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SYNTHETIC STUDIES ON DENSANINS: STEREOSELECTIVE CONSTRUCTION OF A PYRROLIDINE RING CONTAINING A QUATERNARY CARBON

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Abstract – We disclose our synthetic studies on densanins, which feature the stereoselective cycloaddition of a cycloheptenone and an azomethine ylide to construct a pyrrolidine ring containing a quaternary carbon.

Natural products featuring a nitrogen-containing polycyclic core fused with macrocyclic rings have been isolated from sponges.[1] Densanins A (**1**) and B (**2**) are examples of such molecules that have been isolated from the sponge *Haliclona densaspicula* by Rho and coworkers in 2012 (Figure 1).[2] The core structure of densanins is a cycloheptanone ring fused with two heterocycles, a pyrrolidine and a pyrrole. The nitrogen atom in the pyrrolidine forms a quaternary ammonium cation as well as an *N*,*O*-acetal. The nitrogen atom in the pyrrole is substituted with a 10-carbon bridge that is connected to the quaternary carbon in the pyrrolidine ring, forming a macrocyclic ring. The structures of densanins A and B differ in the nature of the macrocyclic ring fused with the pyrrolidine ring. These intriguing structural features make densanins attractive synthetic targets. Yang and coworkers reported their synthetic studies on densanins in 2016,[3] but no total synthesis of densanins has been reported to date. Herein, we disclose our synthetic studies on densanins that resulted in the stereoselective construction of a tricyclic system containing a cycloheptanone fused with a pyrrolidine ring and a macrocyclic ring.

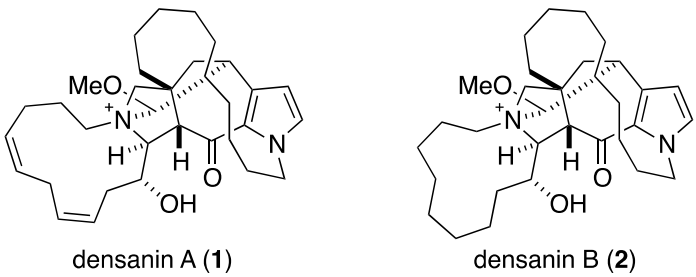
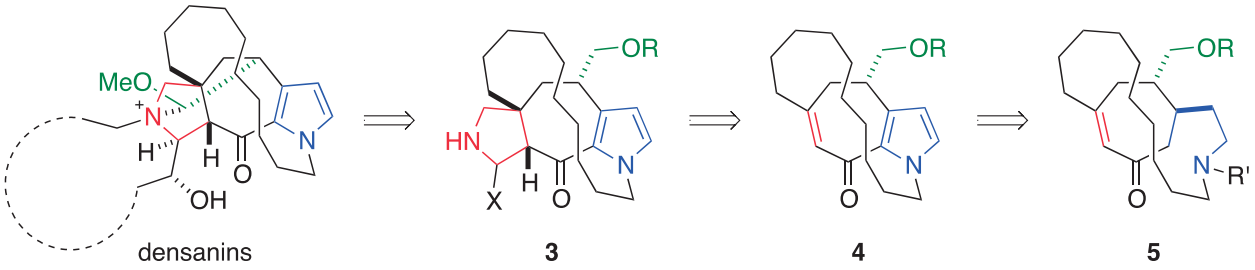


