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Total Syntheses of Ningalins D and G

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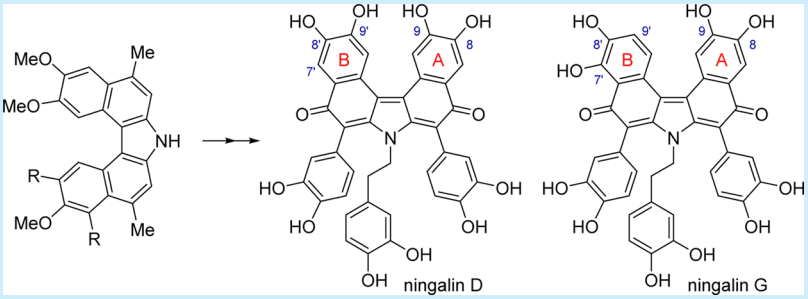
Supporting Information



ABSTRACT: A flexible synthetic strategy for the total syntheses of ningalins D and G is described. The highly effective TMS-OTf/2,6-lutidine-mediated [3,3]-sigmatropic rearrangement of densely loaded dinaphthyl hydrazides and cyclization of the resulting 2,2′-diamino-1,1′-dinaphthyls afforded the key 7*H*-dibenzo[*c*,*g*]carbazole intermediates. Successful conversions to biphenylene quinone methides followed by regioselective brominations completed the total syntheses of the titled marine alkaloids.

Ningalin D is a benzocarbazole marine alkaloid isolated from a western Australian unidentified ascidian belonging to the genus *Didemnum*.[1] Ningalin D contains a biphenylene quinone methide framework with a multiply hydroxylated dibenzocarbazole core containing one dihydroxyphenethyl and two dihydroxyphenyl groups (**1**, Figure 1).[2] Recently, Capon et al. isolated a closely related marine natural product, ningalin G, from an

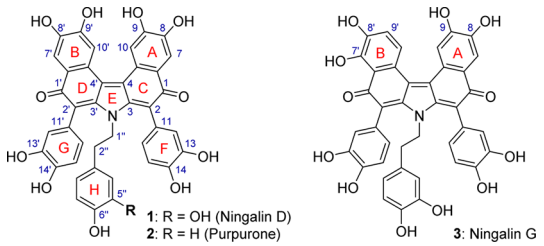


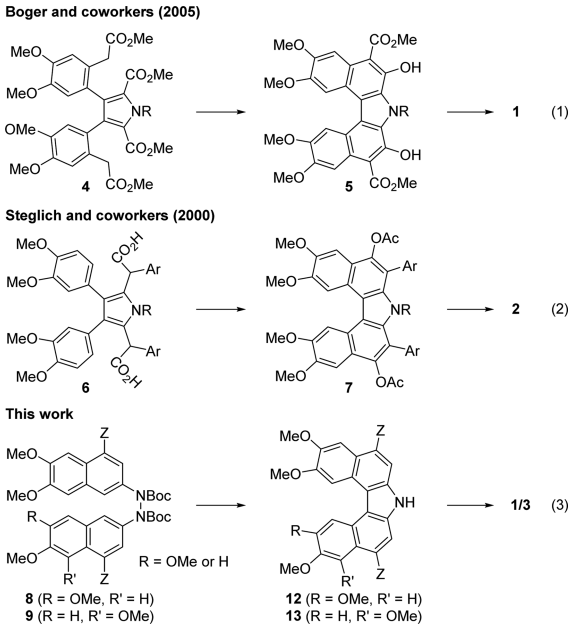
Figure 1. Structures of ningalin D, G, and purpurone.

extract of a Southern Australian marine ascidian, *Didemnum* (**3**, Figure 1).[3] Unlike ningalin D, its hydroxyl groups present in an unsymmetrical pattern (C7′ vs C9′ in ningalin D). Together with other ningalin natural products, ningalins D and G exhibit various intriguing bioactivities ranging from antidiabetic effects to kinase inhibitory activities, as well as multidrug resistance reversal properties.[4] Despite the growing interest in their functions, there are very few synthetic studies regarding these compounds (vide infra).

