Synthesis of natural products containing spiroketals *via* intramolecular hydrogen abstraction

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Although known for over a quarter of a century, the oxidative radical cyclisation route to spiroketals has found limited use in natural product synthesis in comparison to classical approaches. Its successful application in this field of research forms the subject of this perspective.

Introduction

Spiroketals are found in a wide range of natural products that exhibit a broad range of biological properties. Traditionally, the synthesis of spiroketals has been conducted by the acid-catalysed cyclisation of a dihydroxyketone precursor, often producing the thermodynamic products arising from the maximum number of anomeric effects and minimum steric interactions.[1a–d] Despite the popularity of this method, it is not always amenable to the synthesis of delicate substrates and several natural products are known to contain non-anomeric spiroketals.[2a–c]

The oxidative radical cyclisation approach provides a valuable alternative to the classical spiroketal synthesis (Scheme 1). It is particularly useful when delicate or acid-labile substrates are involved. If spiroketals of a particular configuration are required, this method often facilitates the synthesis of kinetic products.

The first spiroketal synthesis using a radical cyclisation of an aliphatic alcohol was reported in 1969.[3] It was found that a series of diols **1a–c** underwent a double intramolecular hydrogen abstraction (IHA) when treated with lead tetraacetate in benzene under reflux, furnishing the spiroketals **2a–c** (Scheme 2).

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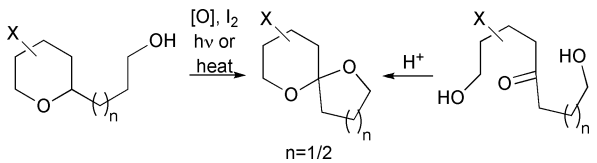

Scheme 1 Classical and oxidative radical cyclisation approach to spiroketals.

Using this methodology several years later, Suárez[4] carried out the oxidative cyclisation of labdanediol **3** using lead tetraacetate and iodine under light irradiation, demonstrating that the reaction was amenable to complex substrates and proceeds in high yield under photolytic conditions. The reaction provided a 77% yield of spiroketals **4a** and **4b** in a 3 : 1 ratio (Scheme 3).

Suárez later investigated the cyclisation of the ε-hydroxy-tetrahydropyran (26-hydroxyfurostan) **5** to spirostan sapogenin **6** and subsequently elucidated the likely mechanism (Scheme 4).[5] Initially, the alkoxy radical is formed from a thermal or photochemical homolytic cleavage of the O–I bond in the alkyl hypoiodite **8**. The alkyl hypoiodite itself is formed from reaction of alcohol **7** with acetyl hypoiodite which is generated *in situ* from the reaction between lead tetraacetate and iodine. Initially, both the 1,5 and 1,6-hydrogen shift pathways were thought feasible. However, subsequent use of deuterium-labelled substrates during

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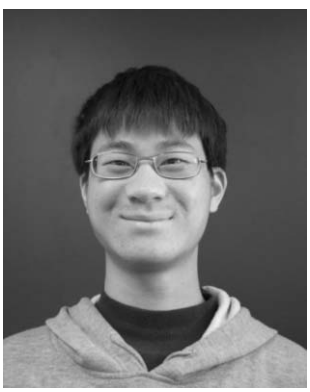
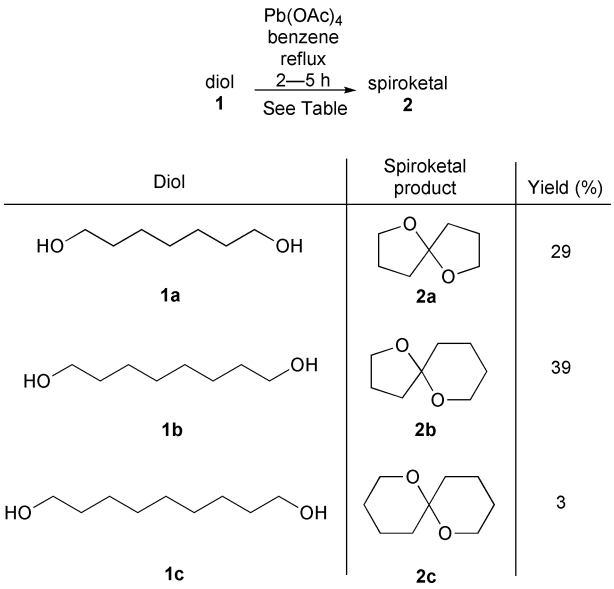


Yen-Cheng (William) Liu

Yen-Cheng (William) Liu was born in Taipei, Taiwan. He studied medicinal chemistry at The University of Auckland, New Zealand, and obtained a BSc (Hons) degree in 2006 under the supervision of Professor Margaret Brimble working on the synthesis of spiroketals related to the rubromycins. He is currently a fourth year PhD student in the Brimble research group investigating the synthesis of aryl spiroketals by oxidative radical cyclisation involving the intramolecular hydrogen abstraction process.