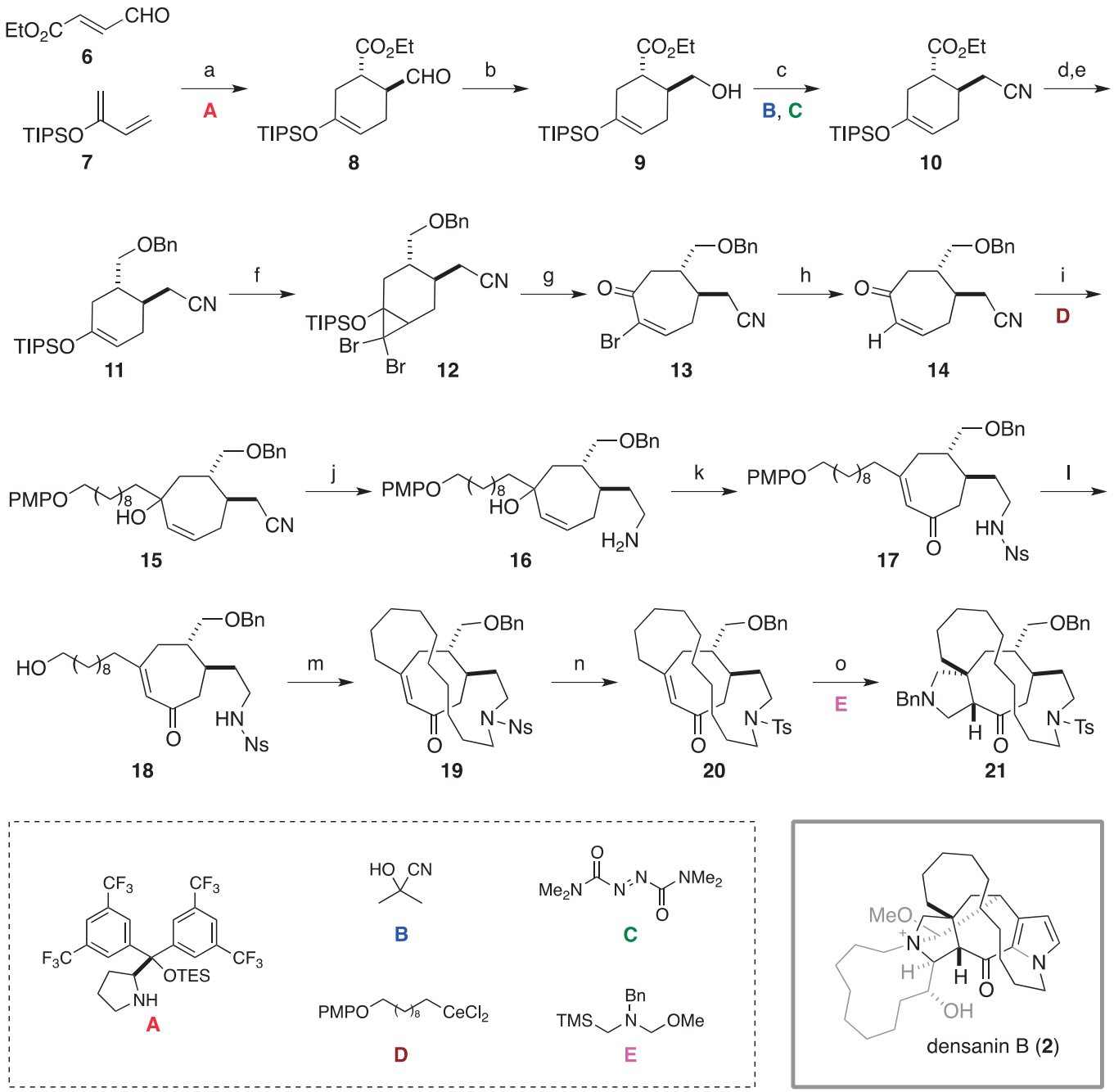
Figure 1. Structures of Densanins A and B

Our retrosynthetic analysis is shown in Scheme 1. We envisioned that the *N*,*O*-acetal moiety and the pyrrolidine-fused macrocyclic ring would be formed at a later stage of the synthesis. The pyrrolidine ring in intermediate **3** would be constructed from cycloheptenone **4**, with the stereochemistry of the reaction controlled by steric hindrance of the 10-carbon bridge that forms a macrocyclic ring.[4] Cleavage of the C–N bond in the pyrrole in **4** would lead to **5**, in which the bridge is connected to the cycloheptenone ring via a stereogenic center that would control the atropisomerism of the resultant bridge in **4**.



