

The First Total Synthesis of (Corrected)
Ritterazine M

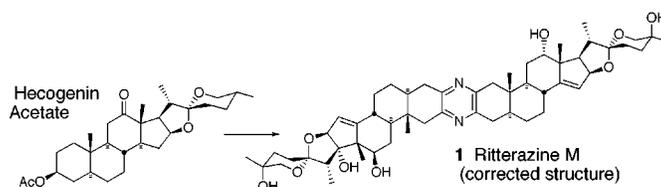
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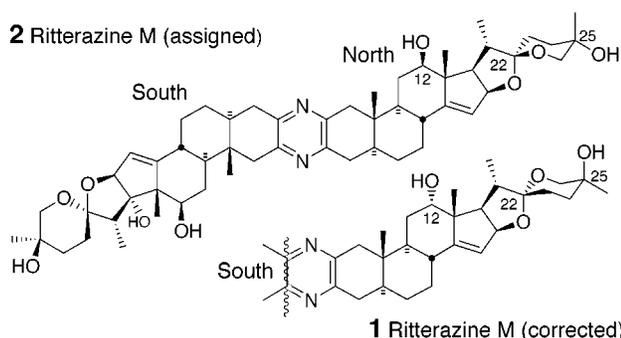
ABSTRACT



Hecogenin acetate was converted to ritterazine M in 16 operations with an average yield per operation 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

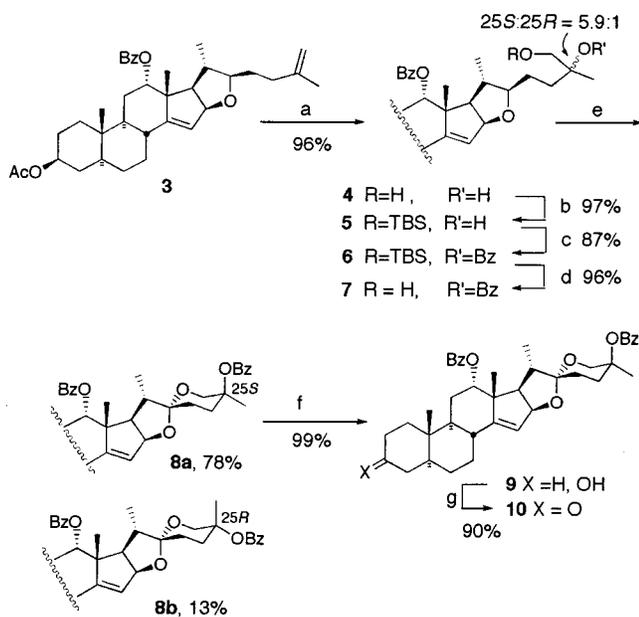
(1) Cephalostatin Support Studies. 21. For 20, see: Lee, S. M.; LaCour, T. G.; Lantrip, D. A.; Fuchs, P. L. *Org. Lett.* **2001**, *3*, 313.

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

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 $\text{BF}_3 \cdot \text{OEt}_2$ 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

(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.; Hernandez, 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.

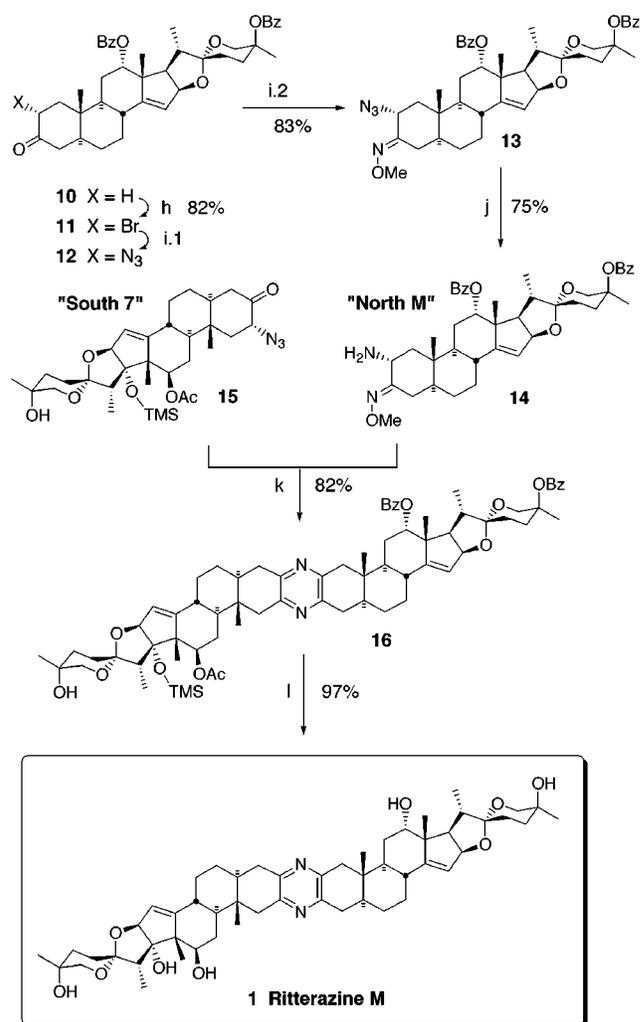
Scheme 2^a

^a (a) OsO₄ (2 mol %), (DHQ)₂PHAL (10 mol %), K₃Fe(CN)₆, K₂CO₃, t-BuOH/H₂O, 0 °C, 8 h; (b) TBSCl, imidazole, DMAP, DMF; (c) Bz₂O, MgBr₂·OEt₂, TEA, DCM, 25 °C, 18 h; (d) BF₃·OEt₂, DCM, 0 °C, 5 min; (e) PhI(OAc)₂, I₂, c-hexane/DCM, 0 °C, 8 h; (f) K₂CO₃, MeOH/H₂O, 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.

Acknowledgment. We thank the National Institutes of Health (CA 60548) for support of this work. We are most grateful to professors Matsunaga and Fusetani for helpful discussions and an authentic sample of ritterazine M.

(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) TMGN₃, MeNO₂, 25 °C, 6 h; MeONH₂·HCl, DCM/pyridine, 25 °C, 6 h; (j) PPh₃, H₂O, THF, 25 °C, 2 d; (k) Bu₂SnCl₂, PVP, benzene, reflux, 3 h; (l) i. TBAF, THF, 0 °C, 5 h; ii. K₂CO₃, MeOH/H₂O, reflux, 5 h.

Supporting Information Available: Experimental procedures and ¹H and ¹³C NMR spectra. The material is available free of charge via the Internet at <http://pubs.acs.org>. OL016572L

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