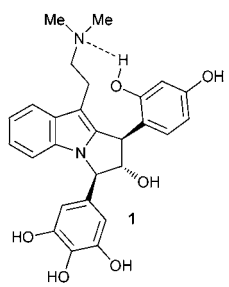

Fig. 1 Yuremamine (**1**) and proposed intramolecular hydrogen bond.

The skeletal rearrangement of **2** to **1** is analogous to the process by which various condensed tannins are converted into their regioisomeric 'phlobatannins'.[12] The stereochemical information present in yuremamine can be traced back to the 4-β-flavanol derivative **2** and it is intriguing that lotthanongine, a natural product isolated from the Thai medicinal plant *Trigonostemon reidioides* and the only known natural flavonoidal indole,[13] exists as the 4-β isomer and possesses the same relative stereochemistry as the hypothetical intermediate **2** (Scheme 1).

To examine the biomimetic hypothesis outlined in Scheme 1, a synthesis of the flavonoidal indole **2** was required. The condensation of acetophenone **4**[14] with benzaldehyde **5**[15] gave chalcone **6** which underwent a facile reduction–cyclisation–dihydroxylation sequence[13b,16] to give the diol (±)-**7**. Following a screen of various Lewis acids, it was found that trimethylsilyl trifluoromethanesulfonate (TMSOTf) was most effective at executing the desired β-selective coupling[13b] between DMT and (±)-**7**, delivering (±)-**8** (d.r. > 30 : 1) in acceptable yield. Facile debenzylation gave the proposed biomimetic rearrangement precursor (±)-**2**, as a single diastereomer (Scheme 2).

While the characterisation of (±)-**2** was being undertaken in d_4-methanol, we noticed that the NMR data was strikingly similar to that reported for yuremamine (also recorded in d_4-methanol).[4] Upon converting (±)-**2** to its TFA salt,[17] we were astonished to observe that its NMR data matched that of the natural product (Table 1). A co-spiked sample of authentic yuremamine[18] and synthetic (±)-**2** gave one spot by TLC and