Specifically, Boger and co-workers reported the only synthetic method for ningalin D.[5] They prepared pyrrole **4** from the cycloaddition product between 1,2-diaryl ethyne with tetrazine dicarboxylate (eq 1, Scheme 1).

Construction of the C and D rings via Dieckmann condensation delivered the key dibenzocarbazole intermediate **5**. Subsequent transformations including Suzuki−Miyaura coupling and Curtius rearrangements completed the total synthesis of ningalin D. Before this work, Steglich and co-workers reported a

Scheme 1. Approaches to Ningalin D and Purpurone



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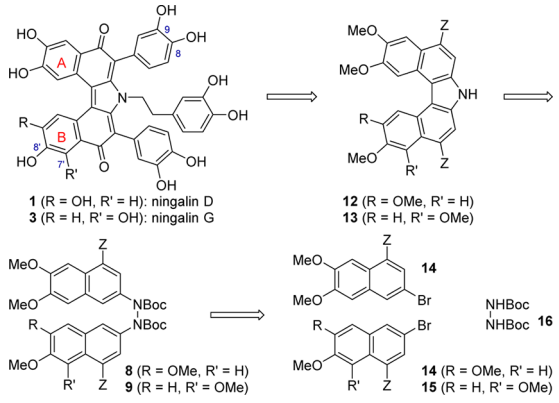
strategy employing pyrrole **6** en route to the total synthesis of purpurone (**2**). In this report, tetra-substituted pyrrole dicarboxylic acid **6** was subjected to Ac_2O/KOAc mediated Friedel–Craft cyclization reactions to construct the C and D rings of dibenzocarbazole intermediate **7** (eq 2).[6] However, there are no reports regarding the synthesis of ningalin G. The unsymmetrical substitution pattern of the hydroxyl groups likely levies an additional synthetic challenge. In accord with our ongoing research program exploring synthetic utilities of aryl hydrazide,[7] we elaborated a flexible synthetic route that provides access to both ningalin D and G by way of highly substituted 7*H*-dibenzo[*c*,*g*]carbazoles **12**/**13**. Herein, we report a TMSOTf/2,6-lutidine catalyzed [3,3]-sigmatropic rearrangement and cyclization of dinaphthyl hydrazides **8**/**9** to key intermediates **12**/**13** and successful transformations for the total syntheses of ningalins D and G (eq 3).

Previously we reported that diaryl hydrazides may undergo acid-catalyzed [3,3]-sigmatropic rearrangements to afford 1,1′-biaryl-2,2′-diamines.[7f,h] Furthermore, the resulting diamines, on isolation or in situ, can cyclize into the corresponding carbazoles, upon heating in acidic media.[7e] Based on these observations, we devised a new synthetic strategy toward ningalins D and G, given the easy access to the key intermediates, 7*H*-dibenzo[*c*,*g*]-carbazole **12**/**13**, from the acid catalyzed [3,3]-sigmatropic rearrangement and cyclization cascade of dinaphthyl hydrazides **10** with proper latent hydroxyl surrogates Z, as illustrated in the retrosynthesis (Scheme 2). It is anticipated that the

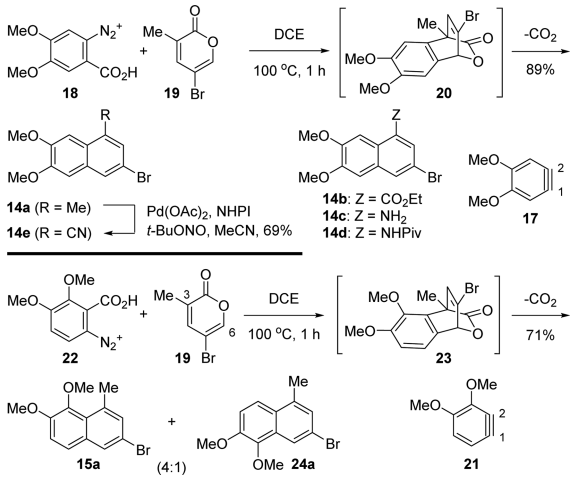
Scheme 2. Retrosyntheses of Ningalins D and G



groups Z para to the reaction sites are likely to affect the pivotal [3,3]-sigmatropic rearrangements of **10**/**11**. Further retrosynthetic analysis calls for naphthyl bromides **14**/**15** with electronically different Z groups and di-*tert*-butyl hydrazine-1,2-dicarboxylate (**16**).

