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Total synthesis and ^{13}C NMR revision of nagelamide C[†]

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Nagelamide C (**1**), a dimeric pyrrole-imidazole alkaloid, exhibits antimicrobial and antibacterial activities. We demonstrate herein the first total synthesis of nagelamide C. This concise work was enabled by a series of significant transformations featuring: an imidazole benzylic Wittig olefination, a site selective bromination, and a regioselective *trans*-hydrostannylation/Stille coupling to construct a unique trisubstituted olefin. In addition, we show the original ^{13}C NMR data of nagelamide C to be in error and revise the data.

Introduction

The nagelamide alkaloids, a small family of marine sponge derived metabolites, consist of 26 pyrrole 2-aminoimidazole natural products with monomeric or dimeric frameworks (for a comprehensive list, Q.V. Fig. S1 in ESI[†]).¹ Their biosynthesis is generally rationalized through dimerization, rearrangement, or oxidation from the parent monomeric clathrodin (**2**), hymenidin (**3**), or oroidin (**4**).¹ The structure of nagelamide C (**1**, Fig. 1) was disclosed by Kobayashi and coworkers in 2004, which was isolated in trace amount from extracts of the Okinawan marine sponge *Agelas* sp. (0.00032% yield from 1.3 kg wet sponge).² Structurally, **1** presents an asymmetric skeleton bearing a rare trisubstituted *Z*-olefin wherein two oroidin subunits are joined *via* a single C–C bond at C10 and C15'. Many nagelamide alkaloids have been found to exhibit biological activities, nagelamide C displayed antimicrobial and antibacterial activities against Gram-positive bacteria.²

The fascinating and intriguing structure of nagelamide alkaloids, containing cyclic guanidines, halogenated heterocycles, polar properties and nitrogen-rich skeletons, have been attracting synthetic chemists for decades.³ To date, however, only a few nagelamide alkaloids have been synthesized. In 2006, Horne *et al.* completed the first synthesis of nagelamide A (**5**) and D (**6**) featuring a biomimetic oxidative dimerization.⁴ Baran and coworkers accomplished a collective total synthesis of nagelamide E (**7**), ageliferin (**8**), and sceptrin (**9**).⁵ In 2009, Lovely and coworkers developed an elegant synthesis of putative nagelamide D, in which they found the synthetic sample

did not completely match to the originally isolated spectroscopic data, but it was in good consistency with Horne's synthetic data.⁶ Thus far, the correct structure of **6** still yet to be

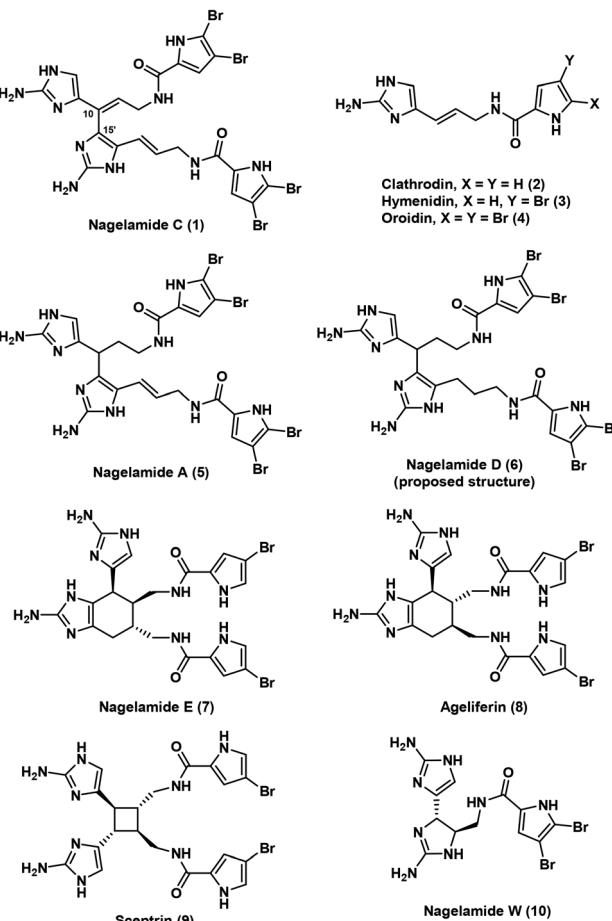


Fig. 1 Representative pyrrole–aminoimidazole alkaloids.

