# Review of Cytotoxic Cephalostatins and Ritterazines: Isolation and Synthesis[†,‡]

Bryan R. Moser*

*United States Department of Agriculture, Agricultural Research Service, National Center for Agricultural Utilization Research, Peoria, Illinois 61604*

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The cephalostatins and ritterazines comprise a family of structurally related natural products reported by Professors G. R. Pettit and N. Fusetani from 1988 –1998. Isolated from the invertebrate marine chordates *Cephalodiscus gilchristi* and *Ritterella tokioka*, the cephalostatins and ritterazines exhibit potent cytotoxicity toward the murine P388 lymphocytic leukemia cell line. In fact, cephalostatin 1 (**1**, $ED_{50}$ 0.1–0.001 pM) proved to be one of the most powerful cancer cell growth inhibitors ever tested by the U.S. National Cancer Institute. The ritterazines and cephalostatins share many common structural features in which two highly oxygenated steroidal units with side chains forming either 5/5 or 5/6 spiroketals are fused via a pyrazine core. Professor P. L. Fuchs and colleagues reported the total syntheses of **1**, cephalostatins 7 (**7**), and 12 (**12**), ritterazines K (**30**) and M (**32**), and cytotoxic analogues. The synthesis of **1**, described in 1998, required 65 synthetic operations to complete.

## *Cephalodiscus gilchristi* and Its Constituents

In the shark-infested waters of the Indian Ocean off the coast of southeastern Africa resides the small (ca. 5 mm in length) colonial marine worm *Cephalodiscus gilchristi* (family Cephalodiscidae).[1] Predominately found in shallow, temperate waters, this unusual and relatively rare tube worm is divided into three body regions—cephalic shield, collar, and trunk—and displays distinctive tentacled arms emanating from the collar dorsal side.[1] Interestingly, *C. gilchristi* is not confined to the coenecium (worm tube) but is independent and can move out of the tube onto the coenecium surface by emitting a secretion from the sucker-like proboscis of the buds. Locomotion outside of the worm tube is accomplished by shifting the organism's points of attachment.[1] Tubes containing colonies of these tiny marine animals are commonly found attached to, for example, bryozoans and sponges.

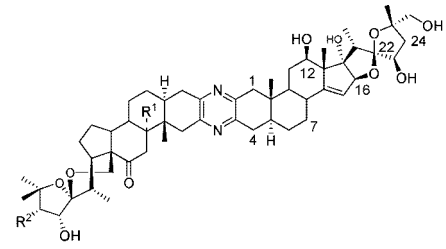
In 1972, Pettit and co-workers collected specimens of *C. gilchristi* by scuba (depth of 20 m) in waters inhabited by *Carcharodon carcharias* (great white shark), which had previously been unexplored with respect to biologically active and other chemical constituents. After fifteen years of diligent research directed at structure elucidation of the active constituents of the methanol and aqueous extracts of *C. gilchristi*, including re-collection efforts in 1981, cephalostatin 1 (**1**) was finally reported in 1988 in very low yield ($8.36 \times 10^{-4}$ wt %) from crude marine worm material.[2] Consisting of two highly oxygenated hexacyclic steroidal monomers linked by a pyrazine core, final structural assignment of **1** (12*R*, 16*S*, 17*S*, 20*S*, 22*S*, 23*R*, 25*S*, 17′*R*, 20′*S*, 22′*R*, 23′*R*) was accomplished upon crystallization from pyridine–hexane and subsequent X-ray crystallographic analysis.[2] This trisdecacyclic, bis-steroidal alkaloid, with an $ED_{50}$ of 0.1–0.001 pM (Table 1, P388 lymphocytic leukemia cell line, PS cell system),[2] proved to be one of the most powerful cell growth inhibitors ever tested by the U.S. National Cancer Institute (NCI), which is considerably more active in vitro than paclitaxel.[3]