Scheme 1. Retrosynthetic Analysis

Our synthetic studies commenced with the preparation of a cycloheptenone bearing two contiguous stereogenic centers (Scheme 2). A Diels-Alder reaction between aldehyde **6** and siloxydiene **7** was carried out using the Hayashi-Jørgensen catalyst (**A**).[5,6] After reduction of the aldehyde moiety in cyclohexene **8** with sodium borohydride, a cyano group was introduced via a Mitsunobu reaction employing acetone cyanohydrin (**B**) and *N*,*N*,*N'*,*N'*-tetramethylazodicarboxamide (TMAD, **C**).[7] After selective reduction of the ester moiety in **10** with lithium aluminum hydride in tetrahydrofuran (THF) at 0 °C, the resultant primary alcohol was protected as its benzyl ether. The cyclohexene ring in **11** was then expanded to a cycloheptene ring using a 2-step approach.[5] Dibromocyclopropanation of **11** under usual conditions afforded dibromocyclopropane **12**, which was heated in 1,4-dioxane and aqueous sodium bicarbonate to induce electrocyclic ring-opening of the dibromocyclopropane to afford cycloheptenone **13** in 57% yield over 2 steps.[8] After reductive removal of the bromo group at the α-position of the carbonyl group, a carbon chain was introduced onto the carbonyl group via 1,2-addition of the organocerium reagent **D** to afford alcohol **15**.[9] After reduction of the cyano group of **15** with lithium aluminum hydride in refluxing THF, the resultant product **16** was sequentially subjected to introduction of a *o*-nitrobenzenesulfonyl (nosyl, Ns) group and oxidative rearrangement of the allyl alcohol moiety with pyridinium dichromate (PDC) as a one-pot process to furnish enone **17** in 84% yield over 2 steps.[10] Oxidative removal of the *p*-methoxyphenyl (PMP) group with ceric ammonium nitrate (CAN) liberated a primary alcohol moiety.[11] Intramolecular Mitsunobu reaction of the resultant hydroxy-nosylamide **18** proceeded smoothly at room temperature to form a 17-membered macrocyclic ring.[12] The nosyl group was replaced with a tosyl (Ts) group to furnish **20**.



Scheme 2. Reagents and conditions: (a) **A**, TFA, toluene, –10 °C, 85%; (b) $NaBH_4$, MeOH, 0 °C, 74%; (c) acetone cyanohydrin (**B**), TMAD (**C**), *n*-Bu_3P, benzene, rt, 78%; (d) $LiAlH_4$, THF, 0 °C; (e) BnBr, TBAI, NaH, DMF, rt, 62% (2 steps); (f) $CHBr_3$, KO*t*-Bu, petroleum ether, –10 °C; (g) aq $NaHCO_3$, 1,4-dioxane, 70 °C, 57% (2 steps); (h) Zn, AcOH, EtOH, rt, 79%; (i) **D**, THF, –20 °C, 76%; (j) $LiAlH_4$, THF, reflux; (k) NsCl, Et_3N, CH_2Cl_2, 0 °C, then PDC, celite, 84% (2 steps); (l) $Ce(NH_4)_2(NO_3)_6$, MeCN-H_2O, 99%; (m) DEAD, Ph_3P, toluene, rt; (n) PhSH, Cs_2CO_3, MeCN, 50 °C, then TsCl, 0 °C, 74% (2 steps); (o) **E**, LiF, MeCN, 140 °C, 26%.

Having obtained the requisite enone with the bridge forming a macrocyclic ring, we next tried to construct the pyrrolidine ring containing a quaternary carbon. After extensive investigations, we found

that cycloaddition of an azomethine ylide was effective for this transformation.[13] Heating enone **20** with amine **E**, a precursor for azomethine ylide,[14] in the presence of lithium fluoride at 140 °C afforded pyrrolidine **21** in 26% yield as a sole isomer. The stereochemistry was confirmed by NOESY spectroscopy,[15] indicating that the cycloaddition occurred as expected from the α-face of the cycloheptenone to avoid the steric hindrance of the bridge.

In conclusion, our synthetic studies on densanins included the stereoselective construction of a pyrrolidine ring containing a quaternary carbon via cycloaddition of an azomethine ylide to a cycloheptenone. The stereochemistry of the cycloaddition was controlled by a bridge that formed the macrocyclic ring.

ACKNOWLEDGEMENTS

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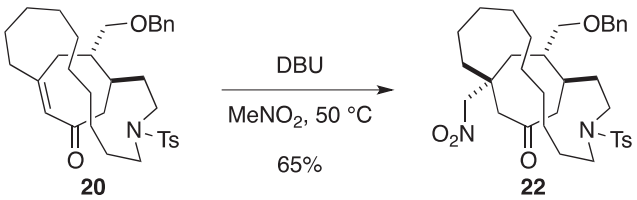
SUPPORTING INFORMATION

Supplementary data (experimental procedures, characterization for new compounds, including ^{1}H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at URL:

REFERENCES AND NOTES

1. (a) J.-F. Hu, M. T. Hamann, R. Hill, and M. Kelly, 'The Manzamine Alkaloids,' in *The Alkaloids: Chemistry and Biology*, Vol. 60, ed. by G. A. Cordell, Academic Press, 2003, pp. 207-285; (b) B. Delpech, 'The Saraine Alkaloids,' in *The Alkaloids: Chemistry and Biology*, Vol. 73, ed. by H.-J. Knölker, Academic Press, 2014, pp. 223-329; (c) M. Amat, M. Pérez, R. Ballette, S. Proto, and J. Bosch, 'The Alkaloids of the Madangamine Group,' in *The Alkaloids: Chemistry and Biology*, Vol. 74, ed. by H.-J. Knölker, Academic Press, 2015, pp. 159-199.
2. B. S. Hwang, J. S. Oh, E. J. Jeong, C. J. Sim, and J.-R. Rho, *Org. Lett.*, 2012, **14**, 6154.
3. S. Shi, H. Shi, J. Li, F. Li, L. Chen, C. Zhang, Z. Huang, N. Zhao, N. Li, and J. Yang, *Org. Lett.*, 2016, **18**, 1949.
4. K. Orihara, F. Kawagishi, S. Yokoshima, and T. Fukuyama, *Synlett*, 2018, **29**, 769.
5. L. You, X.-T. Liang, L.-M. Xu, Y.-F. Wang, J.-J. Zhang, Q. Su, Y.-H. Li, B. Zhang, S.-L. Yang, J.-H. Chen, and Z. Yang, *J. Am. Chem. Soc.*, 2015, **137**, 10120.
6. H. Gotoh and Y. Hayashi, *Org. Lett.*, 2007, **9**, 2859.

7. (a) T. Tsunoda, K. Uemoto, C. Nagino, M. Kawamura, H. Kaku, and S. Itô, *Tetrahedron Lett.*, 1999, **40**, 7355; (b) T. Tsunoda and S. Itô, *Yuki Gosei Kagaku Kyokaishi*, 1994, **52**, 113; (c) T. Tsunoda and S. Itô, *Yuki Gosei Kagaku Kyokaishi*, 1997, **55**, 631.
8. (a) B. Halton and J. Harvey, *Synlett*, 2006, 1975; (b) A. P. Thankachan, K. S. Sindhu, K. K. Krishnan, and G. Anilkumar, *Org. Biomol. Chem.*, 2015, **13**, 8780.
9. (a) T. Imamoto, Y. Sugiura, and N. Takiyama, *Tetrahedron Lett.*, 1984, **25**, 4233; (b) T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka, and M. Yokoyama, *J. Org. Chem.*, 1984, **49**, 3904; (c) T. Imamoto, Y. Tawarayama, T. Kusumoto, and M. Yokoyama, *Yuki Gosei Kagaku Kyokaishi*, 1984, **42**, 143.
10. (a) J. H. Babler and M. J. Coghlan, *Synth. Commun.*, 1976, **6**, 469; (b) W. G. Dauben and D. M. Michno, *J. Org. Chem.*, 1977, **42**, 682; (c) P. Sundararaman and W. Herz, *J. Org. Chem.*, 1977, **42**, 813.
11. T. Fukuyama, A. A. Laird, and L. M. Hotchkiss, *Tetrahedron Lett.*, 1985, **26**, 6291.
12. (a) O. Mitsunobu, *Synthesis*, 1981, 1; (b) T. Fukuyama, C.-K. Jow, and M. Cheung, *Tetrahedron Lett.*, 1995, **36**, 6373; (c) T. Kan and T. Fukuyama, *Yuki Gosei Kagaku Kyokaishi*, 2001, **59**, 779; (d) T. Kan, H. Kobayashi, and T. Fukuyama, *Synlett*, 2002, 0697; (e) T. Kan and T. Fukuyama, *Chem. Commun.*, 2004, 353.
13. 1,4-Addition of nitromethane also occurred to afford the corresponding product **22** in 65% yield as a single isomer. For details, see supporting information.



14. (a) A. Hosomi, Y. Sakata, and H. Sakurai, *Chem. Lett.*, 1984, **13**, 1117; (b) A. Padwa and W. Dent, *J. Org. Chem.*, 1987, **52**, 235.
15. For details, see Supporting Information.