To begin, naphthalene **14a** (Z = Me) was prepared as a starting point for derivatization (Scheme 3). A Diels–Alder reaction of 3-methyl-5-bromo-2-pyrone **19**[8] was implemented with 4,5-dimethoxy-benzyne generated from diazonium salt **18**[9] to give naphthalene **14a** in 89% yield. In this tandem process, the initially formed cycloadduct **20** underwent a retro-Diels–Alder reaction, extruding CO_2. The methyl group was then oxidized to a nitrile (**14e**),[10] before conversion to ester **14b** (Z = CO_2Et), amine **14c** (Z = NH_2), and pivalamide **14d** (Z = NHPiv). Similarly, the synthesis of ningalin G required naphthalene **15a** with two uniquely positioned methoxy groups. Toward this end, a Diels–Alder reaction between 2-pyrone **19** and 3,4-dimethoxy benzyne **23**[11] was carried out, anticipating that cycloadduct **21** would form based on the aryne distortion model.[12] The reaction

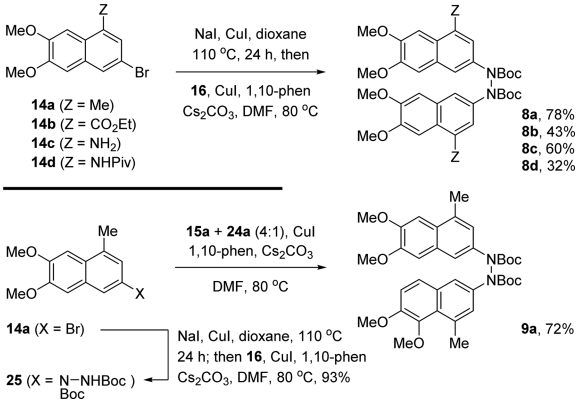
Scheme 3. Preparation of Naphthalene Bromides



indeed proceeded to give **15a** along with regioisomer **24a** as a 4:1 inseparable mixture in 71% combined yield. In this process, the more electron-rich 2-pyrone C6 carbon appeared to attack the more electrophilic C1 carbon of benzyne **21**.[13]

Toward the preparation of diaryl hydrazides **8a**–**8d** with various Z group, naphthyl bromide **14a** was converted into a more reactive iodide via a Finkelstein-type halogen exchange reaction under the protocol developed by Buchwald and co-worker.[14] Subsequent one-pot Cu(I)-catalyzed C–N coupling with di-*tert*-butyl hydrazine-1,2-dicarboxylate (**16**) delivered diaryl hydrazides **8a** – **8d** with various Z groups in good to reasonable yields (Scheme 4). Dinaphthyl hydrazide **9a** with an unsymmetrical

Scheme 4. Synthesis of Diaryl Hydrazides 8a–8d and 9a



substitution pattern around the naphthalene rings was prepared via two successive C–N coupling reactions. Naphthyl hydrazide **25** prepared from **14a** and **16** was then coupled with a 4:1 mixture of naphthyl bromides **15a** and **24a** to give dinaphthyl hydrazide **9a** in 72% yield after isolation.

