Organic LETTERS

Letter

pubs.acs.org/OrgLett

Synthesis of the BCD Tricyclic Core of Densanins A and B

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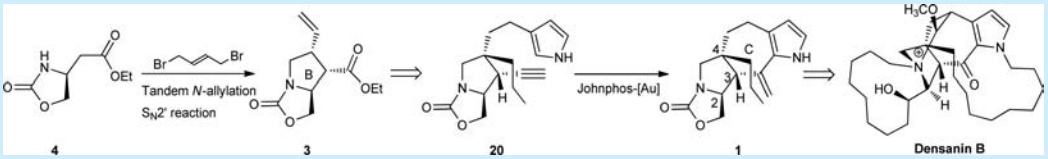
Supporting Information



ABSTRACT: A substrate stereocontrolled synthesis of the BCD tricyclic ring system of densanins A and B has been developed. The key transformations include the assembling of ring B via an unprecedented tandem N-allylation/S_N2' reaction and the construction of ring C via gold-catalyzed alkenylation of terminal alkyne and pyrrole.

Macrocyclic diamine alkaloids are believed to be produced by marine sponges via a common biogenesis from simple bispyridine macrocycles.[1] Considerable synthetic interests have been attracted to the total synthesis and biosynthesis of such alkaloids because of their unique architecture and bioactivities.[2] Densanins A and B (Figure 1), reported by Rho and co-workers

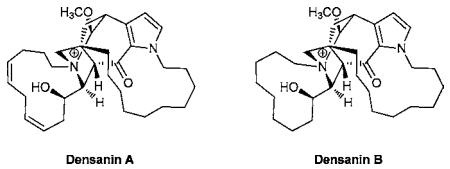
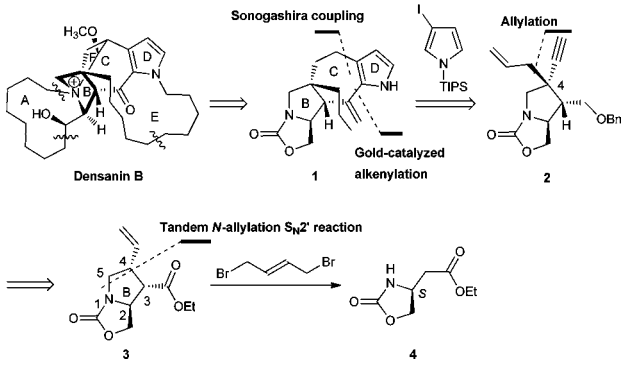


Figure 1. Densanins A and B.

in 2012, are produced by the sponge *Haliclona densaspicula*, displaying moderate inhibitory effect to lipopolysaccharide-induced nitric oxide production in BV2 microglial cells with an IC_{50} of 1.05 and 2.14 μM, respectively. The structures of densanins have been elucidated to be fused hexacyclic diamine alkaloids with an unprecedented tricyclic core consisting of jointed multisubstituted pyrrolidine, cycloheptanone, and pyrrole.[3] The inherent difficulty of constructing adjacent chiral centers and a functionally complex ring system makes the synthesis of densanins a challenging task. Herein, we report a concise, substrate stereocontrolled synthesis of the BCD tricyclic core of densanins.

As illustrated in the retrosynthetic analysis (Scheme 1), our strategy features a late-stage formation of rings A, E, and F via amidation, RCM reaction, and hemiaminal formation from a BCD tricycle intermediate. The formation of ring C could be readily accomplished by an elegant gold-catalyzed alkenylation of terminal alkyne and pyrrole.[4] Pyrrole ring D, theoretically, could be prepared via Sonogashira coupling of 3-iodopyrrole with alkyne **2**, which could be synthesized from pyrrolidine **3** after a

Scheme 1. Retrosynthetic Analysis



series of functional group transformations and allylation on the C-4 position. Disconnection of **3** at N-1/C-5 and C-3/C-4 gives enantiopure starting material **4**,[5] in which the NH and α position of ester could react with (*E*)-1,4-dibromo-2-butylene to form the N-1/C-5 and C-3/C-4 bonds via N-allylation followed by S_N2' reaction. The major advantage of this disconnection is that the chiral amine moiety can be preserved as a chiral auxiliary to control the newly generated C-3 and C-4 chiral centers.