Scheme 2 Double IHA of aliphatic diols **1** using lead tetraacetate.[3]

the cyclisation proved the reaction proceeds exclusively *via* a 1,6-hydrogen shift[5] and the existence of the acetyl hypoiodite was later confirmed by NMR studies.[6] Although the formation of five-membered rings generally produces higher yields than their six-membered counterparts,[7] the yield for the formation of six-membered rings can be increased if the proton to be abstracted is attached to an oxygen-substituted carbon.[8,9] For a successful IHA to occur, the optimum distance between the O-radical and the proton to be abstracted should be around 3 Å.[9]

In 1983, the scope of this reaction was expanded when it was shown that the oxidative radical cyclisation of alcohol **9** could be conducted with mercuric oxide and iodine, affording spiroketals **10a** and **10b**. Acid-catalysed equilibration of the spiroketal mixture led to the exclusive formation of the thermodynamically favoured spiroketal **10a** (Scheme 5).[10] This mercury-mediated protocol was

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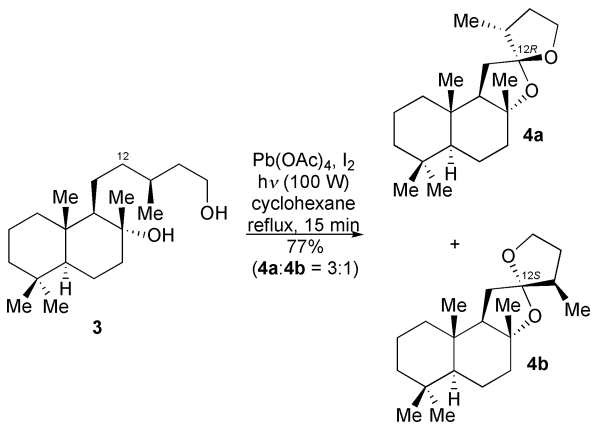
Margaret Brimble was born in Auckland, New Zealand. She completed an MSc in Chemistry at the University of Auckland. She was awarded a UK Commonwealth Scholarship to undertake her PhD studies at Southampton University. In 1986 she was appointed as a lecturer at Massey University, and in 2000 she took up the Chair in Organic and Medicinal Chemistry at the University of Auckland where her research program focuses on the synthesis of spiroacetal-containing natural products, pyranonaphthoquinone antibiotics, alkaloids and peptidomimetics for the treatment of neurodegenerative disorders.



Scheme 3 Oxidative radical cyclisation of labdanediol **3** by Suárez.[4]

subsequently used by Kay in the synthesis of the avian toxin (±)-talaromycin B.[11]

A major breakthrough came in 1984 when Suárez reported the diastereoselective synthesis of the spiroketal-containing steroid **6** by the photolytic oxidative radical spiroketalisation of alcohol **5** using the non-toxic hypervalent iodine reagent iodobenzene diacetate ($PhI(OAc)_2$) (Scheme 6).[12a–b] Only one equivalent of $PhI(OAc)_2$ and iodine is required for completion of the reaction, in contrast to the excess of lead tetraacetate and iodine usually required for its variant. Further superiority of this reagent was subsequently demonstrated during the cyclisation of labdanediol **3**[12a,13a–b] although in the presence of light, carboxylic acid substrates tend to undergo a Hunsdiecker-type reaction in preference to spiroketal formation.[13a,14]

In 2000, Markó showed that the diastereoselective synthesis of spiroketals **12** could be achieved by the electrochemical oxidative cyclisation of a series of hydroxy-tetrahydropyrans **11**. This analogous procedure proceeds through a similar mechanism, wherein the vital oxidation step is carried out electrochemically (Scheme 7).[15]