With dinaphthyl hydrazides **8a**–**8d** and **9a** in hand, we investigated the optimal conditions for the acid-catalyzed [3,3]-sigmatropic rearrangement and cyclization reaction using **8a** as the model substrate under various solvents, acids, and temperatures. The best results were obtained when the reaction was conducted in *n*-PrOH with aqueous HCl under reflux, affording **12a** in 54% yield (entry 1, Table 1). Notably, **8b** with an electron-withdrawing ester group did not give the corresponding carbazole product even after prolonged heating (entry 2). Hydrazides **8c** and **8d** with electron-donating NH_2 and NHPiv

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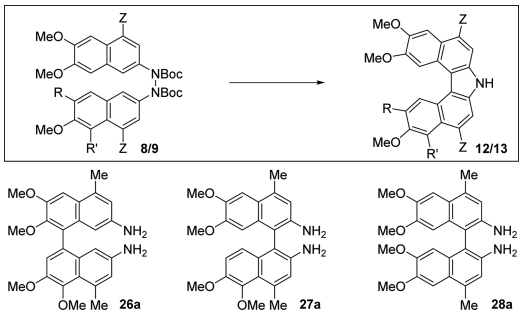
Table 1. IMFIS of 6b under Various Conditions[a]



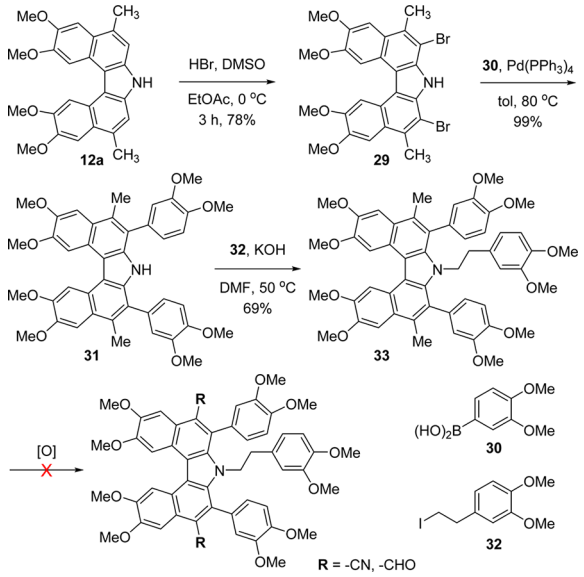
entry	8/9	conditions	results (%)
1	**8a** (R = OMe, R′ = H, Z = Me)	A	**12a** (54)
2	**8b** (R = OMe, R′ = H, Z = CO_2Et)	A	**12b** (trace)
3	**8c** (R = OMe, R′ = H, Z = NH_2)	A	**12c** (36)
4	**8d** (R = OMe, R′ = H, Z = NHPiv)	A	**12d** (38)
5	**9a** (R = H, R′ = OMe, Z = Me)	A	**13a** (24), **26a** (30)
6	**9a** (R = H, R′ = OMe, Z = Me)	B	**13a** (36), **26a** (18)
7	**9a** (R = H, R′ = OMe, Z = Me)	C	**13a** (44), **26a** (21)
8	**9a** (R = H, R′ = OMe, Z = Me)	D	**13a** (85), **26a** (0)
9	**8a** (R = OMe, R′ = H, Z = Me)	D	**12a** (65)

[a]Reaction conditions: (A) HCl (aq) in *n*-PrOH (0.4 M), 120 °C, 12 h; (B) HCl in 1,4-dioxane (0.4 M), rt, 4 h, then *n*-PrOH, 120 °C, 24 h; (C) 0.4 M HCl in dioxane, rt, 4 h, then microwave irradiation, *n*-PrOH, 5 min; (D) TMS-OTf, 2,6-lutidine, 0 °C, 2 h, then microwave irradiation, 5 min.

groups afforded carbazoles **12c** and **12d** in moderate yields of 36% and 38%, respectively (entries 3 and 4). Under the optimized conditions, hydrazide **9a** gave carbazole **13a** in 24% yield in addition to diamine **26a** in 35% yield owing to the unexpected [5,5]-sigmatropic rearrangement (entry 5). Meaningful improvements were observed when the rearrangement was carried out at room temperature before thermal heat or microwave irradiation was applied for the cyclization (entries 6 and 7). Therefore, we opted to unmask the *N*-Boc groups to facilitate the rearrangement at lower temperatures. Surprisingly, treatment with excess TMS-OTf/2,6-lutidine15 at 0 °C gave the corresponding [3,3]-sigmatropic rearrangement product **27a** along with a small amount of carbazole **13a**. Subsequent heating in *n*-PrOH under microwave irradiation afforded carbazole **13a** in 85% overall yield (entry 8). When this procedure was applied with dinaphthyl hydrazide **8a**, an increased yield of **12a** was observed (65%, entry 9).