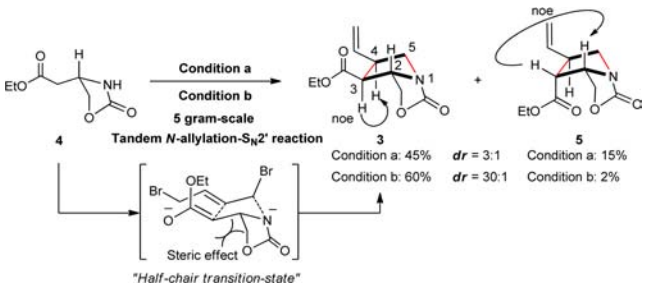
Intramolecular S_N2' reactions have been successfully applied to the synthesis of vinylcyclopropanes, cyclobutane, cyclopentane, cyclohexane, and O, N, and S heterocycles,[6] yet no tandem N-allylation/S_N2' process is evident in the literature. As both N-allylation and S_N2' reactions can be conducted under alkaline conditions, a tandem process is highly possible if the reaction is carried out under appropriate conditions. To our delight, when this reaction was carried out in DMF at −30 to −20 °C in the presence of NaH, pyrrolidines **3** and **5** were produced

Received: March 3, 2016
Published: April 11, 2016

DOI: 10.1021/acs.orglett.6b00606
Org. Lett. 2016, 18, 1949−1951

in a 45 and 15% yield, respectively. Notably, it appears that the ratio of **5** to **3** increases with the extension of reaction time and elevation of reaction temperature, suggesting that **5** is mainly produced by the isomerization of **3**. To mitigate this isomerization reaction, the N-allylation reaction was first carried out at −45 °C, and then the reaction solution was cooled to −58 °C followed by the addition of LiHMDS, ultimately affording pyrrolidine **3** in a 60% yield with 30:1 dr (Scheme 2). The relative

Scheme 2. Synthesis of Ring B via a Tandem N-Allylation/S_N2' Reaction[a]

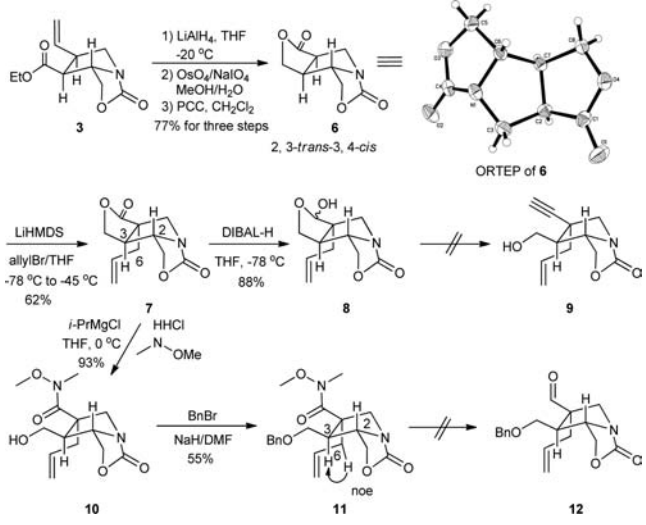


[a]Condition a: 2.4 equiv of NaH, 1.1 equiv of (*E*)-1,4-dibromo-2-butylene, −30 to −20 °C, 5 h. Condition b: 1.5 equiv of NaH, 1.1 equiv of (*E*)-1,4-dibromo-2-butylene, −45 °C, 3 h then cooled to −58 °C, 2.0 equiv, LiHMDS, 4 h.

configuration of major isomer **3** has been determined to be 2,3-*trans*-3,4-*cis*, and minor isomer **5** has been determined to be 2,3-*cis*-3,4-*trans* by NOEDS analysis. The excellent diastereoselectivity exhibited in this chemistry can originate from two factors: (1) the steric effect between the 1,2-oxazolidone ring and 3-ester leads to the 2,3-*trans* configuration; and (2) a more stable, half-chair transition state of pyrrolidine is present, resulting in the 3,4-*cis* configuration. Further efforts aiming to improve the yield and diastereoselectivity by changing solvent (THF/toluene/DMSO), base (LiHMDS/NaHMDS/KH), and temperature (−78 to 0 °C) appear to be futile.

