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The First Total Synthesis of (Corrected) Ritterazine M

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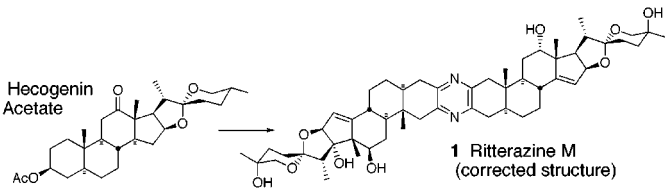
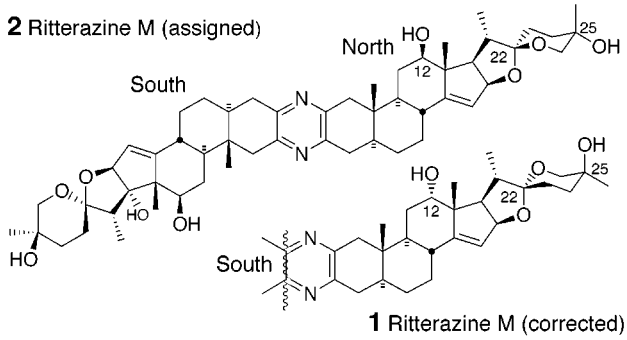
ABSTRACT



Hecogenin acetate was converted to ritterazine M in 16 operations with an average yield per opearation of 87%. The overall linear yield was 12%. This confirmed 1 as the corrected structure for ritterazine M by total synthesis.

In the previous paper we proposed that the structure assigned for ritterazine M was incorrect and made a new assignment, **1**,[1] based upon NMR difference correlation with the values published by Fusetani.[2] We now confirm this assignment by providing the first total synthesis of this trisdecacyclic pyrazine, **1** (Scheme 1).

Scheme 1



Asymmetric dihydroxylation of terminal olefin **3**[1] provided a 5.9:1 mixture of diols **4**, which were not readily separable at this stage. In preparation for cyclization to the 5/6 spiroketal (1,6-dioxaspiro[4,5]decane) it was necessary to selectively protect the 1,2-diol moiety. This was accomplished by monosilylation of the primary alcohol to afford the corresponding mixture of inseparable TBS silyl ethers **5** in essentially quantitative yield. Without purification, **5** was reacted with benzoic anhydride, magnesium bromide, and triethylamine to provide **6** in 87% yield, again (presumably) as a 5.9:1 mixture. Again without purification, this mixture was desilylated by using $BF_3{\cdot}OEt_2$ to give a fourth inseparable mixture, **7**, which was subjected to the Suarez iodine[III] oxidation[1,3] to give spiroketals **8a** and **8b** which were separated by chromatography, hydrolyzed, and then oxidized to the A-ring C-3 ketone **10** (Scheme 2).

Completion of the total synthesis required PTAB bromination of **10** to give the α-bromoketone **11** in 82% yield along with small amounts of the 2,2-dibromide. Displacement of this material using our optimal conditions provided the labile equatorial α-azidoketone **12**, which was immediately converted to methoxime **13**. Staudinger reduction of **13** gave the "North M" amino-methoxime **14** in 75% yield. Using

(1) Cephalostatin Support Studies. 21. For 20, see: Lee, S. M.; LaCour, T. G.; Lantrip, D. A.; Fuchs, P. L. *Org. Lett.* **2001**, *3*, 313.

(2) Fukuzawa, S.; Matsunaga, S.; Fusetani, N. *Tetrahedron* **1995**, *51*, 6707.

(3) Concepcion, J. L.; Francisco, C. G.; Hernandez, R.; Salazar, J. A.; Suarez, E. *Tetrahedron Lett.* **1984**, *25*, 1953−1956. de Armas, P.; Concepcion, J. I.; Francisco, C. G.; Hernanez, R.; Salazar, J. A.; Suarez, E. *J. Chem. Soc., Perkin Trans. 1* **1989**, 405−411. Martin, A.; Salazar, J. A.; Suarez, E. *Tetrahedron Lett.* **1995**, *36*, 4489−4492. Furuta, K.; Nagata, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 2215−2218. Betancor, C.; Dorta, R. L.; Freire, R.; Prange, T.; Suarez, E. *J. Org. Chem.* **2000**, *65*, 8822−8825.