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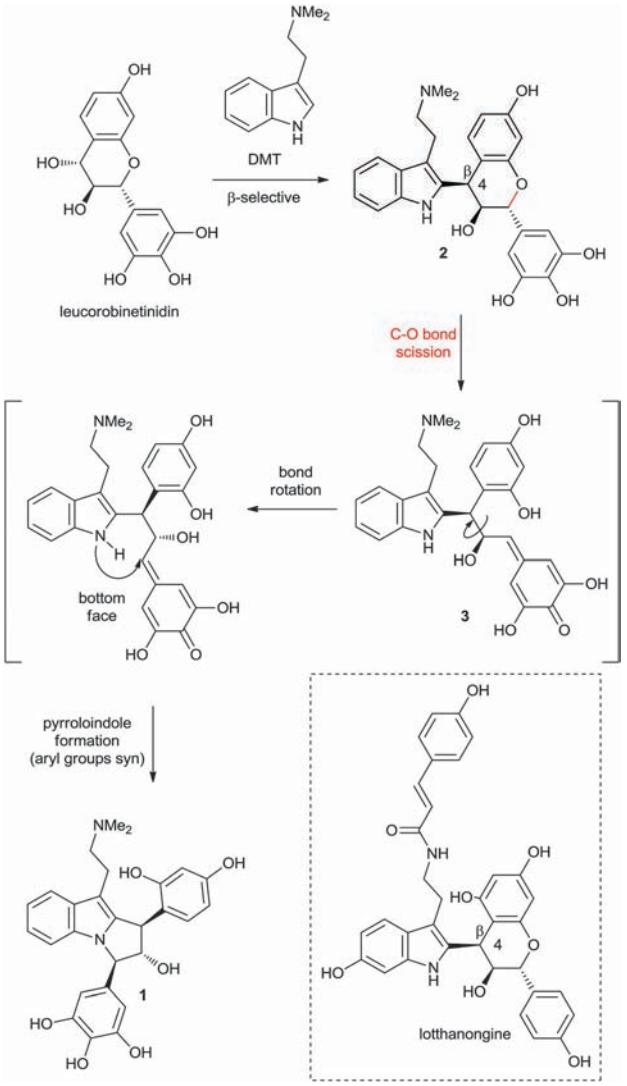
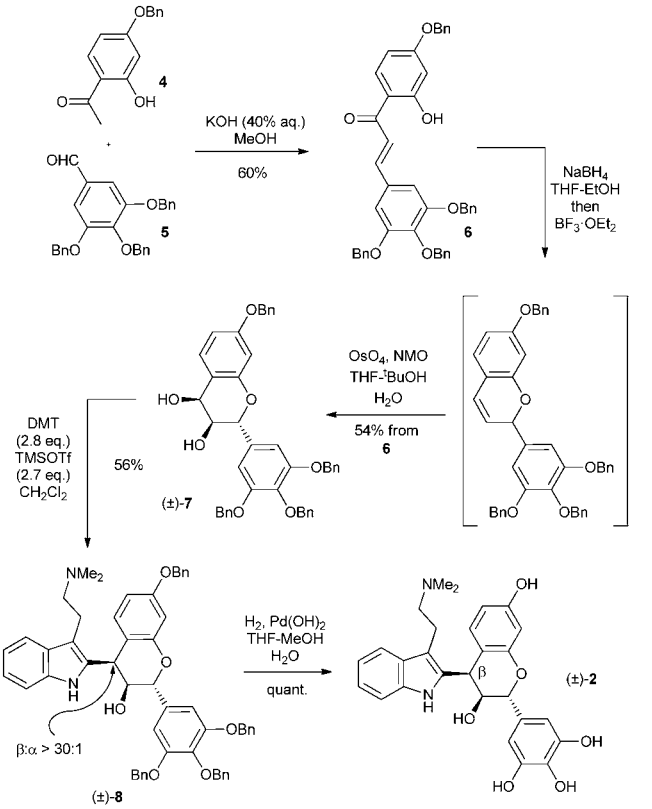


Scheme 1 Proposed biosynthesis of yuremamine (**1**) from flavonoidal indole **2**.



Scheme 2 Synthesis of flavonoidal indole (±)-**2**.

a single set of peaks by ^{1}H NMR,[20] confirming that they are indeed the same compound. Considering it highly unlikely that structures **1** and **2** possess the same NMR data,[19] it was possible that **2** may have spontaneously undergone the proposed biomimetic rearrangement to form pyrroloindole **1** (Scheme 1). This was ruled out using NOESY and ^{1}H–^{15}N HSQC experiments, the latter clearly indicating the presence of an indole N–H (Fig. 2)[20] that would not be observed in structure **1**.

As the HMBC data reasonably fits both **1** and **2**, distinguishing the two regioisomeric structures from this information alone is not straightforward (Table 1). The absence of any HMBC correlations from D3 into the indole nucleus infers that these entities are not fused, evidence against the pyrroloindole **1**. Careful analysis of the HMBC spectrum for the natural product[20] helped confirm that yuremamine does indeed possess structure **2**. The critical D3 to E2′ correlation (dotted arrow, Fig. 3) effectively confirms the structural reassignment as it would represent a $^{3}J_{H\rightarrow C}$ coupling in structure **2** or an improbable $^{5}J_{H\rightarrow C}$ coupling[21] in the initially proposed pyrroloindole **1**. This correlation has been overlooked in the isolation report, despite being present in the HMBC spectrum of the natural product.[20] Based on all the accumulated evidence, yuremamine can be confidently reassigned as the flavonoidal indole **2**, which had been initially proposed as a hypothetical biosynthetic precursor to the putative pyrroloindole structure **1**.

