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Efficient Synthetic Access to the Hetisine C_{20}-Diterpenoid Alkaloids. A Concise Synthesis of Nominine via Oxidoisoquinolinium-1,3-Dipolar and Dienamine-Diels−Alder Cycloadditions

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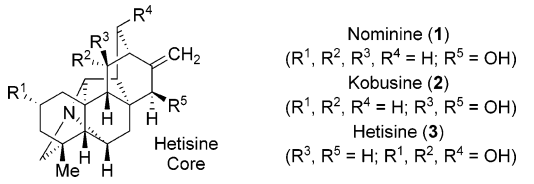
The hetisine natural products are a family of complex C_{20}-diterpenoid alkaloids isolated from the *Aconitum*, *Consolida*, *Delphinium*, *Rumex*, and *Spiraea* genera, plants that have been widely used in traditional herbal medicine.[1] Several of the more than 100 members of the hetisine alkaloids, exemplified by nominine (**1**, Chart 1),[2] kobusine (**2**),[3] and hetisine (**3**),[4] exhibit a diverse spectrum of biological activities, including potent vasodilating, antiarrhythmic, immunomodulating, and analgesic activities, in vivo.[1] Although the hetisine alkaloids have been known for more than a half-century, the majority of synthetic efforts directed at these complex targets have involved only a handful of synthetic model preparations of aza-polycyclic substructures.[5] In fact, the total synthesis of any member of the hetisine alkaloids remained elusive until the recent landmark work of Muratake and Natsume, in which a 40-step synthesis of (±)-nominine (**1**) was accomplished in 2004.[6] We now report a convergent, dual-cycloaddition approach to the hetisine alkaloids, illustrated by an exceedingly concise synthesis of the antiarrhythmic agent nominine (**1**).

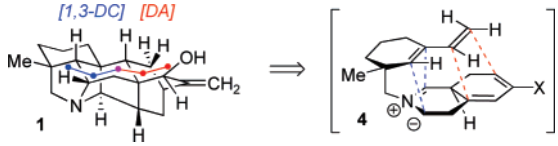
Consideration of the structure of nominine (**1**) in a conformational representation (Scheme 1) reveals a potentially expedient route to the hetisine core via two cycloaddition processes (i.e., **4**). These include an aza-1,3-dipolar cycloaddition (1,3-DC) to construct the bridged pyrrolidine ring, followed by a Diels-Alder (DA) reaction to assemble the [2.2.2]-bicyclic substructure within **1**. Because functional group compatibility issues would likely preclude a tandem double-cycloaddition event, synthetic efforts commenced with the preparation of a substrate incorporating the requisite dipole-dipolarophile complement in conjunction with a latent diene-dienophile pair.

Synthesis of a suitable dipolarophile precursor was accomplished in a short series of steps, beginning with *ortho*-lithiation of *p*-anisaldehyde dimethyl acetal (**5**, Scheme 2),[7] followed by its nucleophilic addition to 2-chloro-*N*-methoxyl-*N*-methylacetamide, to provide the aryl ketone **6** (52%). Subsequent exchange of the α-chloro substituent in **6** to its α-azido counterpart (NaN_3, 95%) and acid-catalyzed rearrangement afforded the cyclic bis(acetal) **7** as a 3:2 mixture of diastereomers (99%). The dipolarophile component was accessed efficiently from 3-methylcyclohexenone (**8**), in which conjugate cyanation[8] followed by enolate trapping with Tf_2O led to enol triflate **9** (81%). Sequential nitrile reduction to the aldehyde (DIBAL-H, 92%) and Pd^0-catalyzed cross coupling with $Zn(CN)_2$[9] provided the ene-nitrile dipolarophile **10** (85%), ready to be condensed with the aza-dipole precursor **7**. This convergent step was accomplished with a Staudinger−aza-Wittig reaction (**7**, **10**, PBu_3) in conjunction with imine reduction ($NaBH(OAc)_3$) to afford the amine **11** (79%) as a mixture of four diastereomers. All four diastereomers **11** were then converged via