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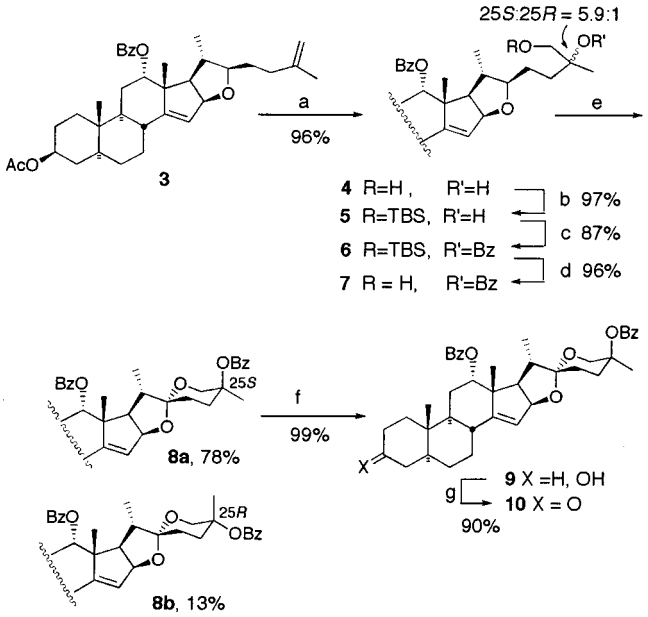
Scheme 2[a]



[a] (a) OsO_4 (2 mol %), $(DHQ)_2PHAL$ (10 mol %), $K_3Fe(CN)_6$, K_2CO_3, t-BuOH/H_2O, 0 °C, 8 h; (b) TBSCl, imidazole, DMAP, DMF; (c) Bz_2O, $MgBr_2 \cdot OEt_2$, TEA, DCM, 25 °C, 18 h; (d) $BF_3 \cdot OEt_2$, DCM, 0 °C, 5 min; (e) $PhI(OAc)_2$, I_2, c-hexane/DCM, 0 °C, 8 h; (f) K_2CO_3, MeOH/H_2O, 25 °C 5h (g) TPAP (5 mol %), NMO, 4A molecular sieves, DCM, 25 °C, 20 min.

the Guo unsymmetrical pyrazine synthesis,[4] substrate **14** was united with a stoichiometric amount of the "South 7" α-azidoketone **15**.[5] This provided **16**, the protected form of ritterazine M, which was globally deprotected to deliver compound **1** which was shown to have proton and carbon NMR parameters equivalent to those of authentic ritterazine M (North section $r^2 = 0.99996$; South section $r^2 = 0.99998$; see Supporting Information). Thus, the structural revision to **1** (Scheme 3) has been firmly secured by synthesis.

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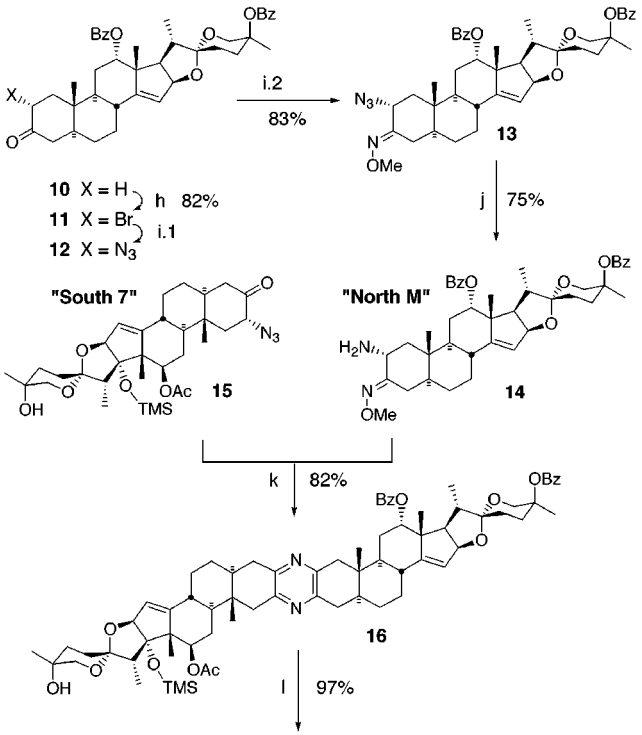
(4) Guo, C.; Bhandaru, S.; Fuchs, P. L.; Boyd, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10672.

Scheme 3[a]



[a] (h) PTAB, THF, 0 °C, 15 min; (i) $TMGN_3$, $MeNO_2$, 25 °C, 6 h; $MeONH_2 \cdot HCl$, DCM/pyridine, 25 °C, 6 h; (j) PPh_3, H_2O, THF, 25 °C, 2 d; (k) Bu_2SnCl_2, PVP, benzene, reflux, 3 h; (l) i. TBAF, THF, 0 °C, 5 h; ii. K_2CO_3, MeOH/H_2O, reflux, 5 h.

Supporting Information Available: Experimental procedures and ^1H and ^{13}C NMR spectra. The material is available free of charge via the Internet at http://pubs.acs.org.

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(5) Jeong, J.; Guo, C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1999**, *121*, 2071.