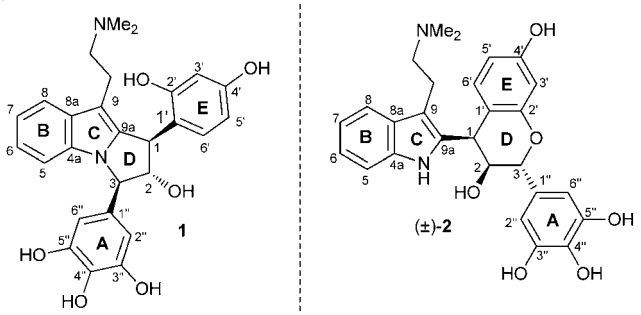
With a structural reassignment of yuremamine complete, some interesting observations noted in the isolation report were examined. The purification procedure used during the isolation of the natural product provided yuremamine as its trifluoroacetate salt, which is responsible for some of its distinctive characteristics.[4] First, its striking purple colour (the free base is colourless) and second, the non-equivalent chemical shifts of the methyl groups, which is not a result of intramolecular hydrogen bonding as initially thought.[4] In the free base of yuremamine, the NMe_2 group appears as a singlet in the ^{1}H NMR spectrum and a single peak in the ^{13}C NMR spectrum.[20] The quaternization of a NMe_2 group with TFA can result in non-equivalent chemical shifts of the methyl groups, as observed in the NMR of the dimethyltryptophan natural product amphibin A.[22]

By pursuing a biomimetic synthesis of the putative yuremamine pyrroloindole **1**, we have serendipitously uncovered the true structure of the natural product to be flavonoidal indole **2**, initially proposed as a biosynthetic intermediate. Considering **1** and **2** possess quite structurally distinct heteroaromatic frameworks, it is unlikely that the structural revision would have been

Table 1 1D and 2D NMR data assigned to pyrroloindole **1** (isolation report) and synthetic (±)-**2**[a,b]

Putative yuremamine **1** and originally assigned NMR data (CD_3OD)				Synthetic **2** and revised HMBC correlations (CD_3OD)			
Atom	^{1}H (500 MHz)	^{13}C (125 MHz)	$HMBC_{H\rightarrow C}$	Atom	^{1}H (500 MHz)	^{13}C (125 MHz)	$HMBC_{H\rightarrow C}$
A3″/5″	—	147.3	—	A3″/5″	—	147.3	—
A4″	—	132.2	—	**A1″**	—	132.1	—
A2″/6″	6.39 (2H, d, J = 0.7)	105.9	A3″/5″, A4″, A2″/6″, A1″, D3	A2″/6″	6.39 (2H, s)	105.8	A3″/5″, A4″, A2″/6″, A1″, D3
A1″	—	133.9	—	**A4″**	—	133.9	—
B4a	—	137.7	—	B4a	—	137.7	—
B5	7.32 (ddd, 8.2, 1.0, 0.8)	112.3	B7, B8a	B5	7.32 (d, 8.1)	112.3	B7, B8a
B6	7.09 (ddd, 8.2, 7.1, 1.1)	122.6	B4a, B8	B6	7.09 (ddd, 8.0, 6.7, 1.1)	122.6	B4a, B8
B7	7.04 (ddd, 8.0, 7.1, 1.0)	120.2	B5, B8a	B7	7.04 (ddd, 7.9, 7.2, 1.1)	120.2	B5, B8a
B8	7.53 (ddd, 8.0, 1.1, 0.8)	118.4	B4a, B6, B8a, C9	B8	7.54 (d, 7.9)	118.3	B4a, B6, B8a, C9
B8a	—	128.5	—	B8a	—	128.5	—
C9	—	108.0	—	C9	—	107.9	—
C9a	—	136.5	—	C9a	—	136.6	—
D1	4.26 (dd, 3.9, 1.0)	36.4	C9, C9a	D1	4.25 (d, 3.8)	36.3	C9a, E1′, **E2′**
D2	4.22 (dd, 4.9, 3.9)	71.8	C9a, E1′	D2	4.22 (t, 4.3)	71.8	C9a, E1′
D3	5.17 (dt, 4.9, 0.7)	81.2	A4″, A2″/6″, D1, D2	D3	5.17 (d, 4.6)	81.2	A1″, A2″/6″, D1, D2, **E2′**
E1′	—	113.6	—	E1′	—	113.6	—
E2′	—	158.9	—	**E4′**	—	158.9	—
E3′	6.48 (d, 2.5)	103.8	E1′, E5′, E4′, E2′	E3′	6.48 (d, 2.4)	103.8	E1′, E5′, E4′, E2′
E4′	—	156.0	—	**E2′**	—	156.0	—
E5′	6.30 (dd, 8.4, 2.5)	109.7	E1′, E3′	E5′	6.30 (dd, 8.5, 2.4)	109.6	E1′, E3′, E4′
E6′	6.51 (dd, 8.4, 1.0)	131.3	D1, E4′, E2′	E6′	6.51 (d, 8.5)	131.2	D1, E4′, E2′
CCH_2	3.29–3.20 (1H)	20.9	—	CCH_2	3.10–2.99 (3H) and	20.9	CCH_2, C9, C9a, B8a, NMe′
CH_2N	3.11–3.00 (3H)	59.5	—	CH_2N	3.28–3.20 (1H)	59.5	
NMe	2.82	43.8	CH_2N, NMe′	NMe	2.82	43.8	CH_2N, NMe′
NMe′	2.76	43.4	CH_2N, NMe	NMe′	2.76	43.4	CH_2N, NMe