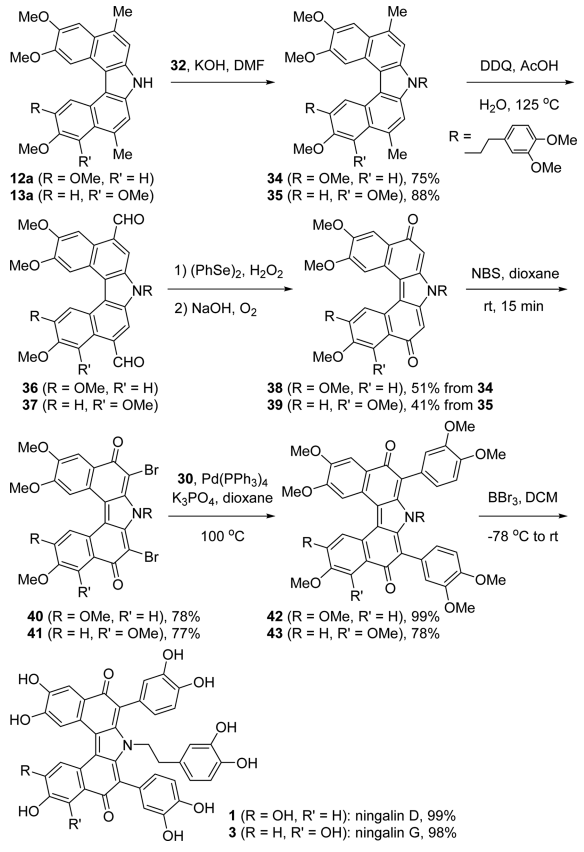
With the efficient synthesis of carbazole **12a** established, we surveyed various literature methods to regioselectively halogenate the C6 and C8 carbons as a prelude for the installation of the F and G rings. After extensive optimization,[16] bromination with HBr in DMSO under modified conditions of those reported by Jiao and co-workers[17] turned out to be the most effective, delivering desired dibromide **29** in a remarkably high yield of 78%, considering the presence of other potentially competing sites (Scheme 5). Suzuki−Miyaura reactions of **29** with (3,4-dimethoxyphenyl)boronic acid (**30**) afforded carbazole **31** with rings G and H in quantitative yield. *N*-Alkylation with 3,4-dimethoxyphenethyl iodide (**32**) gave *N*-3,4-dimethoxyphenethyl dibenzo-carbazole **33**, which contained all necessary groups for the final synthesis. Unfortunately, the oxidation of the methyl groups was problematic. All attempts to convert them into either nitriles[10,18] or aldehydes[19] were unsuccessful, presumably due to the steric impediment of the flanking aryl groups.

Scheme 5. Synthesis and Oxidation of Dibenzocarbazole 33



With no other options remaining, we returned to 7*H*-dibenzo[*c*,*g*]-carbazole **12a** and attempted the methyl group oxidation before installation of the sterically demanding aryl groups (Scheme 6). Accordingly, **12a** was converted into **34** and

Scheme 6. Total Syntheses of Ningalins D and G



subjected to various oxidation conditions. Gratifyingly, the methyl groups were cleanly oxidized to formyl groups when heated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in an aqueous acidic solution under reflux.[20] Subsequent Dakin oxidation