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confirmed. Recently, Tepe achieved the synthesis of nagelamide W (**10**).⁷ Lindel reported the only synthetic study of nagelamide C in 2010.⁸

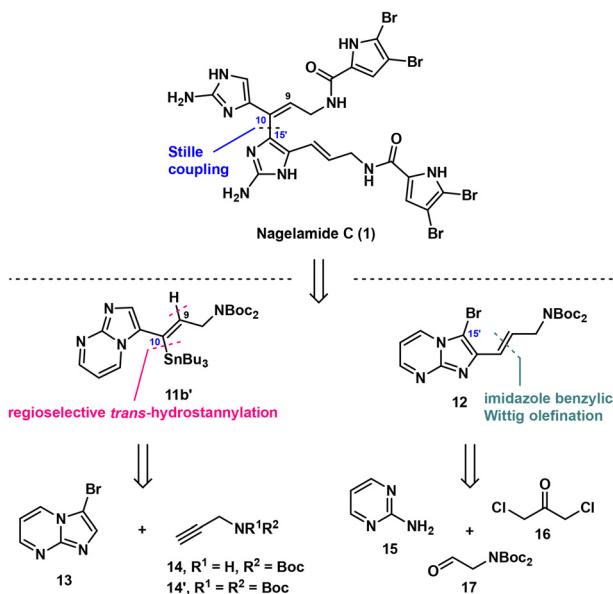
Results and discussion

Our interest in synthesizing dimeric pyrrole-imidazole natural products led to an efficient synthesis of sceptryn.⁹ The challenging structure and interesting activity of **1** drew our attention as synthetic target. As depicted in Scheme 1, a convergent strategy was designed, in which nagelamide C could be cross-coupled through vinylstannane **11b'** and bromide **12**. Based on its proven utility as a building block within the context of these alkaloids, we sought to incorporate functionalized imidazo[1,2-*a*]pyrimidine as a precursor of the 2-aminoimidazole motif.¹⁰ Both **12** and **11b'** could be accessed by imidazole formation or Pd-catalyzed coupling. A sequence of selective bromination followed by Wittig olefination from **15**, **16** and **17** would rapidly construct **12**. To retain *Z*-trisubstituted olefin geometry in the proposed Stille coupling,¹¹ a challenging regioselective *trans*-hydrostannylation¹² was required to properly set the stannane at C10 from the corresponding internal alkyne. The requisite alkyne could be traced back to Sonogashira coupling between 3-bromoimidazo[1,2-*a*]pyrimidine **13** and propargylamines **14**/**14'**.

Our synthesis commenced with the key *trans*-hydrostannylation investigation. Known amide **18** was readily prepared through Sonogashira coupling from commercially available **13** and *N*-Boc propargylamine **14**.¹³ A general hydrostannylation condition¹⁴ was initially performed (Table 1, entry 1). Exposure of **18** to $\text{Bu}_3\text{SnH}/\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ in DCM at ambient temperature afforded *cis*-hydrostannylation product **11a** exclusively in excellent yield (92%). The ruthenium-catalyzed *trans*-hydrostannylation

protocol developed by Fürstner *et al.*¹⁵ was next evaluated. Although the desired stannane **11b** could be observed (12–23% yield), the outcome of the *trans*-hydrostannylation was confronted with poor regioselectivity. Catalysts such as tetrameric $[\text{Cp}^*\text{RuCl}]_4$ and oligomeric $[\text{Cp}^*\text{RuCl}_2]_n$ favored formation of proximal isomer **11c** and **11d** (entries 2 and 3). Presumably, the mono-protected amine ($-\text{NHBOC}$) could form a hydrogen bond with the ruthenium species,^{15d} then drive *trans*-hydrostannylation in favor of proximal adduct **11c** and **11d**. Moreover, $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$ gave **11a** and **11d** as major products (entry 4), the cationic acetonitrile adduct $[\text{Cp}^*\text{Ru}(\text{MeCN})_3]\text{PF}_6$ and $[\text{Cp}^*\text{Ru}(\text{MeCN})_3]\text{PF}_6$ provided *cis*-adduct **11a**/**11c** in modest yields (entries 5 and 6). Accordingly, we devised that installing an additional Boc group on the propargyl amide might improve regioselectivity in two ways: (1) $-\text{NBoc}_2$ lacks an H-bond donor, preventing intermolecular hydrogen bond formation, (2) increasing steric hindrance around C9 might favor the formation of distal adduct **11b'**. Upon treatment of amide **18'** (prepared from **13** and **14'**) with $[\text{Cp}^*\text{RuCl}]_4$ (entry 7), the desired product **11b'** was obtained as an inseparable mixture (50 : 20 : 30) with **11a'** and **11d'** in excellent yield. To our delight, $[\text{Cp}^*\text{RuCl}_2]_n$ polymer further improved regioselectivity of the transformation, and **11b'** was isolated as a 2 : 1 mixture with **11d'** in 89% yield on gram scale (entry 8). $[\text{Cp}^*\text{Ru}(\text{MeCN})_3]\text{PF}_6$ (entry 9), showed similar selectivity compare to $[\text{Cp}^*\text{RuCl}]_4$, while its triflate salt (entry 10) provided no product. Ru-complexes such as $[\text{Cp}^*\text{Ru}(\text{MeCN})_3]\text{PF}_6$, $\text{Cp}^*\text{Ru}(\text{cod})\text{Cl}$, $[\text{Ru}(\text{benzene})\text{Cl}_2]_2$ as well as $[\text{Ru}(\text{p-cymene})\text{Cl}_2]_2$ all provided *cis*-adduct **11a'** as the major isomer in good yields (entries 11–14). Other literature approaches that could access *trans*-hydrostannylation product were also investigated. Both catalytic and stoichiometric Lewis acid dibutyl magnesium^{16a} decomposed starting material (entry 15), while zirconium mediated hydrostannylation^{16b} provided mono-Boc protected **18** (entry 16). Only *cis*-adduct **11a'** was obtained in 53% yield under radical conditions^{16c} (AIBN, entry 17). Switching to Pd $(\text{PPh}_3)_2\text{Cl}_2$, **11a'** was afforded in 93% isolated yield (entry 18).