In 1988 additional bioassay-directed (PS cell system) separation of *C. gilchristi* extracts by Pettit and colleagues yielded three additional bis-steroidal alkaloids closely related to **1**, designated cephalostatins 2–4 (**2**–**4**), which each contained a 9′α-hydroxy moiety not found in **1**.[4] Compounds **2**–**4** exhibited cell growth inhibitory activities (PS $ED_{50}$ 0.1–0.001 pM, Table 1) similar to **1**.[4]

**Table 1.** Murine P388 Lymphocytic Leukemia Inhibitory Activity ($ED_{50}$, nM) and Total Inhibition Concentration ($TI_{50}$, nM) of Cephalostatins 1–19 (**1**–**19**)[a]

| cephalostatin | year reported | P388 (nM) | ref |
|---|---|---|---|
| 1 (**1**) | 1988 | 0.0001–0.000001 | 2 |
| 2 (**2**) | 1988 | 0.0001–0.000001 | 4 |
| 3 (**3**) | 1988 | 0.0001–0.000001 | 4 |
| 4 (**4**) | 1988 | 0.0001–0.000001 | 4 |
| 5 (**5**) | 1989 | 42.5 | 5 |
| 6 (**6**) | 1989 | 2.3 | 5 |
| 7 (**7**) | 1992 | 1–<0.1 | 6 |
| 8 (**8**) | 1992 | 1–<0.1 | 6 |
| 9 (**9**) | 1992 | 1–<0.1 | 6 |
| 10 (**10**) | 1994 | 3.2 | 7a |
| 11 (**11**) | 1994 | 2.7 | 7a |
| 12 (**12**) | 1994 | 76.2 | 7b |
| 13 (**13**) | 1994 | 47.9 | 7b |
| 14 (**14**) | 1994 | 4.4 | 7c |
| 15 (**15**) | 1994 | 26.2 | 7c |
| 16 (**16**) | 1995 | <1.1 | 8a |
| 17 (**17**) | 1995 | 4.4 | 8a |
| 18 (**18**) | 1998 | 4.6 | 8b |
| 19 (**19**) | 1998 | 7.9 | 8b |

[a] **7**, **8**, **9**: $TI_{50}$ (nM).



**1** Cephalostatin 1 $R^1 = R^2 = H$; 14',15'-Δ
**2** Cephalostatin 2 $R^1 = OH$; $R^2 = H$;14',15'-Δ
**3** Cephalostatin 3 $R^1 = OH$; $R^2 = CH_3$; 14',15'-Δ
**4** Cephalostatin 4 $R^1 = OH$; $R^2 = H$;14',15'-epoxy

Cephalostatins 5 (**5**) and 6 (**6**) were reported by Pettit and co-workers in 1989 after further bioassay-guided study of *C. gilchristi* and possessed significantly less cell growth inhibitory activity (PS $ED_{50}$ 42.5 and 2.3 nM, respectively, Table 1) than **1**–**4**.[5] Alkaloids

* To whom correspondence should be addressed. Tel: 309-681-6511. Fax: 309-681-6340. E-mail: Bryan.Moser@ars.usda.gov.

† Dedicated to Dr. G. Robert Pettit of Arizona State University for his pioneering work on bioactive natural products.

‡ Disclaimer: Product names are necessary to report factually on available data; however, USDA neither guarantees nor warrants the standard of the product, and the use of the name by USDA implies no approval of the product to the exclusion of others that may also be suitable.