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and hydrolysis of the resulting formate under air gave rise to biphenylene quinone methide **38** in 51% total yield from **34**.[21] Although not anticipated, treatment with 2.0 equiv of NBS under the standard conditions facilitated the remarkably selective dibromination affording dibromide **40** in 78% yield. Subsequent Suzuki−Miyaura coupling with arylboronic acid **30** gave fully decorated biphenylene quinone methide **42** in quantitative yield.[22] Removal of the methyl protecting groups with BBr_3 gave ningalin D in 13% total yield over 10 steps from 3-methyl-5-bromo-2-pyrone **19**. Notably, a simple aqueous workup afforded analytically pure ningalin D in 99% yield, in contrast to the previous approach, which required reversed phase HPLC purification.[23] Following the successful synthesis of ningalin D, we attempted the synthesis of ningalin G by subjecting dibenzocarbazole **13a** to the same reaction sequence used for ningalin D. *N*-Phenethylation and a series of oxidations including DDQ-mediated methyl oxidations and phenylseleninic acid and air oxidations gave **39** in 41% overall yield. Highly regioselective brominations with 2.0 equiv of NBS gave **41** in 78% yield. Subsequent installation of the F and G rings via Suzuki−Miyaura coupling with arylboronic acid **30** afforded fully decorated biphenylene quinone methide **43** in 85% yield. Demethylation of the phenolic alcohol protecting groups gave ningalin G (**3**) in 7% total yield over 10 linear steps from 2-pyrone **19**. Again, a simple aqueous workup afforded analytically pure ningalin G.[24]

In summary, we devised a flexible synthetic strategy that allows for the syntheses of ningalins D and G. The TMS-OTf/2,6-lutidine-mediated [3,3]-sigmatropic rearrangement and cyclization cascades of highly substituted dinaphthyl hydrazides provided rapid access to the key intermediates, 7*H*-dibenzo[*c*,*g*]carbazoles

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02372.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Kang, H.; Fenical, W. *J. Org. Chem.* **1997**, *62*, 3254.

(2) (a) Schmidt, A. W.; Reddy, K. R.; Knölker, H.-J. *Chem. Rev.* **2012**, *112*, 3193. (b) Chan, G. W.; Francis, T.; Thureen, D. R.; Offen, P. H.; Pierce, N. J.; Westley, J. W.; Johnson, R. K.; Faulkner, D. J. *J. Org. Chem.* **1993**, *58*, 2544.

(3) Plisson, F.; Conte, M.; Khalil, Z.; Huang, X.-C.; Piggott, A. M.; Capon, R. J. *ChemMedChem* **2012**, *7*, 983.

(4) (a) Bailly, C. *Mar. Drugs* **2015**, *13*, 1105. (b) Sugumaran, M.; Robinson, W. E. *Mar. Drugs* **2010**, *8*, 2906. (c) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264. (d) Chou, T.-C.; Guan, Y.; Soenen, D. R.; Danishefsky, S. J.; Boger, D. L. *Cancer Chemother. Pharmacol.* **2005**, *56*, 379.

(5) Hamasaki, A.; Zimpleman, J. M.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 10767.

(6) Peschko, C.; Steglich, W. *Tetrahedron Lett.* **2000**, *41*, 9477.

(7) (a) Park, J.; Kim, D.-H.; Das, T.; Cho, C.-G. *Org. Lett.* **2016**, *18*, 5098. (b) Lim, B.-Y.; Jung, B.-E.; Cho, C.-G. *Org. Lett.* **2014**, *16*, 4492. (c) Park, J.; Kim, S.-Y.; Kim, J.-E.; Cho, C.-G. *Org. Lett.* **2014**, *16*, 178. (d) Park, I.-K.; Park, J.; Cho, C.-G. *Angew. Chem., Int. Ed.* **2012**, *51*, 2496. (e) Lim, B.-Y.; Choi, M.-K.; Cho, C.-G. *Tetrahedron Lett.* **2011**, *52*, 6015. (f) Suh, S.-E.; Park, I.-K.; Lim, B.-Y.; Cho, C.-G. *Eur. J. Org. Chem.* **2011**, *2011*, 455. (g) Kim, H.-Y.; Lee, W.-J.; Kang, H.-M.; Cho, C.-G. *Org. Lett.* **2007**, *9*, 3185. (h) Lim, Y.-K.; Jung, J.-W.; Lee, H.; Cho, C.-G. *J. Org. Chem.* **2004**, *69*, 5778.