With sufficient **11b'** in hand, we turned our attention to the construction of bromide **12**. Condensation of 2-aminopyrimidine **15** with 1,3-dichloroacetone **16** under reflux in THF gave the corresponding HCl salt **19**, which underwent water elimination upon treatment with triphenylphosphine (PPh_3) in acetonitrile at 85 °C for 16 h. The resulting precipitates were easily collected and washed with acetone to furnish pure phosphonium salt **20** in 56% yield over two steps. Due to the instability of imidazo[1,2-*a*]pyrimidines towards strong bases, optimization of the benzylic Wittig olefination proved challenging. Inorganic base such as *n*-BuLi, LiHMDS, NaOMe, etc. all led to the decomposition of starting material. NaH, KOt-Bu gave variable and unscalable results. Unlike conventional Wittig reactions where an aldehyde was usually set on the imidazole ring, olefinations using imidazole benzylic phosphonium salt are far less documented.¹⁷ After exhaustive experimentation (Scheme 2B, see ESI† for details), an organic base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was found to be optimal, furnishing the desired olefin **21** in 72% yield as a



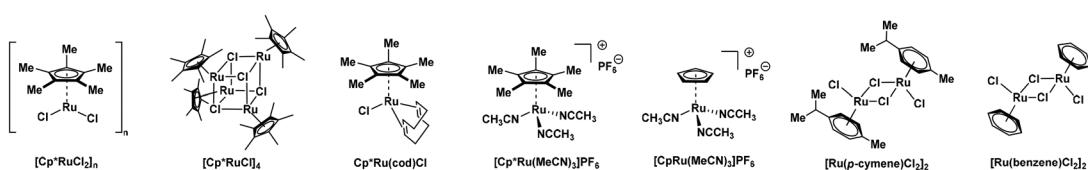
Scheme 1 Synthesis design.



Table 1 Optimization of hydrostannylation^a

Entry	R ¹ , R ²	Conditions	Yield%	11a/11b/11c/11d%
				11a/11b/11c/11d%
1	H, Boc	Pd(PPh ₃) ₂ Cl ₂ (10 mol%), DCM, rt	92	100/0/0/0
2	H, Boc	[Cp [*] RuCl] ₄ (10 mol%), DCM, rt	91	5/23/22/50
3	H, Boc	[Cp [*] RuCl ₂] _n (10 mol%), DCM, rt	84	6/17/21/56
4	H, Boc	Cp [*] Ru(cod)Cl (10 mol%), DCM, rt	88	39/12/18/31
5	H, Boc	[Cp [*] Ru(MeCN) ₃]PF ₆ (10 mol%), DCM, rt	65	64/0/36/0
6	H, Boc	[CpRu(MeCN) ₃]PF ₆ (10 mol%), DCM, rt	69	51/12/37/0
Entry	R ¹ , R ²	Conditions	Yield%	11a'/11b'/11c'/11d'%
				11a'/11b'/11c'/11d'%
7	Boc, Boc	[Cp [*] RuCl] ₄ (10 mol%), DCM, rt	96	20/50/0/30
8	Boc, Boc	[Cp [*] RuCl ₂] _n (10 mol%), DCM, rt	89 ^b	5/63/0/32
9	Boc, Boc	[Cp [*] Ru(MeCN) ₃]PF ₆ (10 mol%), DCM, rt	72	24/47/0/29
10	Boc, Boc	[Cp [*] Ru(MeCN) ₃]OTf (10 mol%), DCM, rt	NR	—
11	Boc, Boc	[CpRu(MeCN) ₃]PF ₆ (10 mol%), DCM, rt	87	71/19/0/10
12	Boc, Boc	Cp [*] Ru(cod)Cl (10 mol%), DCM, rt	82	55/34/0/11
13	Boc, Boc	[Ru(benzene)Cl ₂] ₂ (10 mol%), DCM, rt	69	100/0/0/0
14	Boc, Boc	[Ru(p-cymene)Cl ₂] ₂ (10 mol%), DCM, rt	80	100/0/0/0
15	Boc, Boc	MgBu ₂ (1.0 equiv.), THF, 50 °C	Decom.	—
16	Boc, Boc	ZrCl ₄ (1.0 equiv.), THF, rt	52 ^c	—
17	Boc, Boc	AIBN (10 mol%), THF, 70 °C	53	100/0/0/0
18	Boc, Boc	Pd(PPh ₃) ₂ Cl ₂ (10 mol%), DCM, rt	93 ^d	100/0/0/0