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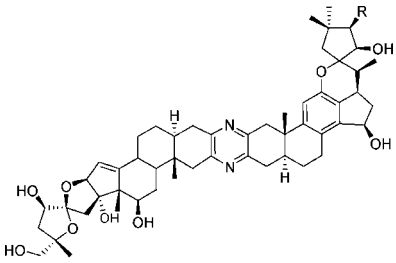
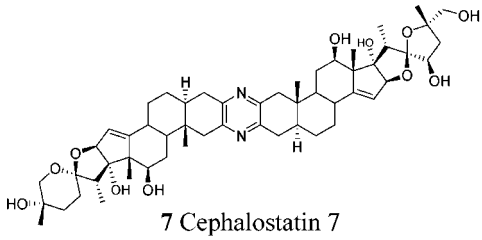
**5** and **6** are unusual in that they both contain an aromatic C ring. While naturally occurring and synthetic steroids with aromatic A rings are well-known, steroids bearing an aromatic C ring are quite rare, and examples of biosynthetic origin were essentially unknown prior to identification of **5** and **6**. The dramatic reduction in PS cell growth inhibition displayed by **5** and **6** in comparison to **1**–**4** suggested that preservation of structural integrity in the right-hand side unit, including C/D ring stereochemistry, is very important to realizing powerful cytotoxicity.[5]

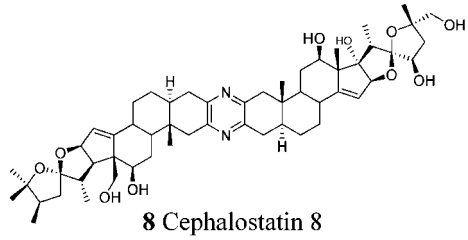


**5** Cephalostatin 5 R = $CH_3$
**6** Cephalostatin 6 R = H

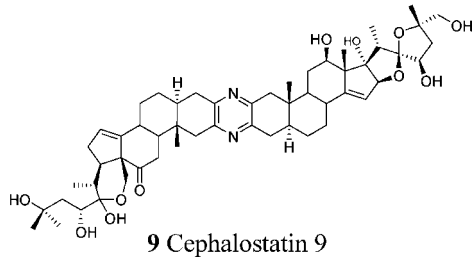
Isolation and structural elucidation of cephalostatins 7–9 (**7**–**9**) in 1992 by Pettit and colleagues provided three additional steroidal pyrazines that exhibited potent growth inhibitory and cytotoxic activity ($TI_{50}$ 1–<0.1 nM) against diverse human solid tumor types (e.g., non-small-cell lung HOP 62, small-cell lung DMS-273, renal RXF-393, brain U-251 and SF-295, leukemia CCRF-CEM, HL-60, and RPM1-8226 cell lines; Table 1) in the NCI in vitro, disease-oriented antitumor cell culture screen.[6] Discovery of **1**–**4** and **7**–**9** with potent cytotoxicity against certain human cancer cell lines suggested that the right-hand side unit is essential for exceptional potency. Minor configurational and substitution alterations in the left-hand side had little influence on cytotoxicity, but aromatization of the right-hand side C ring of **5** and **6** resulted in markedly diminished inhibitory behavior.