With pyrrolidine **3** in hand, we next attempted to install the quaternary carbon center at C-4 with desired stereoconfiguration then to convert the ester group to alkyne for Sonogashira coupling. As described in Scheme 3, the reduction of ester to

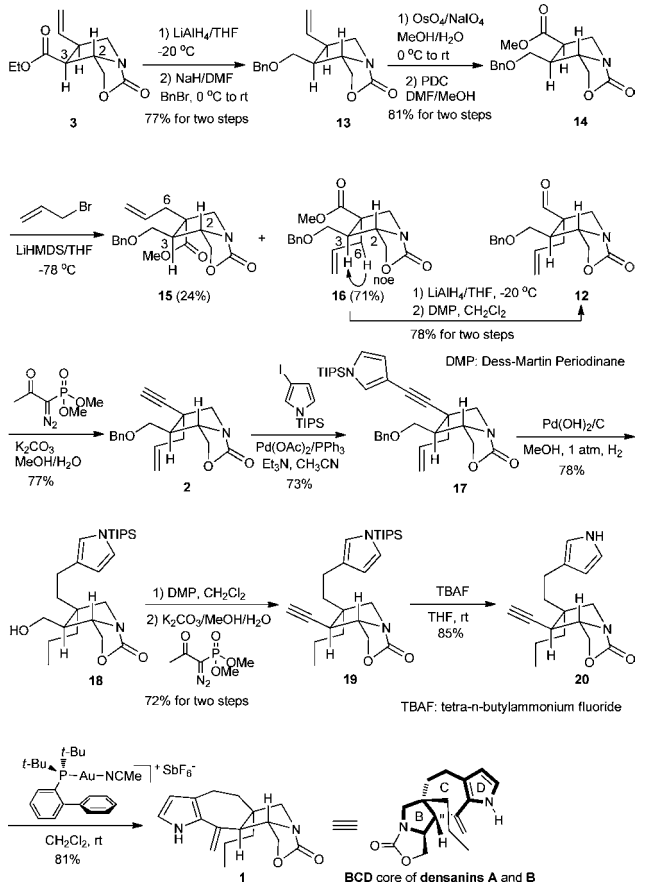
Scheme 3. Attempted Synthesis of Alkyne 2



alcohol with $LiAlH_4$/THF at −20 °C followed by cleavage of the double bond with OsO_4/$NaIO_4$ in aqueous methanol afforded an acetal, which can be oxidized by PCC in CH_2Cl_2 to give lactone **6** in a 77% yield as a white crystal. The X-ray analysis of **6** further confirmed that pyrrolidine **3** possesses a 2,3-*trans*-3,4-*cis* relative configuration. Treatment of **6** with LiHMDS in dry THF at −78 °C followed by the addition of allylBr affords product **7** in a 62% yield as a single isomer. Although the configuration of **7** was not determined at this time because the H-2, H-3, and H-6 are not separable on ^1H NMR spectrum, we believe that the configuration of C-4 should be correct as the C-3 methylol and C-4 formate ester of lactone backbone favor *cis* configuration. Reduction of lactone **7** with DIBAL-H in CH_2Cl_2 at −78 °C gives acetal **8** in an 88% yield. However, treating **8** with $TMSCHN_2$/LDA[7] and Bestmann−Ohira reagent/K_2CO_3[8] failed to produce alkyne **9**. We next opened the lactone with Weinreb amine, which gives Weinreb amide **10** in a 93% yield. Protecting alcohol **10** with a benzyl group affords **11** in 55% yield. The H-2, H-3, and H-6 of **11** are separable on the ^1H NMR spectrum, and subsequent NOEDS analysis proved that the configuration of C-4 is correct. Unfortunately, the reduction of Weinreb amide **11** with $LiAlH_4$[9] or DIBAL-H[10] did not afford aldehyde **12** (Scheme 3).