^a Reactions were carried out on 0.1 mmol scale (0.1 M), ratio in the crude reaction mixture was determined by ¹H NMR spectroscopy, 1,3,5-trimethoxybenzene as internal standard. **18** and **18'** were prepared from *N*-Boc-propargylamine and *N,N*-diBoc propargylamine, respectively. ^b The product was isolated in gram scale, 2.4 equiv. *n*Bu₃SnH was used. ^c **18** was isolated as the product. ^d Isolated yield. DCM: dichloromethane, THF: tetrahydrofuran. NR: no reaction.

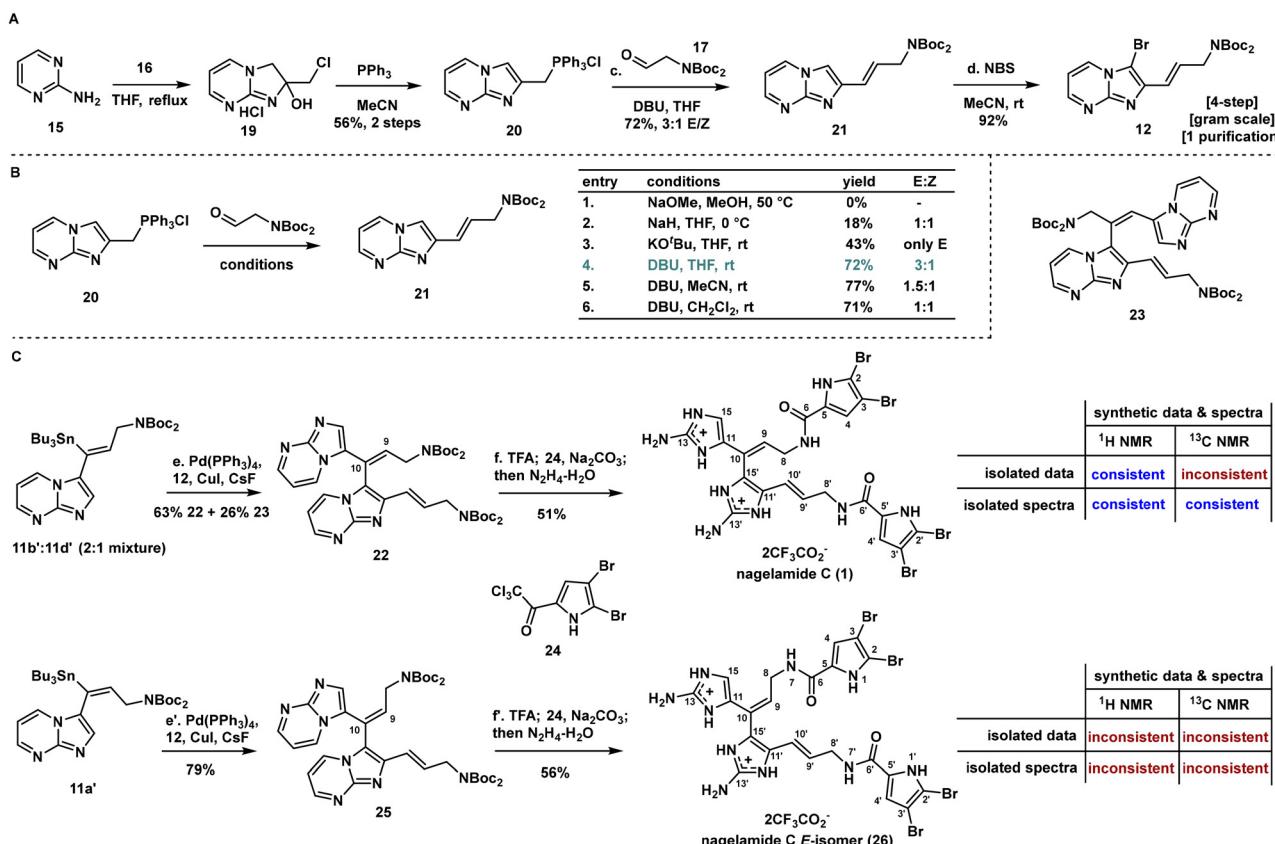


3 : 1 ratio of *E/Z* isomers which were easily separated on silica gel. In addition, when we subjected 3-bromoimidazole phosphonium salt to the same Wittig conditions, protodebromination was observed. Other attempted methods such as Julia-Kocienski olefination, Suzuki coupling/bromination, or cross-metathesis were fruitless (see ESI† for full details). It is noteworthy that a selective bromination on the imidazole ring of **21** was achieved utilizing *N*-bromosuccinimide (NBS) to provide **12** in excellent yield (92%) without any bromination observed on the *E*-olefin. This 4-step sequence could be executed on gram scale and required a single chromatographic purification.

With straight-forward access to the desired building blocks, we pursued the total synthesis of **1**. Pd-catalyzed coupling of **12** and a 2 : 1 mixture of **11b'/11d'** was achieved in the presence of 10 mol% CuI and 2 equiv. of CsF,¹⁸ delivering 63% diene **22** and 26% **23** after chromatograph separation. Boc removal with

TFA followed by acylation with 2,3-dibromo-5-trichloroacetyl-pyrrole (**24**) in the same flask produced the corresponding bis-pyrrole. Polar 2-aminoimidazoles were unveiled following exposure to an excess of hydrazine hydrate, delivering nagelamide C in 51% yield. The ¹H NMR data for synthetic **1** was consistent with the reported ¹H NMR data (Table 2). However, ¹³C NMR data of our synthetic sample was not in agreement with the reported spectroscopic data,² where significant discrepancies were shown on multiple carbons: C8', C9', C10, C10', C11, C11', and C15 (Table 