[a] Both natural and synthetic samples were characterised as their TFA salts. [b] Putative yuremamine (**1**) numbering has been transferred to structure **2** for comparison and clarity purposes.



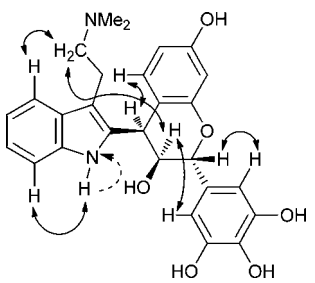


Fig. 2 NOESY (double headed arrows) and ^{1}H–^{15}N HSQC (dotted arrow) correlations for revised yuremamine **2** (TFA salt; d_6-DMSO).

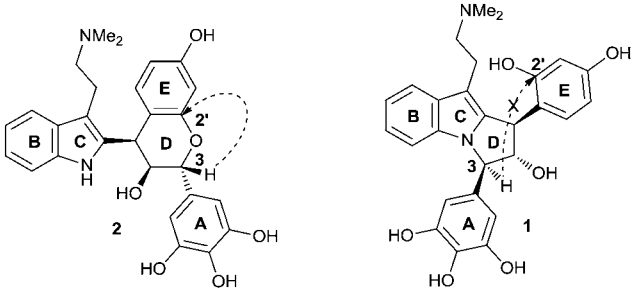


Fig. 3 The critical D3 to E2′ coupling (dotted arrow) supports structure **2**.

as straightforward without considering the biosynthetic origins of the natural product.[23] It is noteworthy that the biomimetic synthesis of yuremamine involves only six-steps and two chromatographic purifications, clearly demonstrating the power of biomimetic strategies in natural product synthesis.[24] In order to determine if yuremamine is an MAO inhibitor and/or psychoactive, a synthetic sample has been submitted to the Psychoactive Drug Screening Program at the University of North Carolina (https://pdspdb.unc.edu/pdspWeb/), the results of which will be made available in due course. We anticipate this information will help define the role of yuremamine in the sacred brew *yurema*.