**7** Cephalostatin 7

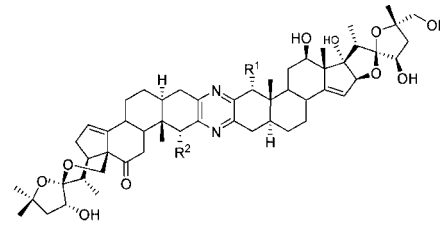


**8** Cephalostatin 8

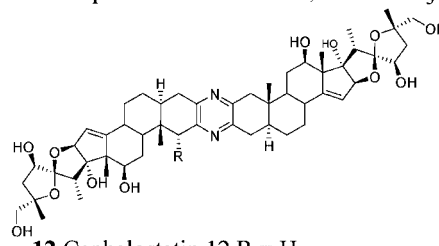


**9** Cephalostatin 9

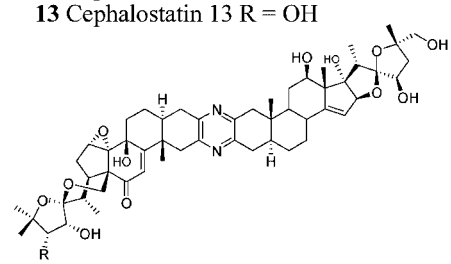
In 1994, six new cephalostatins, designated cephalostatins 10–15 (**10**–**15**), were reported by Pettit and co-workers.[7] Each compound exhibited potent cell growth inhibitory activity (PS $ED_{50}$ 2.7–76.2 nM, Table 1), but significantly less than **1**. Cephalostatin 12 (**12**), the only symmetric constituent (right unit = left unit), afforded significantly reduced inhibitory activity (PS $ED_{50}$ 76.2 nM) in comparison to other cephalostatins, suggesting that asymmetry is necessary for optimum cytotoxicity. Cephalostatin 10 (**10**), which contains a 1α-methoxy moiety on the right steroidal unit, was the first cephalostatin elucidated that differed in right-hand side molecular architecture from previously reported constituents.



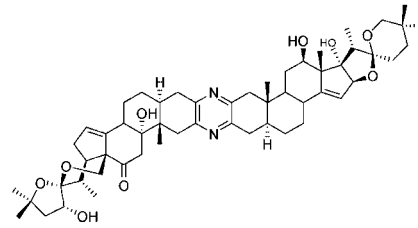
**10** Cephalostatin 10 $R^1 = OCH_3$; $R^2 = H$
**11** Cephalostatin 11 $R^1 = H$; $R^2 = OCH_3$



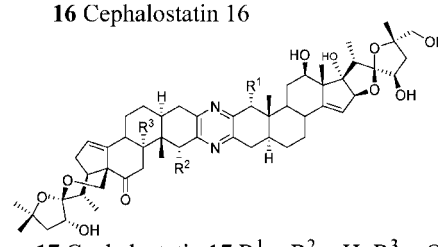
**12** Cephalostatin 12 R = H
**13** Cephalostatin 13 R = OH



**14** Cephalostatin 14 R = H
**15** Cephalostatin 15 R = $CH_3$

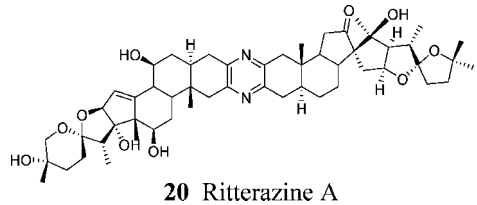


**16** Cephalostatin 16

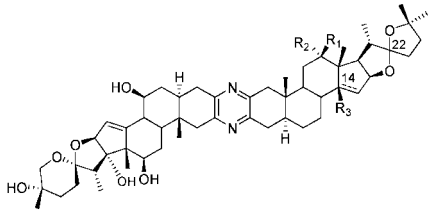


**17** Cephalostatin 17 $R^1 = R^2 = H$; $R^3 = OH$
**18** Cephalostatin 18 $R^1 = OCH_3$; $R^2 = R^3 = H$
**19** Cephalostatin 19 $R^1 = R^3 = H$; $R^2 = OCH_3$

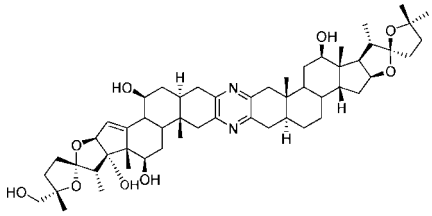
The remaining cephalostatins, designated cephalostatins 16–19 (**16**–**19**), were reported in 1995 and 1998 by Pettit and associates.[8] These exceptionally potent (PS $ED_{50}$ < 1.1–7.9, Table 1) cancer cell growth inhibitors continued to exhibit perhydropyran/spiroketal ring systems characteristic of other remarkable marine antineoplastic constituents discovered by Pettit and colleagues, such as spongistatin 1,[9] the halistatins,[10] and of course the cephalostatins.