3). Interestingly, the original ¹³C chemical shift of both C8 and C8' were reported as 37.40 ppm. We anticipated that since these two carbons are influenced by different chemical environment, their ¹³C chemical shifts are not likely the same. Besides the 1D & 2D NMR acquisition of synthetic **1**, we also conducted two additional experiments to further determine its structure. 1. Addition of trifluoroacetic acid directly to a solution of free base **1** in DMSO-





Scheme 2 (A) Construction of bromide 12, (B) Optimization of Wittig olefination. (C) Synthesis of nagelamide C and nagelamide C *E*-isomer.

Table 2 ¹H NMR comparison of natural nagelamide C, synthetic nagelamide C, and synthetic nagelamide C *E*-isomer

Proton	Natural nagelamide C ^a	Synthetic nagelamide C ^b	Δδ ^c /ppm	Synthetic <i>E</i> -isomer 26 ^b	Δδ ^c /ppm
1-NH	12.71 (s)	12.72 (d, <i>J</i> = 2.9 Hz)	-0.01	12.74 (d, <i>J</i> = 2.8 Hz)	-0.03
1'-NH	12.68 (s)	12.69 (d, <i>J</i> = 2.8 Hz)	-0.01	12.64 (d, <i>J</i> = 2.8 Hz)	-0.04
4	6.93 (brs)	6.93 (d, <i>J</i> = 2.7 Hz)	0	6.94 (d, <i>J</i> = 2.8 Hz)	-0.01
4'	6.91 (brs)	6.92 (d, <i>J</i> = 2.7 Hz)	-0.01	6.92 (d, <i>J</i> = 2.8 Hz)	-0.01
7-NH	8.46 (t, <i>J</i> = 5.6 Hz)	8.49 (t, <i>J</i> = 5.7 Hz)	-0.03	8.54 (t, <i>J</i> = 5.6 Hz)	-0.08
7'-NH	8.45 (t, <i>J</i> = 5.8 Hz)	8.46 (t, <i>J</i> = 5.8 Hz)	-0.01	8.41 (t, <i>J</i> = 5.8 Hz)	0.04
8	3.96 (m)	3.95 (t, <i>J</i> = 5.7 Hz)	0.01	4.11 (t, <i>J</i> = 6.2 Hz)	-0.05
8'	3.86 (m)	3.86 (t, <i>J</i> = 6.2 Hz)	0	3.89 (t, <i>J</i> = 5.2 Hz)	-0.03
9	6.24 (t, <i>J</i> = 6.7 Hz)	6.25 (t, <i>J</i> = 6.7 Hz)	-0.01	5.90 (t, <i>J</i> = 6.8 Hz)	0.34
9'	6.16 (dt, <i>J</i> = 15.9, 5.9 Hz)	6.17 (dt, <i>J</i> = 16.1, 5.9 Hz)	-0.01	6.17–6.05 (m)	
10'	6.05 (d, <i>J</i> = 15.9 Hz)	6.05 (d, <i>J</i> = 16.0 Hz)	0	6.17–6.05 (m)	
12-NH	12.95 (brs)	12.93 (s)	0.02	12.47 (s)	0.48
12'-NH	13.12 (brs)	13.10 (s)	0.02	12.79 (s)	0.33
13-NH ₂	7.87 (s)	7.86 (s)	0.01	7.66 (s)	0.21
13'-NH ₂	7.73 (s)	7.72 (s)	0.01	7.60 (s)	0.13
14-NH	12.52 (brs)	12.49 (brs)	0.03	12.43 (s)	0.09
14'-NH	12.79 (brs)	12.77 (brs)	0.02	12.57 (s)	0.22
15	6.79 (s)	6.79 (s)	0	7.20 (s)	-0.41