(8) (a) Cho, H.-K.; Tam, N. T.; Cho, C.-G. *Bull. Korean Chem. Soc.* **2010**, *31*, 3382. (b) Ryu, K.; Cho, Y.-S.; Jung, S.-I.; Cho, C.-G. *Org. Lett.* **2006**, *8*, 3343.

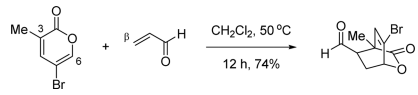
(9) (a) Dockendorff, C.; Sahli, S.; Olsen, M.; Milhau, L.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 15028. (b) Pérez, D.; Guitián, E.; Castedo, L. *J. Org. Chem.* **1992**, *57*, 5911.

(10) Shu, Z.; Ye, Y.; Deng, Y.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 10573.

(11) Gómez, B.; Martín, G.; Guitián, E.; Castedo, L.; Saá, J. M. *Tetrahedron* **1993**, *49*, 1251.

(12) Medina, J. M.; Mackey, J. L.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 15798 and references cited therein.

(13) 3-Methyl-5-bromo-2-pyrone (**19**) undergoes a highly regioselective Diels−Alder reaction with acrolein to afford the corresponding cycloadduct as a result of the preferred interaction between the electronically rich C6 of 2-pyrone and deficient (more electrophilic) *β*-carbon of dienophile (see ref 8b for details).



(14) Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 14844.

(15) Chen, L.-A.; Wang, C.-F.; Gin, M.-G.; Zhang, J.-L.; Huang, P.-Q.; Wang, A.-E. *Asian J. Org. Chem.* **2013**, *2*, 294.

(16) (a) Majetich, G.; Hicks, R.; Reister, S. *J. Org. Chem.* **1997**, *62*, 4321. (b) Racys, D. T.; Sharif, S. A. I.; Pimlott, S. L.; Sutherland, A. *J. Org. Chem.* **2016**, *81*, 772.

(17) Song, S.; Sun, X.; Li, X.; Yuan, Y.; Jiao, N. *Org. Lett.* **2015**, *17*, 2886.

(18) (a) Liu, J.; Zheng, H.-X.; Yao, C.-Z.; Sun, B.-F.; Kang, Y.-B. *J. Am. Chem. Soc.* **2016**, *138*, 3294. (b) Guo, S.; Wan, G.; Sun, S.; Jiang, Y.; Yu, J.-T.; Cheng, J. *Chem. Commun.* **2015**, *51*, 5085.

(19) (a) Mal, D.; Roy, J. *Tetrahedron* **2015**, *71*, 1247. (b) Thomas, C.; Knölker, H. J. *Tetrahedron Lett.* **2013**, *54*, 591. (c) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2001**, *123*, 3183.

(20) Lee, H.; Harvey, R. G. *J. Org. Chem.* **1988**, *53*, 4587.

(21) (a) Dakin, H. D. *Am. Chem. J.* **1909**, *42*, 477. (b) Friedmann, C. J.; Ay, S.; Bräse, S. *J. Org. Chem.* **2010**, *75*, 4612. (c) Abe, T.; Ikeda, T.; Choshi, T.; Hibino, S.; Hatae, N.; Toyata, E.; Yanada, R.; Ishikura, M. *Eur. J. Org. Chem.* **2012**, *2012*, 5018.

(22) The reported ^{13}C NMR spectrum of permethyl ningalin D (**42**) has 12 methyl peaks (ref 5). On the other hand, our sample shows 6 well-resolved methyl peaks under an identical ^{13}C NMR setup.

(23) In the synthesis reported by Boger and co-workers, reversed phase HPLC purification might have been necessary due to the possible presence of inseparable impurities with permethylated ningalin D **42**.

(24) All spectral data are consistent with the structure. However, a discrepancy in ^{13}C NMR spectrum was noticed; we observed C1′ carbonyl resonance at δ190.3, while none was reported in the literature (ref 3). See Supporting Information for details.

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