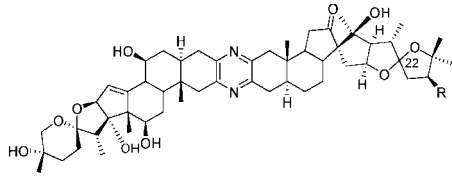
**20** Ritterazine A



**21** Ritterazine B $R^1$ = OH; $R^2$ = $R^3$ = H; 22*R*
**25** Ritterazine F $R^1$ = OH; $R^2$ = $R^3$ = H; 22*S*
**26** Ritterazine G $R^1$ = OH; $R^2$ = H; $\Delta^{14}$; 22*S*
**27** Ritterazine H $R^1$ = $R^2$ = O; $R^3$ = H; 22*R*
**28** Ritterazine I $R^1$ = $R^2$ = O; $R^3$ = OH; 22*S*



**22** Ritterazine C

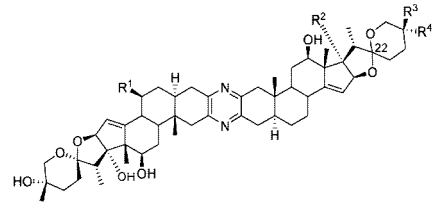


**23** Ritterazine D R = H; 22*S*
**24** Ritterazine E R = Me; 22*S*

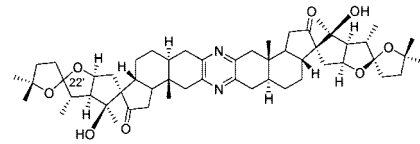
***Ritterella tokioka* and Its Constituents.** Closely related in structure to the cephalostatins are the ritterazines, which were reported by Fusetani and colleagues from 1994 to 1997. The sedentary and colonial marine tunicate *Ritterella tokioka* (family Polyclinidae) is extremely small (adult: 1 mm) and possesses a simple body structure, being essentially an unsegmented sac with two siphons through which water enters and exits.[11] This water is filtered through a sac inside the bag-shaped body to procure food for the organism. Living predominately in intertidal zones, these tiny filter feeding sea squirts rely on suspended plankton for nourishment.[11] The outer surface of the animal is covered by a tough opaque tunic (hence the name tunicate).[12]

As part of a search for cytotoxic metabolites from Japanese marine invertebrates, specimens of the marine tunicate *R. tokioka* were collected by Fusetani and co-workers of the University of Tokyo off the coast of Izu Peninsula, 100 km southwest of Tokyo, Japan. Marine tunicates have historically proven to be a rich source of biologically active nitrogenous secondary metabolites,[13] including cytotoxic compounds such as the didemnins[14] and ecteinascidins.[15] Bioassay-directed fractionation of *R. tokioka* extracts eventually afforded after X-ray crystallographic analysis in 1994 ($5.3 \times 10^{-5}$ wt % from bulk wet material) a trisdecacyclic bis-steroidal alkaloid structurally similar to the cephalostatins, designated ritterazine A (**20**), which exhibited excellent cytotoxicity against P388 murine leukemia cells (PS $ED_{50}$ 4.2 nM, Table 2).[16]

Further work by Fusetani and associates[17] on extracts of *R. tokioka* provided an additional 25 ritterazines (B−Z, **21**–**45**) with P388 inhibitory activities (Table 2) ranging from 3.6 $\mu$M for



**29** Ritterazine J $R^1$ = $R^2$ = $R^4$ = OH; $R^3$ = $CH_3$; 22*R*
**30** Ritterazine K $R^1$ = H; $R^2$ = $R^4$ = OH; $R^3$ = $CH_3$; 22*R*
**31** Ritterazine L $R^1$ = $R^2$ = H; $R^4$ = OH; $R^3$ = $CH_3$; 22*R*
**32** Ritterazine M $R^1$= $R^2$ = H; $R^3$ = OH; $R^4$ = $CH_3$; 22*S*