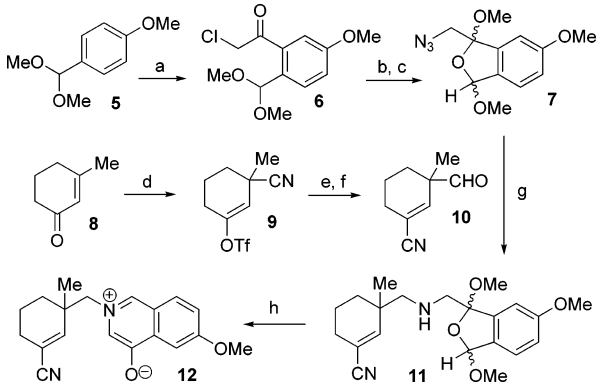
Chart 1



Scheme 1



Scheme 2 [a]



[a] Reagents and conditions: (a) *t*-BuLi, Et_2O, −23 °C; $ClCH_2C(O)N(OMe)Me$, 52%; (b) NaN_3, acetone, 23 °C, 95%; (c) AcCl, MeOH, 23 °C, 99% (3:2 dr); (d) $AlEt_2CN$, benzene, 23 °C; TBAT, Tf_2O, benzene, 23 °C, 81%; (e) DIBAL-H, PhMe, 0 °C, 92%; (f) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 60 °C, 85%; (g) **7**, **10**, PBu_3, $NaBH(OAc)_3$, CH_2Cl_2, 23 °C, 79% (3:3:2:2 dr); (h) 10% TFA in CH_2Cl_2, 0 °C, 93%.

TFA-catalyzed MeOH extrusion and isomerization to the 4-oxido-isoquinolinium betaine **12** (93%), which served as a suitable aza-1,3-dipole.

1,3-Dipolar cycloadditions involving oxidopyridinium betaines have proven to be valuable in alkaloid synthesis;[10] however, the use of oxidoisoquinolinium betaines in this capacity is comparatively rare.[11] When a solution of betaine **12** in THF (5 mM) was heated in a sealed tube at 180 °C (Scheme 3), intramolecular cycloaddition occurred with 97% conversion to provide an easily separable mixture of pyrrolidine constitutional isomers **15** and **16**, each arising from differential facial approach of the dipole-dipolarophile partners. While the desired cycloadduct **15** was formed as the minor constituent (**15**:**16**, 1:3.6),[12] the isomeric ratio was verified to be the result of *thermodynamic* selection. Indeed, the cycloaddition event was found to be *reversible* under the reaction

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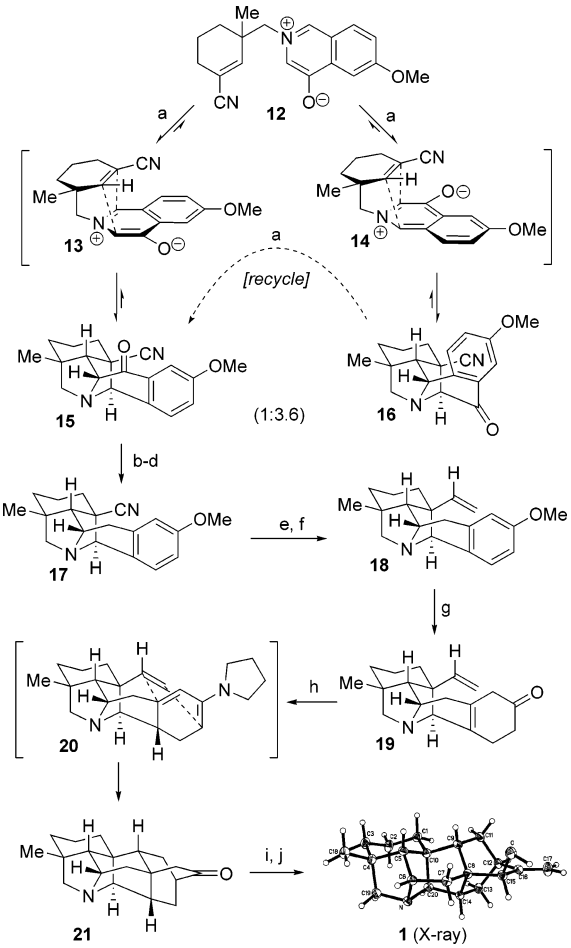
Scheme 3 [a]



