Published in final edited form as:

J Am Chem Soc. 2006 July 12; 128(27): 8734–8735. doi:10.1021/ja0625430.

Efficient Synthetic Access to the Hetsine C₂₀-Diterpenoid Alkaloids. A Concise Synthesis of Nominine via Oxidoisoquinolinium-1,3-Dipolar and Dienamine-Diels–Alder Cycloadditions

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The hetsine natural products are a family of complex C₂₀-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 hetsine alkaloids, exemplified by nominine (**1**; Chart 1),² kobusine (**2**),³ and hetsine (**3**),⁴ exhibit a diverse spectrum of biological activities, including potent vasodilating, antiarrhythmic, immunomodulating, and analgesic activities, in vivo.¹ Although the hetsine 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 hetsine 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 hetsine 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 hetsine 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 (NaN₃, 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 cyanation⁸ followed by enolate trapping with Tf₂O led to enol triflate **9** (81%). Sequential nitrile reduction to the aldehyde (DIBAL-H, 92%) and Pd⁰-catalyzed cross coupling with Zn(CN)₂⁹ 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**, PBu₃) in conjunction with imine

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reduction ($\text{NaBH}(\text{OAc})_3$) to afford the amine **11** (79%) as a mixture of four diastereomers. All four diastereomers **11** were then converged via 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 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; $\text{Ph}_3\text{P}=\text{CH}_2$, 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** ($\text{Ph}_3\text{P}=\text{CH}_2$, 77%) followed by diastereoselective SeO_2 allylic hydroxylation¹⁴ 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 ($\pm$)-nominine (**1**) was accomplished in a 15-step sequence with only a single protective group manipulation. Notable features include a reversible intramolecular 4-oxidoiso-quinolinium 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 guan-fu bases.¹

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This research was supported by the NIH-NIGMS (GM67659), Abbott, Eli Lilly, Johnson & Johnson, Merck, and Pfizer. A Pharmacia (Pfizer) predoctoral fellowship to K.M.P. is acknowledged. We thank Dr. H. Muratake for supplying spectral data for **1**.