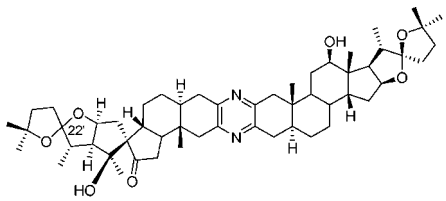
**33** Ritterazine N 22′*R*
**34** Ritterazine O 22′*S*

**Table 2.** Murine P388 Lymphocytic Leukemia Inhibitory Activity ($ED_{50}$ nM) of Ritterazines A–Z (**20**–**45**)

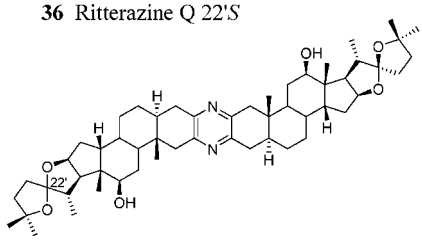
| ritterazine | year reported | P388 (nM) | ref |
|---|---|---|---|
| A (**20**) | 1994 | l4.2 | 16 |
| B (**21**) | 1995 | 0.17 | 17a |
| C (**22**) | 1995 | 102.3 | 17a |
| D (**23**) | 1995 | 17.5 | 17b |
| E (**24**) | 1995 | 3.8 | 17b |
| F (**25**) | 1995 | 0.81 | 17b |
| G (**26**) | 1995 | 0.81 | 17b |
| H (**27**) | 1995 | 17.8 | 17b |
| I (**28**) | 1995 | 15.3 | 17b |
| J (**29**) | 1995 | 14.0 | 17b |
| K (**30**) | 1995 | 10.4 | 17b |
| L (**31**) | 1995 | 11.1 | 17b |
| M(**32**) | 1995 | 16.7 | 17b |
| N (**33**) | 1997 | 522 | 17c |
| O (**34**) | 1997 | 2383 | 17c |
| P (**35**) | 1997 | 819 | 17c |
| Q (**36**) | 1997 | 657 | 17c |
| R (**37**) | 1997 | 2461 | 17c |
| S (**38**) | 1997 | 539 | 17c |
| T (**39**) | 1997 | 522 | 17c |
| U (**40**) | 1997 | 2341 | 17c |
| V (**41**) | 1997 | 2341 | 17c |
| W(**42**) | 1997 | 3631 | 17c |
| X (**43**) | 1997 | 3404 | 17c |
| Y (**44**) | 1997 | 4.0 | 17c |
| Z (**45**) | 1997 | 2200 | 17c |

ritterazine W (**42**) to 0.17 nM for ritterazine B (**21**). Not surprisingly, the most active constituent of *R. tokioka* (ritterazine B, **21**) contained nearly the same right-hand side steroidal unit (**21**: no 17α-hydroxy moiety) as the most active cephalostatins (**1**–**4**, **7**–**9**). Additionally, the same right-hand side unit is found in eight ritterazines (A, N, O, T, U, V, X, Z). A corrected structure of **32** was later reported by Fuchs and colleagues.[18]

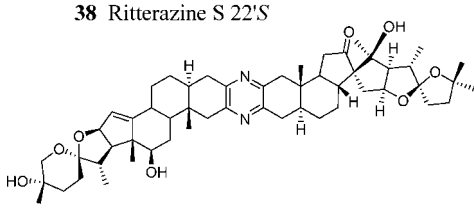
The ritterazines and cephalostatins share many common structural features in which two highly oxygenated $C_{27}$ steroidal units are fused via a pyrazine ring at C-2 and C-3 and both chains of the steroidal units usually form either 5/5 or 5/6 spiroketals. The cephalostatins in general are more oxygenated on the right side, whereas the ritterazines have the more oxygenated left side. Hydroxyl groups are seen at C-12, C-17, C-23, C-26, C-12′, and C-23′ in the cephalostatins, whereas C-12, C-7′, C-12′, C-17′, and C-25′ are hydroxylated in the ritterazines.[17a] Additionally, the cephalostatins (**1**–**4** and **7**–**9** in particular) in general exhibited more potent cancer cell growth inhibitory activity (P388) than the ritterazines.