^a In DMSO-d₆ in addition to 1% trifluoroacetic acid, see ref. 2. ^b In DMSO-d₆ and the solvent was referenced at 2.50 ppm. ^c In comparison to the isolation data.

d₆ led to clear observation of *in situ* formation of nagelamide C TFA salt. 2. The ¹H-¹⁵N HSQC and HMBC spectra assisted to characterize all nitrogen atoms and their correlation with related protons. Taken together, all these data supported our structural assignment.

On the other hand, we suspected the reported structure of nagelamide C might be an *E*-isomer at the C9–C10 olefin. To this end, the nagelamide C *E*-isomer (26) was quickly synthesized following the established route to 1. Stannane 11a' (Table 1, entry 18) was employed in the Stille coupling, and

Table 3 ^{13}C NMR comparison of natural nagelamide C, synthetic nagelamide C, and synthetic nagelamide C *E*-isomer

Carbon	Natural nagelamide C ^a	Synthetic nagelamide C ^b	$\Delta\delta^c$ / ppm	Synthetic <i>E</i> -isomer 26 ^b	$\Delta\delta^c$ / ppm
2	104.75	104.84	-0.09	105.04	-0.29
2'	104.64	104.73	-0.09	104.78	-0.14
3	97.83	97.90	-0.07	97.96	-0.13
3'	97.83	97.90	-0.07	97.91	-0.08
4	112.82	112.86	-0.04	112.91	-0.09
4'	112.74	112.72	-0.02	112.64	0.10
5	127.88	127.82	0.06	127.89	-0.01
5'	127.76	127.82	-0.06	127.73	0.03
6	158.75	158.81	-0.06	159.10	-0.35
6'	158.67	158.73	-0.06	158.69	-0.02
8	37.40	37.47	-0.07	37.85	-0.45
8'	37.40	40.24	-2.84	40.58	-3.18
9	129.39	129.47	-0.08	133.05	-3.66
9'	125.39	127.94	-2.55	128.01	-2.62
10	115.85	116.60	-0.75	116.67	-0.82
10'	116.76	115.91	0.85	116.28	0.48
11	123.30	125.45	-2.15	120.70	2.60
11'	116.54	123.37	-6.83	122.47	-5.93
13	148.21	148.23	-0.02	147.59	0.62
13'	148.04	148.07	-0.03	147.57	0.47
15	112.66	112.52	0.14	114.65	-1.99
15'	116.82	116.81	0.01	121.74	-4.92

^a In DMSO-d₆ in addition to 1% trifluoroacetic acid, see ref. 2. ^b In DMSO-d₆ and the solvent was referenced at 39.50 ppm. ^c In comparison to the isolation data.

diene **25** was isolated in 79% yield. Lastly, a sequence of Boc-deprotection, acylation, and pyrimidine deprotection in one pot provided **26** in 56% yield. Both ¹H and ¹³C NMR of **26** are inconsistent with natural nagelamide C's spectroscopic data. In the meantime, we communicated with the original isolation chemists in the Kobayashi group and copies of the ¹H and ¹³C NMR spectra of natural nagelamide C were shared with us. Gratifyingly, the original ¹³C NMR spectra aligned well with our synthetic spectra (see ESI† for the comparison). Thus, the original ¹³C NMR data was revised and the structure of nagelamide C was confirmed.

Conclusions

In conclusion, we have accomplished the first total synthesis of nagelamide C. This concise route (6 longest linear steps from 2-aminopyrimidine) features an imidazole benzylic Wittig olefination, a site selective bromination, and a regioselective *trans*-hydrostannylation/Stille coupling sequence. The bromide **12** developed for this synthesis has a common protected 2-aminoimidazole motif which could be conveniently used to access other nagelamide alkaloids. The ¹³C NMR data of nagelamide C was revised through alignment of our synthetic spectra with the original NMR spectra. Therefore, the structure of **1** was confirmed. We hope the lessons learned here will inform the structural confirmation of other nagelamide alkaloids in the context of total synthesis. Moreover, utilizing bromide **12** to access relevant nagelamide alkaloids are under investigation and will be reported in due course.