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Notes and references

1 U. P. de Albuquerque, *Acta Farm. Bonaerense*, 2001, **20**, 139–144.
2 (*a*) M. Meckes-Lozoya, X. Lozoya, R. J. Marles, C. Souchy-Breau, A. Varasen and J. T. Arnason, *Arch. Invest. Med.*, 1990, **21**, 175–177; (*b*) A. Gaujac, A. Aquino, S. Navickiene and J. B. de Andrade, *J. Chromatogr. B: Anal. Technol. Biomed. Life Sci.*, 2012, **881–882**, 107–110; (*c*) A. Gaujac, S. T. Martinez, A. A. Gomes, S. J. de Andrade, A. da Cunha Pinto, J. M. David, S. Navickiene and J. B. de Andrade, *Microchem. J.*, 2013, **109**, 78–83.
3 Another psychedelic brew consumed in Brazil, *ayahuasca*, is prepared from the leaves of DMT-rich *Psychotria viridis* along with *Banisteriopsis caapi*, a source of the MAO inhibitor harmine, see: J. C. Callaway, D. J. McKenna, C. S. Grob, G. S. Brito, L. P. Raymon, R. E. Poland, E. N. Andrade, E. O. Andrade and D. C. Mash, *J. Ethnopharmacol.*, 1999, **65**, 243–256.
4 J. J. Vepsäläinen, S. Auriola, M. Tukiainen, N. Ropponen and J. Callaway, *Planta Med.*, 2005, **71**, 1053–1057.
5 (*a*) M. B. Johansen and M. A. Kerr, *Org. Lett.*, 2008, **10**, 3497–3500; (*b*) D. H. Dethe, R. Boda and S. Das, *Chem. Commun.*, 2013, **49**, 3260–3262; (*c*) L. Hong, W. Sun, C. Liu, L. Wang and R. Wang, *Chem. – Eur. J.*, 2010, **16**, 440–444; (*d*) L. Li, D. Du, J. Ren and Z. Wang, *Eur. J. Org. Chem.*, 2011, 614–618; (*e*) K. Chen, Z. Zhang, Y. Wei and M. Shi, *Chem. Commun.*, 2012, **48**, 7696–7698; (*f*) A. Ghosh and L. M. Stanley, *Chem. Commun.*, 2014, **50**, 2765–2768; (*g*) H.-D. Xu, Z.-H. Jia, K. Xu, H. Zhou and M.-H. Shen, *Org. Lett.*, 2015, **17**, 66–69.
6 (*a*) D. V. Patil, M. A. Cavitt and S. France, *Org. Lett.*, 2011, **13**, 5820–5823; (*b*) W. B. Liu, X. Zhang, L. X. Dai and S. L. You, *Angew. Chem., Int. Ed.*, 2012, **51**, 5183–5187 (*Angew. Chem.*, 2012, **124**, 5273–5277); (*c*) H.-G. Cheng, L.-Q. Lu, T. Wang, Q.-Q. Yang, X.-P. Liu, Y. Li, Q.-H. Deng, J.-R. Chen and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2013, **52**, 3250–3254 (*Angew. Chem.*, 2013, **125**, 3332–3336); (*d*) N. Kern, M. Hoffmann, A. Blanc, J.-M. Weibel and P. Pale, *Org. Lett.*, 2013, **15**, 836–839; (*e*) T. Piou, L. Neuville and J. Zhu, *Tetrahedron*, 2013, **69**, 4415–4420; (*f*) A. H. Shinde, S. Vidyacharan and D. S. Sharada, *Tetrahedron Lett.*, 2014, **55**, 3064–3069; (*g*) H. Lu, J. B. Lin, J. Y. Liu and P. F. Xu, *Chem. – Eur. J.*, 2014, **20**, 11659–11663.
7 For a review on this unusual class of natural products, see: S. Khadem and R. J. Marles, *Molecules*, 2012, **17**, 191–206.