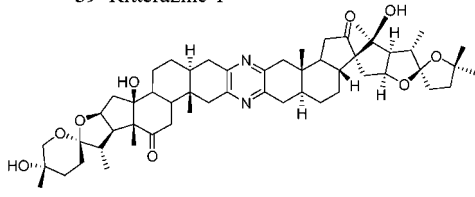
**35** Ritterazine P 22′*R*
**36** Ritterazine Q 22′*S*



**37** Ritterazine R 22′*R*
**38** Ritterazine S 22′*S*



**39** Ritterazine T

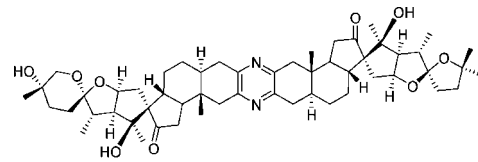


**40** Ritterazine U

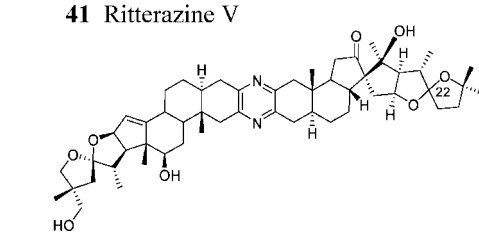
**Origin of Cephalostatins and Ritterazines.** It has been speculated that perhaps exposure of *C. gilchristi* to predators has necessitated, in part, the biosynthetic development of the cephalostatins.[4] However, occurrence of the cephalostatins and ritterazines in different phyla may indicate that a common or nearly identical marine microorganism ingested by both *C. gilchristi* and *R. tokioka* is actually responsible for the biosynthesis of these compounds.[8b,17a]

**Synthetic Efforts.** The availability of the cephalostatins and ritterazines from their only known natural sources, the marine worm *C. gilchristi* and the marine tunicate *R. tokioka*, is extremely limited. As a result, in vivo evaluation of these potent materials has been unfortunately rather limited to date. Outstanding cytotoxic potency combined with new and interesting molecular architecture and poor availability from nature immediately led to synthetic endeavors by various laboratories once the structure of **1** was published, most notably Professor P. L. Fuchs and colleagues at Purdue University.

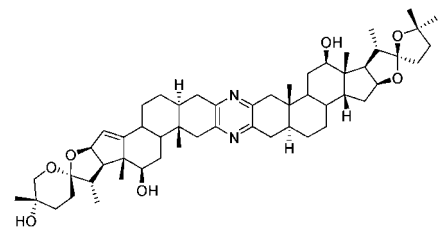
In 1998, ten years after **1** was reported, Fuchs and associates described the total synthesis of **1**, which required 65 synthetic operations and yielded 2 mg of material ($10^{-5}$% overall yield).[19] Also reported was the synthesis of two highly cytotoxic interphylal hybrids, designated ritterostatin $G_N1_N$ (**46**) and ritterostatin $G_N1_S$ (**47**). Ritterostatin $G_N1_N$, which is composed of the right unit of **1** and the right unit of ritterazine G, displayed inhibitory activity similar to **1** against several cancer cell lines. Ritterostatin $G_N1_S$, which is composed of the right unit of ritterazine G and the left unit of **1**, displayed cytotoxicity nearly equal to paclitaxel.[19,20] In 1996, Fuchs and colleagues reported the synthesis of dihydrocephalostatin 1 (**48**), which does not contain the Δ−14′ moiety found in **1**.[21] Significantly, investigation of **48** demonstrated that Δ−14′ is unnecessary for extremely potent cytotoxicity, as this compound was found to have a cytotoxicity profile essentially indistinguishable from **1** (compare correlation coefficients ≥0.9).[22]