[a] Reagents and conditions: (a) THF, 180 °C; 97% conversion to **15** and **16**, (1:3.6, with reversible recycling **15** ⇄ **16**); (b) $NaBH_4$, EtOH, 23 °C; (c) $SOCl_2$, CH_2Cl_2, reflux; (d) Bu_3SnH, AIBN, PhH, reflux, 68% (3 steps); (e) DIBAL-H, PhMe, 0 °C, 85%; (f) $Ph_3P{=}CH_2$, THF, 23 °C, 96%; (g) Na^0, Me_2CHOH, THF, −78 °C; $HCl_{(aq)}$, 97%; (h) 9:1 MeOH/pyrrolidine, 60 °C, 78%; (i) $Ph_3P{=}CH_2$, THF, 70 °C, 77%; (j) SeO_2, *t*-BuOOH, CH_2Cl_2, 23 °C, 66% (dr 7:1).

conditions, thereby enabling reiterative thermal re-equilibration of the isolated undesired cycloadduct **16** to enhance the production of **15** with minimal loss of material.

Advancement of the cycloadduct **15** continued with a ketone-to-methylene reduction to form **17** ($NaBH_4$; $SOCl_2$; Bu_3SnH, AIBN, 68% overall) and conversion of the nitrile to the alkene **18** (DIBAL-H; $Ph_3P{=}CH_2$, 82% overall) to reveal the dienophile functionality. Birch reduction (Na^0, Me_2CHOH, THF, NH_3, −78 °C)[13] of the aromatic ring in **18** and acidic workup led to the formation of the β,γ-unsaturated cyclohexenone **19** (97%), which, upon exposure to pyrrolidine in MeOH at 60 °C, afforded the intramolecular Diels-Alder adduct **21** in 78% yield after silica gel chromatography. Although not explicitly detected, a small equilibrating quantity of the dienamine isomer **20** was presumably formed and funneled productively to the committed [4+2] cycloaddition. The final steps of the synthesis involved Wittig methylenation of the ketone **21** ($Ph_3P{=}CH_2$, 77%) followed by diastereoselective SeO_2 allylic hydroxylation[14] to afford nominine (**1**, 66%, 7:1 dr), whose structure was verified by X-ray analysis.

Through the establishment of a dual cycloaddition strategy, a short total synthesis of (±)-nominine (**1**) was accomplished in a 15-step sequence with only a single protective group manipulation. Notable features include a reversible intramolecular 4-oxidoisoquinolinium betaine 1,3-dipolar cycloaddition as well as a pyrrolidine-induced dienamine isomerization/Diels-Alder cascade. This rapid synthetic access into the hetisine skeleton should pave the way for the construction of other, more highly oxidized, members of the C_{20}-diterpenoid alkaloids such as the antiarrhythmic guanfu bases.[1]