Even though the lactone backbone remarkably improves the diastereoselectivity of allylation, the conversion of lactone to alkyne seems to be difficult. To circumvent this obstacle, we synthesized ester **14** from **3** via ester reduction, followed by benzyl protection of alcohol and cleavage of the double bond to aldehyde, which was then converted to ester (Scheme 4). The

Scheme 4. Synthesis of the BCD Core of Densanins A and B



DOI: 10.1021/acs.orglett.6b00606
Org. Lett. 2016, 18, 1949−1951

incorporation of a C-4 quaternary carbon center was achieved by the allylation reaction on the α position of ester with LiHMDS/allylBr in THF at −78 °C, affording **15** and **16** in a 24 and 71% yield, respectively. The relative configuration of allyl group was determined by NOEDS analysis. Although the overall diastereoselectivity is not as promising as we expected, the 71% isolated yield of **16** is acceptable. Ester **16** was transformed to aldehyde **12**, followed by conversion to alkyne by Bestmann−Ohira reagent, affording **2** in a 60% yield over three steps. The pyrrole ring D was then assembled via a Sonogashira reaction of 3-iodo-1-(triisopropylsilyl)pyrrole with alkyne **2**, affording **17** in a 73% yield. Deprotection of benzyl and reduction of vinyl and alkynyl groups of **17** by hydrogenation afforded **18** in a 78% yield. Alcohol **18** was then converted to alkyne **19** by Dess−Martin oxidation followed by treatment with Bestmann−Ohira reagent. Subsequent TIPS deprotection generates **20** as the substrate for gold-catalyzed alkenylation. To our delight, when **20** was treated with Johnphos-[Au] in dry CH_2Cl_2 under N_2 atmosphere at room temperature for 30 min, the BCD tricycle intermediate **1** was obtained in an 81% yield.

In summary, we have developed an efficient approach to the synthesis of the BCD tricyclic core of densanins. Our strategy employs a substrate stereocontrolled tandem N-allylation/S_N2' reaction to generate the key intermediate 2,3-*trans*-3,4-*cis* trisubstituted pyrrolidine, allylation of the α position of ester to installation of the C-4 quaternary stereocenter, and gold-catalyzed alkenylation to construct the seven-membered ring C. Application of this strategy to the total synthesis of densanin B is currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00606.

Experimental procedures for the preparation of new compounds, including spectral data (PDF)
X-ray data for compound **6** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the financial support from National Natural Science Foundation of China (21372149, 21572125), Shaanxi Provincial Natural Science Foundation (2015JM2053), Ministry of Education of the People's Republic of China (GK20150303, GK201503028, GK261001247), and Shaanxi Normal University.

■ REFERENCES

(1) (a) Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 6404. (b) Rodriguez, J. *Studies in Natural Products Chemistry*; Elsevier: New York, 2000; p 573 and refs cited therein. (c) Jimenez, J. I.; Goetz, G.; Mau, C. M. S.; Yoshida, W. Y.; Scheuer, P. J.; Williamson, R. T.; Kelly, M. *J. Org. Chem.* **2000**, *65*, 8465. (d) Jang, K. H.; Kang, G. W.; Jeon, J.-E.; Lim, C.; Lee, H.-S.; Sim, C.-J.; Oh, K.-B.; Shin, J. *Org. Lett.* **2009**, *11*, 1713. (e) Kubota, T.; Kamijyo, Y.; Takahashi- Nakaguchi, A.; Fromont, J.; Gonoi, T.; Kobayashi, J. *Org. Lett.* **2013**, *15*, 610.