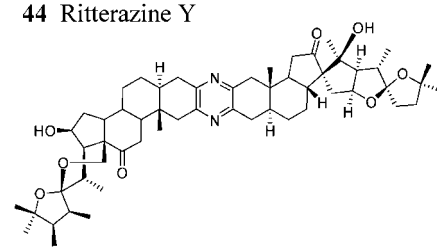
**41** Ritterazine V



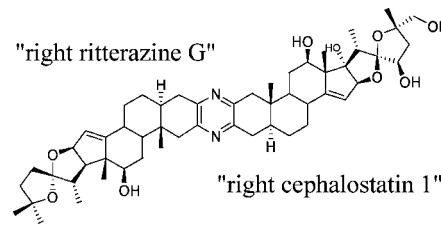
**42** Ritterazine W 22*R*
**43** Ritterazine X 22*S*



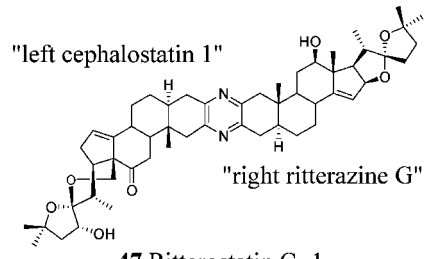
**44** Ritterazine Y



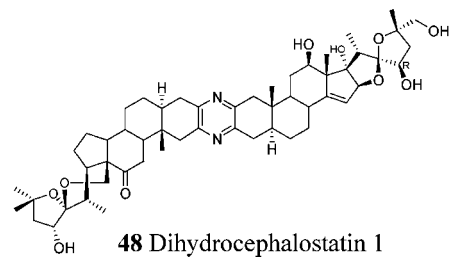
**45** Ritterazine Z




**46** Ritterostatin $G_N1_N$




**47** Ritterostatin $G_N1_S$



**48** Dihydrocephalostatin 1

Fuchs and co-workers also reported the total syntheses of cephalostatins 7 (**7**) and 12 (**12**) and ritterazine K (**30**).[23] Cephalostatins 7 and 12 share the same right-hand side unit as **1**. Both

**12** and **30** are symmetric, which of course reduced inherent synthetic complexity in comparison to **1**. Because the right-hand side steroidal unit of **1** is the most common among the cephalostatins and ritterazines and has been associated with the most potent cytotoxicity, Fuchs and colleagues reported separately the synthesis of this key unit.[24] A more efficient synthesis of the left unit of **7**, which has also been associated with potent cytotoxicity, was subsequently reported in 2005,[25] which rendered the previous synthesis of this unit, reported in 1995, obsolete.[26] Lastly, ritterazine M (**32**) succumbed to total synthesis by Fuchs and associates in 2002 in 16 operations with an overall linear yield of 12%.[27]

Other selected important synthetic contributions to the cephalostatins and ritterazines include the development by Heathcock and co-workers of a methodology to provide unsymmetrical bis-steroidal pyrazines, which, as previously mentioned, is essential for optimum cytotoxicity.[28] Winterfeldt and colleagues also reported the synthesis of unsymmetrical bis-steroidal pyrazines.[29] Phillips and Shair in 2007 reported short, scalable synthetic routes to the right steroidal units of ritterazines B (**21**), F (**25**), G (**26**), and H (**27**), which have only minor structural variations. This contribution also yielded potential structural reassignment of **21** and **25**.[30] A number of other contributions by Fuchs and associates yielded useful insight into cephalostatin and ritterazine synthesis.[31]

**A Brief Note on Nomenclature.** Professor Pettit and colleagues designated the two halves of the cephalostatins "right side" and "left side". Professor Fusetani and co-workers decided on an east/west motif for ritterazine nomenclature. Professor Fuchs, not to be outdone, adopted a north/south naming regimen. Because Professor Pettit was the first to report on this family of 45 bis-steroidal pyrazines, his nomenclature convention is honored here.

## References and Notes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