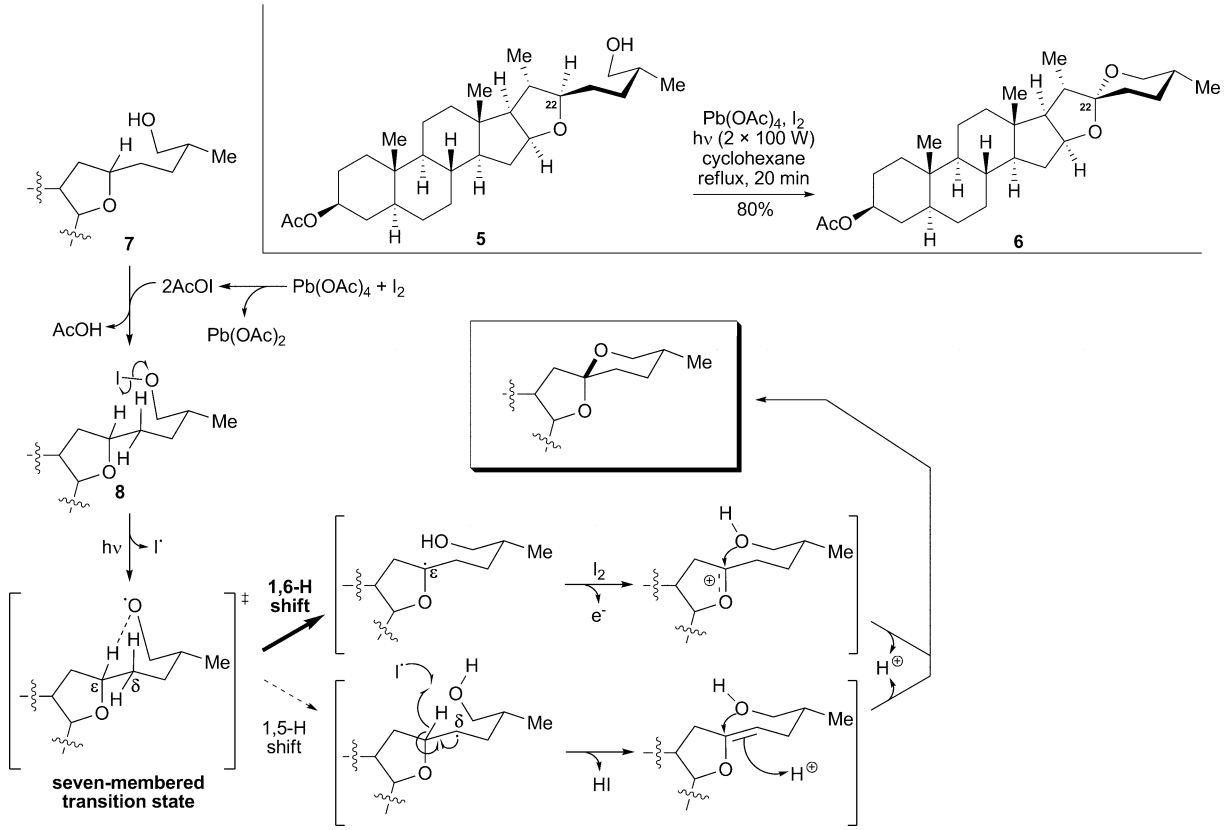
Use in natural product synthesis

Avermectin A_{1a}

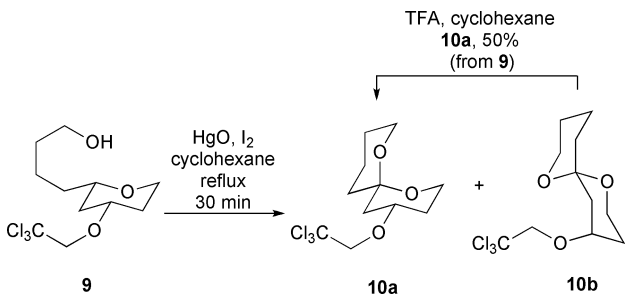
The avermectins are a series of macrocyclic lactone derivatives with potent anthelmintic properties.[16] During the total synthesis of avermectin A_{1a} **13**, the aglycon moiety was constructed using the mercury mediated oxidative radical cyclisation protocol, one of the earliest examples reporting the use of this methodology in a complex molecule synthesis.[17a–b] Alcohol **14** underwent spiroketalisation upon irradiation in the presence of mercuric oxide and iodine to produce spiroketal **15** as a single diastereomer (Scheme 8).