Author contributions

All authors have given approval to the final version of the manuscript. G.T. and T.J. conceptualized the work. G.T. performed the experiments and analyzed the data. L.N. conducted exploratory studies and edited the manuscript. T.J. directed the project. The manuscript is written by G.T.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

The authors declare no competing financial interest.

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References

- For nagelamide reviews, see: (a) J. Das, M. R. Bhandari and C. J. Lovely, Isolation, Bioactivity, and Synthesis of Nagelamides, in *Studies in Natural Products Chemistry*, Elsevier B.V., Amsterdam, 2016, vol. 50, pp. 341–371; (b) T. Lindel, Chemistry and Biology of the Pyrrole-Imidazole Alkaloids, *Alkaloids*, 2017, **77**, 117–219.
- T. Endo, M. Tsuda, T. Okada, S. Mitsuhashi, H. Shima, K. Kikuchi, Y. Mikami, J. Fromont and J. Kobayashi, Nagelamides A-H, New Dimeric Bromopyrrole Alkaloids from Marine Sponge Agelas Species, *J. Nat. Prod.*, 2004, **67**, 1262–1267.
- (a) S. Mukherjee, R. Sivappa, M. Yousufuddin and C. J. Lovely, An Approach to the Oxazoline-Containing Fragments of the Oroidin Dimers Nagelamide R and T, *Synlett*, 2010, 817–821; (b) B. Jiang, J. Wang and Z.-G. Huang, Studies toward the Total Synthesis of Nagelamide K, *Org. Lett.*, 2012, **14**, 2070–2073; (c) E. P. Stout, Y.-G. Wang, D. Romo and T. F. Molinski, Pyrrole Aminoimidazole Alkaloid Metabiosynthesis with Marine Sponges Agelas conifera and Styliissa caribica, *Angew. Chem., Int. Ed.*, 2012, **51**, 4877–4881; (d) E. P. Stout,



B. I. Morinaka, Y.-G. Wang, D. Romo and T. D. Molinski, Novo Synthesis of Benzosceptrin C and Nagelamide H from 7-15N-Oroidin: Implications for Pyrrole-Aminoimidazole Alkaloid Biosynthesis, *J. Nat. Prod.*, 2012, **75**, 527–530.

4 S. Tonsiengsom, *Studies toward the Total Synthesis of Alkaloids: Nagelamide A and D, Agelastatin D, Dragmacidin A-C, Sala-cin and Almazoles*, PhD Dissertation, Oregon State University, 2006.

5 (a) D. P. O'Malley, K. Li, M. Maue, A. L. Zografas and P. S. Baran, Total Synthesis of Dimeric Pyrrole-Imidazole Alkaloids: Sceptrin, Ageliferin, Nagelamide E, Oxsceptrin, Nakamuric Acid, and the Axinellamine Carbon Skeleton, *J. Am. Chem. Soc.*, 2007, **129**, 4762–4775; (b) B. H. Northrop, D. P. O'Malley, A. L. Zografas, P. S. Baran and K. N. Houk, Mechanism of the Vinylcyclobutane Rearrangement of Sceptrin to Ageliferin and Nagelamide E, *Angew. Chem., Int. Ed.*, 2006, **45**, 4126–4130.

6 (a) M. R. Bhandari, R. Sivappa and C. J. Lovely, Total Synthesis of the Putative Structure of Nagelamide D, *Org. Lett.*, 2009, **11**, 1535–1538; (b) M. R. Bhandari, A. K. Herath, R. Sivappa, M. Yousufuddin and C. J. Lovely, Total Synthesis of the Nagelamides—Synthetic Studies toward the Reported Structure of Nagelamide D and Nagelamide E Framework, *J. Org. Chem.*, 2020, **85**, 12971–12987.

7 D. George and J. J. Tepe, Total Synthesis of Nagelamide W, *J. Org. Chem.*, 2023, **88**, 9306–9312.

8 N. Jacobi and T. Lindel, Assembly of the Bis(imidazolyl) propene Core of Nagelamides C and S by Double Grignard Reaction, *Eur. J. Org. Chem.*, 2010, 5415–5425.