8 For the isolation of flavonoids from *Mimosa tenuiflora* (*Mimosa hostilis*), see: (*a*) A. Ohsaki, R. Yokoyama, H. Miyatake and Y. Fukuyama, *Chem. Pharm. Bull.*, 2006, **54**, 1728–1729; (*b*) P. M. Guimarães-Beelen, T. T. Berchielli, R. Beelen, J. Araújo Filho and S. G. de Oliveira, *Sci. Agric.*, 2006, **63**, 522–528; (*c*) T. A. de Sousa Araújo, N. L. Alencar, E. L. C. de Amorim and U. P. de Albuquerque, *J. Ethnopharmacol.*, 2008, **120**, 72–80; (*d*) T. Esatbeyoglu, V. Wray and P. Winterhalter, *J. Agric. Food Chem.*, 2010, **58**, 7820–7830; (*e*) E. Bautista, F. Calzada, A. Ortega and L. Yépez-Mulia, *J. Mex. Chem. Soc.*, 2011, **55**, 251–253.
9 Although we are not aware of any reports detailing the isolation of leucorobinetinidin from *Mimosa tenuiflora* (*Mimosa hostilis*), an unspecified *Mimosa* extract has been shown to contain a high proportion of leucorobinetinidin derived tannins: (*a*) A. Pizzi and A. Stephanou, *J. Appl. Polym. Sci.*, 1993, **50**, 2105–2113; (*b*) A. A. Rahim, E. Rocca, J. Steinmetz, M. J. Kassim, M. S. Ibrahim and H. Osman, *Food Chem.*, 2008, **107**, 200–207. Leucorobinetinidin-derived oligomers have been isolated from the Brazilian legumes *Stryphnodendron obovatum* and *Stryphnodendron adstringens*: (*c*) J. Palazzo de Mello, F. Petereit and A. Nahrstedt, *Phytochemistry*, 1996, **42**, 857–862; (*d*) A. M. D. Zocoler, A. C. C. Sanches, I. Albrecht and J. C. Palazzo de Mello, *Braz. J. Pharm. Sci.*, 2009, **45**, 443–452.
10 For the isolation of leucorobinetinidin from other plants, see: (*a*) D. G. Roux and E. Paulus, *Biochem. J.*, 1962, **82**, 324–329; (*b*) S. E. Drewes and D. G. Roux, *Biochem. J.*, 1964, **90**, 343–350; (*c*) J. Coetzee, J. P. Steynberg, P. J. Steynberg, E. V. Brandt and D. Ferreira, *Tetrahedron*, 1995, **51**, 2339–2352.
11 (*a*) K. Forest, P. Wan and C. M. Preston, *Photochem. Photobiol. Sci.*, 2004, **3**, 463–472; (*b*) A. Wilhelm-Mouton, S. L. Bonnet, Y. Ding, X.-C. Li, D. Ferreira and J. H. van der Westhuizen, *J. Photochem. Photobiol., A*, 2012, **227**, 18–24.
12 (*a*) J. A. Steenkamp, J. P. Steynberg, E. V. Brandt, D. Ferreira and D. G. Roux, *J. Chem. Soc., Chem. Commun.*, 1985, 1678–1679; (*b*) D. A. Young, A. Cronjé, A. L. Botes, D. Ferreira and D. G. Roux, *J. Chem. Soc., Perkin Trans. 1*, 1985, 2521–2527; (*c*) J. P. Steynberg, D. A. Young, J. F. W. Burger, D. Ferreira and D. G. Roux, *J. Chem. Soc., Chem. Commun.*, 1986, 1013–1015.
13 Isolation: (*a*) T. Kanchanapoom, R. Kasai, P. Chumsri, K. Kraisintu and K. Yamasaki, *Tetrahedron Lett.*, 2002, **43**, 2941–2943. Total synthesis: (*b*) K. Hatakayama, K. Ohmori and K. Suzuki, *Synlett*, 2005, 1311–1315.
14 R. S. Khupse, J. G. Sarver, J. A. Trendel, N. R. Bearss, M. D. Reese, T. E. Wiese, S. M. Boue, M. E. Burow, T. E. Cleveland and D. Bhatnagar, *J. Med. Chem.*, 2011, **54**, 3506–3523.
15 T.-J. Ding, X.-L. Wang and X.-P. Cao, *Chin. J. Chem.*, 2006, **24**, 1618–1624.
