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ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · AUGUST 2006

Impact Factor: 12.11 · DOI: 10.1021/ja0625430 · Source: PubMed

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

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

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reduction (NaBH-$(OAc)_3$) 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; $Ph_3P{=}CH_2$, 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-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

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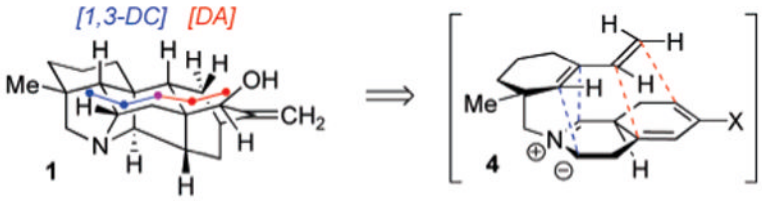
Acknowledgements

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**.

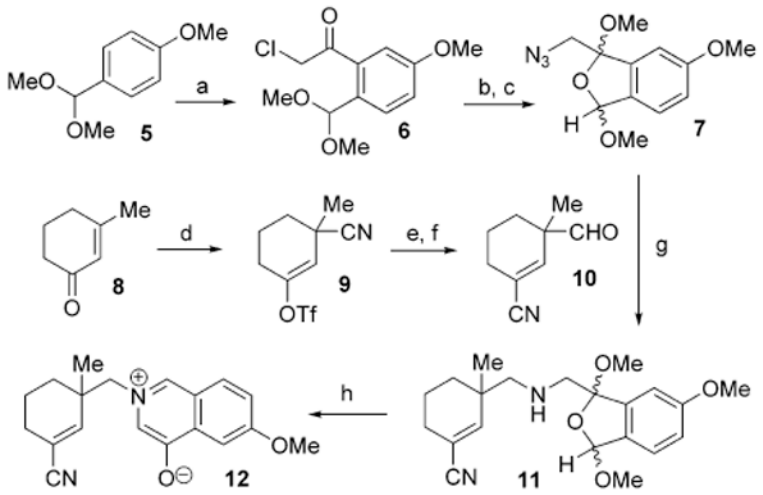
References

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) Shibanuma 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. ^{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 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.

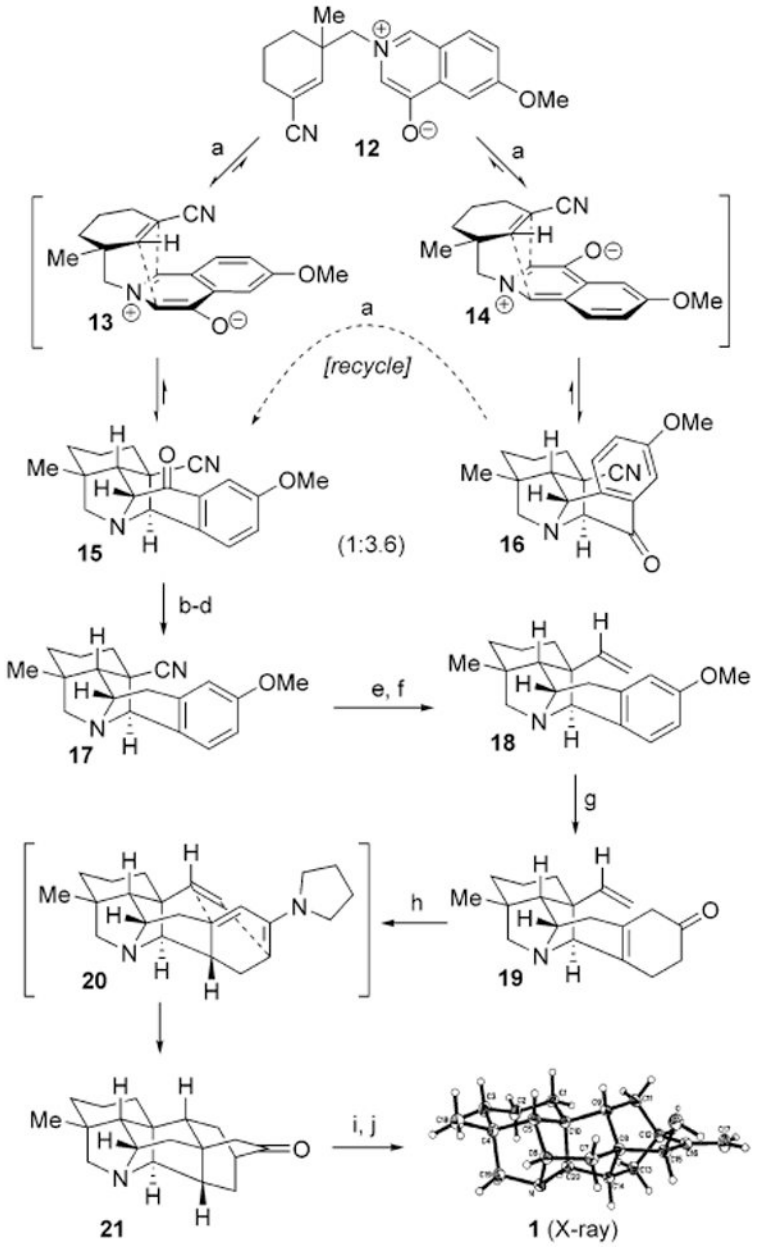


Scheme 1.



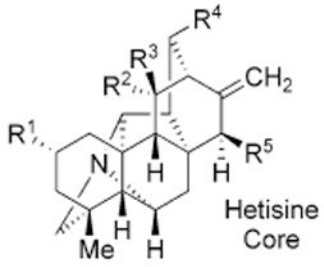
Scheme 2 a.

[a] Reagents and conditions: (a) *t*-BuLi,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%.



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).



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.