9 L. V. Nguyen and T. F. Jamison, Total Synthesis of (\pm)-Sceptrin, *Org. Lett.*, 2020, **22**, 6698–6702.

10 For the review, see: (a) R. Goel, V. Luxami and K. Paul, Synthetic approaches and functionalizations of imidazo[1,2-a]pyrimidines: an overview of the decade, *RSC Adv.*, 2015, **5**, 81608–81637 For imidazo[1,2-a]pyrimidine as the precursor of 2-aminoimidazole, see: (b) C. Schroif-Gregoire, N. Travert, A. Zapa-rucha and A. Al-Mourabit, Direct Access to Marine Pyrrole-2-Aminoimidazoles, Oroidin, and Derivatives, via New Acyl-1,2-Dihydropyridin Intermediates, *Org. Lett.*, 2006, **8**, 2961–2964; (c) S. Picon, E. T. H. Dau, M.-T. Martin, P. Retailleau, A. Zaparucha and A. Al-Mourabit, Biomimetically Inspired Short Access to the 2-Aminoimidazole-Fused Tetracyclic Core of (\pm)-Dibromoagelaspongins, *Org. Lett.*, 2009, **11**, 2523–2526; (d) S. Rasa-palli, V. Kumbam, A. N. Dhawane, J. A. Golen, C. J. Lovely and A. L. Rheingold, Total Syntheses of Oroidin, Hymenidin and Clathrodin, *Org. Biomol. Chem.*, 2013, **11**, 4133–4137.

11 (a) J. K. Stille, Palladium Catalyzed Coupling of Organotin Reagents with Organic Electrophiles, *Pure Appl. Chem.*, 1985, **57**, 1771–1780; (b) J. K. Stille, The Palladium-Catalyzed Cross-Coupling Reaction of Organotin Reagents with Organic Electrophiles, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 508–524.

12 For hydrostannylation review, see: M. Alami, A. Hamze and O. Provot, Hydrostannylation of Alkynes, *ACS Catal.*, 2019, **9**, 3437–3466.

13 C. Juillet, L. Ermolenko, D. Boyarskaya, B. Baratte, B. Josselin, H. Nedev, S. Bach, B. I. Iorga, J. Bignon, S. Ruchaud and A. Al-Mourabit, From Synthetic Simplified Marine Metabolite Analogues to New Selective Allosteric Inhibitor of Aurora B Ki-nase, *J. Med. Chem.*, 2021, **64**, 1197–1219.

14 Y. Ichinose, H. Oda, K. Oshima and K. Utimoto, Palladium Catalyzed Hydrostannylation and Hydrogermylation of Acetylenes, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 3468–3470.

15 (a) S. Rummelt and A. Fürstner, Ruthenium-Catalyzed trans-Selective Hydrostannylation of Alkynes, *Angew. Chem., Int. Ed.*, 2014, **53**, 3626–3630; (b) S. Rummelt, K. Radkowski, D.-A. Roșca and A. Fürstner, Interligand Interactions Dictate the Regioselectivity of trans-Hydrometalations and Related Reactions Catalyzed by $[\text{Cp}^*\text{RuCl}]$. Hydrogen Bonding to a Chloride Ligand as a Steering Principle in Catalysis, *J. Am. Chem. Soc.*, 2015, **137**, 5506–5519; (c) D.-A. Roșca, K. Radkowski, L. Wolf, M. Wagh, R. Goddard, W. Thiel and A. Fürstner, Ruthenium-Catalyzed Alkyne trans-Hydrometalation: Mechanistic Insights and Preparative Implications, *J. Am. Chem. Soc.*, 2017, **139**, 2443–2455; (d) H. Sommer, J. Hamilton and A. Fürstner, A Method for the Late-Stage Formation of Ketones, Acyloins, and Aldols from Alkenylstannanes: Application to the Total Synthesis of Paecilonic Acid A, *Angew. Chem., Int. Ed.*, 2017, **56**, 6161–6165.

16 For other *trans*-hydrostannylation method, see: (a) M. Magre, M. Szewczyk and M. Rueping, Magnesium-Catalyzed Stereoselective Hydrostannylation of Internal and Terminal Alkynes, *Org. Lett.*, 2020, **22**, 1594–1598; (b) V. Gevorgyan, J.-X. Liu and Y. Yamamoto, Lewis acid Catalyzed *trans*-hydrostannylation of Acetylenes, *J. Chem. Soc., Chem. Commun.*, 1995, 2405–2406; (c) M. S. Oderinde, R. D. J. Froese and M. G. Organ, 2,2'-Azobis(2-methylpropionitrile)-Mediated Alkyne Hydro Stannylation: Reaction Mechanism, *Angew. Chem., Int. Ed.*, 2013, **52**, 11334–11338.

17 To the best of our knowledge, there is no imidazole benzylic Wittig olefination reported in the literature. Similar reaction see: A. Khan, M. G. Sarwar and A. Ali, Reactivity and Stability of (Hetero)Benzylidene Alkenes via the Wittig Olefination Reaction, *Molecules*, 2024, **29**, 501.

18 S. P. H. Mee, V. Lee and J. E. Baldwin, Stille Coupling Made Easier—The Synergic Effect of Copper(I) Salts and the Fluoride Ion, *Angew. Chem., Int. Ed.*, 2004, **43**, 1132–1132.