16 (*a*) J. Clark-Lewis and D. Skingle, *Aust. J. Chem.*, 1967, **20**, 2169–2190; (*b*) H. Kawamoto, F. Nakatsubo and K. Murakami, *J. Wood Chem. Technol.*, 1989, **9**, 35–52; (*c*) N. Vaiana, L. Rizzi, M. G. Pezzano, R. Restelli, F. Rota, S. Stefanini, S. Vicentini and S. Romeo, *Lett. Org. Chem.*, 2007, **4**, 288–291.
17 As the purification of yuremamine from the natural source concluded with reverse phase HPLC using an eluent containing TFA, the natural product has been characterised as its TFA salt.
18 An authentic sample of yuremamine provided by Professor Jouko Vepsäläinen had unfortunately degraded since its isolation. However, we were able to purify this sample and obtain sufficient quantities of yuremamine for NMR analysis, which gave a data set that was identical to that initially reported in 2005 (Table 1).
19 For two fascinating articles that discuss the possibility of two separate structures possessing the same NMR spectrum, see: (*a*) G. Saielli and A. Bagno, *Org. Lett.*, 2009, **11**, 1409–1412; (*b*) L. Song, K.-H. Lee, Z. Lin and R. Tong, *J. Org. Chem.*, 2014, **79**, 1493–1497.
20 See ESI†.
21 Although a small number of long range $^{5}J_{H\rightarrow C}$ couplings have been reported in the literature, they are only observed when lower frequency couplings are specifically targeted by employing extended coupling evolution periods. See: (*a*) R. Araya-Maturana, J. A. Gavín-Sazatornil, J. Heredia-Moya, H. Pessoa-Mahana and B. Weiss-López, *J. Braz. Chem. Soc.*, 2005, **16**, 657–661; (*b*) R. Araya-Maturana, W. Cardona and B. Weiss-López, *Curr. Org. Chem.*, 2001, **5**, 253–263.
22 R. Tschesche, E. U. Kauβman and H.-W. Fehlhaber, *Tetrahedron Lett.*, 1972, **9**, 865–868.
23 For bioinspired total syntheses of natural products that resulted in structural reassignment, see: (*a*) M. J. Wanner, A. W. Velzel and G.-J. Koomen, *J. Chem. Soc., Chem. Commun.*, 1993, 174–175; (*b*) H. Takayama, R. Yamamoto, M. Kurihara, M. Kitajama, N. Aimi, L. Mao and S. Sakai, *Tetrahedron Lett.*, 1994, **35**, 8813–8816; (*c*) F. W. Lichtenthaler, K. Nakamura and J. Klotz, *Angew. Chem., Int. Ed.*, 2003, **42**, 5838–5843 (*Angew. Chem.*, 2003, **115**, 6019–6023); (*d*) C. Hoarau and T. R. Pettus, *Org. Lett.*, 2006, **8**, 2843–2846; (*e*) M. Köck, A. Grube, I. B. Seiple and P. S. Baran, *Angew. Chem., Int. Ed.*, 2007, **46**, 6586–6594 (*Angew. Chem.*, 2007, **119**, 6706–6714); (*f*) I. B. Seiple, S. Su, I. S. Young, C. A. Lewis, J. Yamaguchi and P. S. Baran, *Angew. Chem., Int. Ed.*, 2010, **49**, 1095–1098 (*Angew. Chem.*, 2010, **122**, 1113–1116); (*g*) P. D. Brown, A. C. Willis, M. S. Sherburn and A. L. Lawrence, *Angew. Chem., Int. Ed.*, 2013, **52**, 13273–13275 (*Angew. Chem.*, 2013, **125**, 13515–13517).
24 For recent reviews on biomimetic synthesis, see: (*a*) P. G. Bulger, S. K. Bagal and R. Marquez, *Nat. Prod. Rep.*, 2008, **25**, 254–297; (*b*) M. Razzak and J. K. De Brabander, *Nat. Chem. Biol.*, 2011, **7**, 865–875.