(2) (a) Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425. (b) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866. (c) Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584. (d) Garg, N. K.; Hiebert, S.; Overman, L. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 2912. (e) Becker, M. H.; Chua, P.; Downham, R.; Douglas, C. J.; Garg, N. K.; Hiebert, S.; Jaroch, S.; Matsuoka, R. T.; Middleton, J.A.; Ng, F. W.; Overman, L. E. *J. Am. Chem. Soc.* **2007**, *129*, 11987. (f) Toma, T.; Kita, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 10233. (g) Defant, A.; Mancini, I.; Raspor, L.; Guella, G.; Turk, T.; Sepcic, K. *Eur. J. Org. Chem.* **2011**, *2011*, 3761. (h) Ballette, R.; Perez, M.; Proto, S.; Amat, M.; Bosch, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 6202.

(3) Hwang, B. S.; Oh, J. S.; Jeong, E. J.; Sim, C. J.; Rho, J. R. *Org. Lett.* **2012**, *14*, 6154.

(4) Selected gold-catalyzed intramolecular reaction of indole or pyrrole with internal alkyne: (a) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105. (b) Gruit, M.; Michalik, D.; Tillack, A.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7212. (c) Pan, B.; Lu, X. D.; Wang, C. X.; Hu, Y. C.; Wu, F.; Wan, B. S. *Org. Lett.* **2014**, *16*, 2244.

(5) Enantiopure compound **4** could be easily prepared with commercially available chemical (*S*)-3-Cbz-amino-γ-butyrolactone. See: Franklin, A. I.; Bensa, D.; Adams, H.; Coldham, I. *Org. Biomol. Chem.* **2011**, *9*, 1901.

(6) (a) For a review of an intramolecular S_N2' reaction: Paquette, L. A.; Stirling, C. J. M. *Tetrahedron* **1992**, *48*, 7383. (b) Kim, D.; Choi, W. J.; Hong, J. Y.; Park, I. Y.; Kim, Y. B. *Tetrahedron Lett.* **1996**, *37*, 1433. (c) Kim, D.; Lim, J. I.; Shin, K. J.; Kim, H. S. *Tetrahedron Lett.* **1993**, *34*, 6557. (d) Jo, H.; Lee, J.; Kim, H.; Kim, S.; Kim, D. *Tetrahedron Lett.* **2003**, *44*, 7043. (e) Lee, J. K.; Hong, J. Y. *J. Org. Chem.* **2004**, *69*, 6433. (f) Lee, K.; Kim, H. S.; Hong, J. Y. *Org. Lett.* **2009**, *11*, 5202. (g) Kim, H.; Baker, J. B.; Lee, S. U.; Park, Y.; Bolduc, K. L.; Park, H. B.; Dickens, M. G.; Lee, D. S.; Kim, Y. C.; Kim, S. H.; Hong, J. Y. *J. Am. Chem. Soc.* **2009**, *131*, 3192.

(7) Primdahl, K. G.; Tungen, J. E.; Aursnes, M.; Hansen, T. V.; Vik, A. *Org. Biomol. Chem.* **2015**, *13*, 5412.

(8) Casavant, B. J.; Khoder, Z. M.; Berhane, I. A.; Chemler, S. R. *Org. Lett.* **2015**, *17*, 5958.

(9) (a) Mali, S. M.; Bandyopadhyay, A.; Jadhav, S. V.; Kumar, M. G.; Gopi, H. N. *Org. Biomol. Chem.* **2011**, *9*, 6566. (b) Crich, D.; Xu, H. D.; Kenig, F. *J. Org. Chem.* **2006**, *71*, 5016.

(10) (a) Calter, M. A.; Liao, W. S.; Struss, J. A. *J. Org. Chem.* **2001**, *66*, 7500. (b) Ghosh, A. K.; Gong, G. L. *Org. Lett.* **2007**, *9*, 1437.

DOI: 10.1021/acs.orglett.6b00606
Org. Lett. 2016, 18, 1949−1951