References

1. Wang, FP.; Liang, XT. The Alkaloids. Cordell, GA., editor. 59. Academic Press; San Diego, CA: 2002. p. 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 SW, Wright LH, Newton GM, Wright H. *J Chem Soc, Chem Commun* 1970:98–99.
4. (a) Jacobs WA, Craig LC. *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 JL, Bickelhaupt F. *Recl Trav Chim Pays-Bas* 1975;94:109–112. (c) Shibamura Y, Okamoto T. *Chem Pharm Bull* 1985;33:3187–3194. (d) Kwak Y, Winkler JD. *J Am Chem Soc* 2001;123:7429–7430. [PubMed: 11472177] (e) Muratake H, Natsume M. *Tetrahedron Lett* 2002;43:2913–2917. (f) Williams CM, Mander LN. *Org Lett* 2003;5:3499–3502. [PubMed: 12967309] (g) Peese KM, Gin DY. *Org Lett* 2005;7:3323–3325. [PubMed: 16018651] (h) Williams CM, Mander LN, Bernhardt PV, Willis AC. *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 MR, Shönenberger H, Engel J, Wrobel K, Lux F, Haeberlin ST. *J Med Chem* 1988;31:72–83. [PubMed: 3336035]
8. Nagata W, Yoshioka M, Hirai S. *J Am Chem Soc* 1972;94:4635–4643.
9. Tschaen DM, Desmond R, King AO, Fortin MC, Pipik B, King S, Verhoeven TR. *Synth Commun* 1994;24:887–890.
10. (a) Katritzky AR, Takeuchi Y. *J Am Chem Soc* 1970;92:4134–4136. (b) Dennis N, Katritzky AR, Takeuchi Y. *Angew Chem, Int Ed Engl* 1976;15:1–9. [PubMed: 814844] (c) Joshi RA, Ravindranathan T. *Indian J Chem, Sect B* 1984;23:300–302. (d) Katritzky AR, Dennis N. *Chem Rev* 1989;89:827–861. (e) Śliwa W. *Heterocycles* 1996;43:2005–2029. (f) Rumbo A, Mouriño A, Castedo L, Mascareñas JL. *J Org Chem* 1996;61:6114–6120. [PubMed: 11667444] (g) Smith MP, Johnson KM, Zhang M, Flippen-Anderson JL, Kozikowski AP. *J Am Chem Soc* 1998;120:9072–9073. (h) Sung MJ, Lee HI, Chong Y, Cha JK. *Org Lett* 1999;1:2017–2019. [PubMed: 10836058]
11. (a) Dennis N, Katritzky AR, Takeuchi Y. *J Chem Soc, Perkin Trans* 1972;1:2054–2057. (b) Garling DL, Cromwell NH. *J Org Chem* 1973;38:654–658. (c) Dennis N, Katritzky AR, Parton SK. *Chem Pharm Bull* 1975;23:2899–2903. (d) Dennis N, Katritzky AR, Parton SK. *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 JC, Burgess JP, Mascarella SW, Carroll FI. *J Heterocycl Chem* 1994;31:187–192. (g) Edmunds JJ, Cheng X, Tobias B. *J Chem Soc, Perkin Trans* 1 1996:2005–2008. (h) Constable KP, Blough BE, Carroll FI. *Chem Commun* 1996:717–718.
12. ¹H 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 PW, Marcinow Z. *Org React* 1992;42:1–334. (b) Wentland MP, Albertson NF, Pierson AK. *J Med Chem* 1980;23:71–74. [PubMed: 7359514]
14. (a) Umbreit MA, Sharpless KB. *J Am Chem Soc* 1977;99:5526–5528. (b) Furber M, Mander LN. *J Am Chem Soc* 1987;109:6389–6396.

Scheme 1.

Scheme 2 a.

^a Reagents and conditions: (a) *t*-BuLi, Et₂O, -23 °C; ClCH₂C(O)N(OMe)Me, 52%; (b) NaN₃, acetone, 23 °C, 95%; (c) AcCl, MeOH, 23 °C, 99% (3:2 dr); (d) AlEt₂CN, benzene, 23 °C; TBAT, Tf₂O, benzene, 23 °C, 81%; (e) DIBAL-H, PhMe, 0 °C, 92%; (f) Zn(CN)₂, Pd (PPh₃)₄, DMF, 60 °C, 85%; (g) **7**, **10**, PBu₃, NaBH(OAc)₃, CH₂Cl₂, 23 °C, 79% (3:3:2:2 dr); (h) 10% TFA in CH₂Cl₂, 0 °C, 93%.

Scheme 3 a.

^a Reagents and conditions: (a) THF, 180 °C; 97% conversion to **15** and **16**, (1:3.6, with reversible recycling **15** $\rightleftharpoons$ **16**); (b) NaBH₄, EtOH, 23 °C; (c) SOCl₂, CH₂Cl₂, reflux; (d) Bu₃SnH, AIBN, PhH, reflux, 68% (3 steps); (e) DIBAL-H, PhMe, 0 °C, 85%; (f) Ph₃P=CH₂, THF, 23 °C, 96%; (g) Na⁰, Me₂CHOH, THF, -78 °C; HCl_(aq), 97%; (h) 9:1 MeOH/pyrrolidine, 60 °C, 78%; (i) Ph₃P=CH₂, THF, 70 °C, 77%; (j) SeO₂, *t*-BuOOH, CH₂Cl₂, 23 °C, 66% (dr 7:1).

- Nominine (**1**)
($R^1, R^2, R^3, R^4 = H; R^5 = OH$)
Kobusine (**2**)
($R^1, R^2, R^4 = H; R^3, R^5 = OH$)
Hetisine (**3**)
($R^3, R^5 = H; R^1, R^2, R^4 = OH$)

Chart 1.