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Wang, F.-P.; Liang, X.-T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 2002; Vol. 59, pp 1−280.
(2) (a) Ochiai, E.; Okamoto, T.; Sakai, S.; Saito, A. *Yakugaku Zasshi* **1956**, *76*, 1414−1418. (b) Sakai, S.; Yamamoto, I.; Yamaguchi, K.; Takayama, H.; Ito, M.; Okamoto, T. *Chem. Pharm. Bull.* **1982**, *30*, 4579−4582.
(3) (a) Suginome, H.; Shimanouti, F. *Justus Liebigs Ann. Chem.* **1940**, *545*, 220−228. (b) Okamoto, T. *Chem. Pharm. Bull.* **1959**, *7*, 44−49. (c) Pelletier, S. W.; Wright, L. H.; Newton, G. M.; Wright, H. *J. Chem. Soc., Chem. Commun.* **1970**, 98−99.
(4) (a) Jacobs, W. A.; Craig, L. C. *J. Biol. Chem.* **1942**, *143*, 605−609. (b) Przybylska, M. *Can. J. Chem.* **1962**, *40*, 566−568.
(5) (a) Somei, M.; Okamoto, T. *Chem. Pharm. Bull.* **1970**, *18*, 2135−2138. (b) van der Baan, J. L.; Bickelhaupt, F. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 109−112. (c) Shibanuma, Y.; Okamoto, T. *Chem. Pharm. Bull.* **1985**, *33*, 3187−3194. (d) Kwak, Y.; Winkler, J. D. *J. Am. Chem. Soc.* **2001**, *123*, 7429−7430. (e) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **2002**, *43*, 2913−2917. (f) Williams, C. M.; Mander, L. N. *Org. Lett.* **2003**, *5*, 3499−3502. (g) Peese, K. M.; Gin, D. Y. *Org. Lett.* **2005**, *7*, 3323−3325. (h) Williams, C. M.; Mander, L. N.; Bernhardt, P. V.; Willis, A. C. *Tetrahedron* **2005**, *61*, 3759−3769.
(6) Muratake, H.; Natsume, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4646−4649.
(7) Karl, J.; Gust, R.; Spruss, T.; Schneider, M. R.; Shönenberger, H.; Engel, J.; Wrobel, K.; Lux, F.; Haeberlin, S. T. *J. Med. Chem.* **1988**, *31*, 72−83.
(8) Nagata, W.; Yoshioka, M.; Hirai, S. *J. Am. Chem. Soc.* **1972**, *94*, 4635−4643.
(9) Tschaen, D. M.; Desmond, R.; King, A. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. *Synth. Commun.* **1994**, *24*, 887−890.
(10) (a) Katritzky, A. R.; Takeuchi, Y. *J. Am. Chem. Soc.* **1970**, *92*, 4134−4136. (b) Dennis, N.; Katritzky, A. R.; Takeuchi, Y. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 1−9. (c) Joshi, R. A.; Ravindranathan, T. *Indian J. Chem., Sect. B* **1984**, *23*, 300−302. (d) Katritzky, A. R.; Dennis, N. *Chem. Rev.* **1989**, *89*, 827−861. (e) Śliwa, W. *Heterocycles* **1996**, *43*, 2005−2029. (f) Rumbo, A.; Mouriño, A.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **1996**, *61*, 6114−6120. (g) Smith, M. P.; Johnson, K. M.; Zhang, M.; Flippen-Anderson, J. L.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1998**, *120*, 9072−9073. (h) Sung, M. J.; Lee, H. I.; Chong, Y.; Cha, J. K. *Org. Lett.* **1999**, *1*, 2017−2019.
(11) (a) Dennis, N.; Katritzky, A. R.; Takeuchi, Y. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2054−2057. (b) Garling, D. L.; Cromwell, N. H. *J. Org. Chem.* **1973**, *38*, 654−658. (c) Dennis, N.; Katritzky, A. R.; Parton, S. K. *Chem. Pharm. Bull.* **1975**, *23*, 2899−2903. (d) Dennis, N.; Katritzky, A. R.; Parton, S. K. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2285−2288. (e) Hanaoka, M.; Wada, A.; Yasuda, S.; Mukai, C.; Imanishi, T. *Heterocycles* **1979**, *12*, 511−514. (f) Dicesare, J. C.; Burgess, J. P.; Mascarella, S. W.; Carroll, F. I. *J. Heterocycl. Chem.* **1994**, *31*, 187−192. (g) Edmunds, J. J.; Cheng, X.; Tobias, B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2005−2008. (h) Constable, K. P.; Blough, B. E.; Carroll, F. I. *Chem. Commun.* **1996**, 717−718.
(12) ^{1}H NMR analysis of the 1,3-dipolar cycloadditions revealed production of a *clean* 21:76:03 mixture of **15**:**16**:**12**, respectively, with quantitative mass recovery. Silica gel separation of isomers provided pure **15** (20%) and **16** (70%).
(13) (a) Rabideau, P. W.; Marcinow, Z. *Org. React.* **1992**, *42*, 1−334. (b) Wentland, M. P.; Albertson, N. F.; Pierson, A. K. *J. Med. Chem.* **1980**, *23*, 71−74.
(14) (a) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526−5528. (b) Furber, M.; Mander, L. N. *J. Am. Chem. Soc.* **1987**, *109*, 6389−6396.

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