Calyculin A

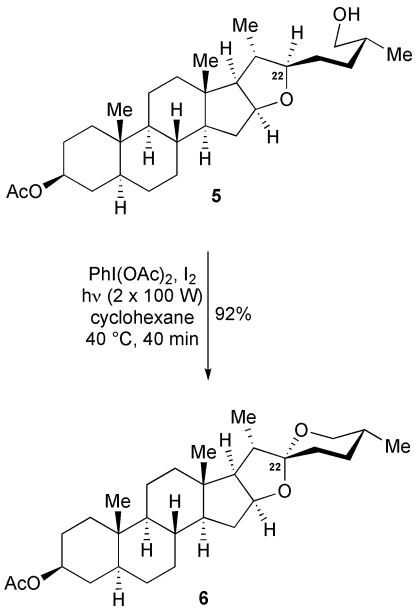
Calyculin A **16** is a nanomolar inhibitor of two of the four major serine/threonine protein phosphatases.[18] Trost reported the synthesis of the 5,6-spiroketal moiety of (–)-calyculin A using the mercury-mediated cyclisation protocol. Thus, a 1 : 1 mixture of keto alcohols **17a-b** underwent oxidative cyclisation using mercuric oxide and iodine to afford a 1 : 1 mixture of epimeric



Scheme 4 Mechanism of the oxidative radical spiroketalisation.[5]



Scheme 5 Use of mercuric oxide by Kay.[10]



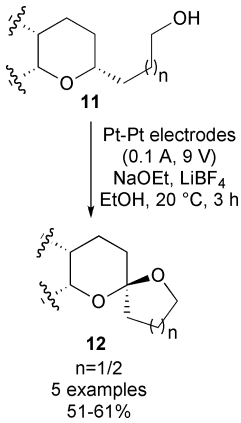
Scheme 6 Use of iodobenzene diacetate by Suárez.[12a–b]

spiroketals **18a** and **18b**. Equilibration unfortunately led to the formation of the undesired diastereomer **18a** as the major product (Scheme 9).[19]

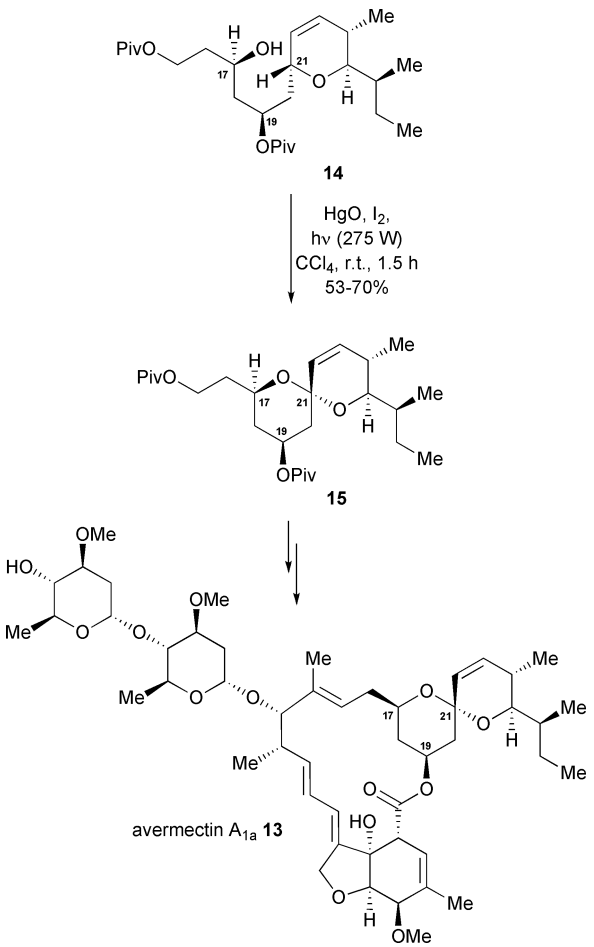
Polyether antibiotics–salinomycins, narasin and CP44,161

The polyether antibiotics, salinomycin **19**,[20] narasin **20**,[21] deoxy-(*O*-8)-*epi*-17-salinomycin **21**[22] and antibiotic CP44,161 **22**[23] all possess a common 1,6,8-trioxadispiro[4.1.5.3]pentadec-13-ene, a rare motif in polyether ionophores (Fig. 1).

Building on previous model work in our own laboratory,[24a–b] the stereoselective synthesis of the bis-spiroketal fragment present in deoxy-(*O*-8)-*epi*-17-salinomycin **21** was successfully achieved.[25] Photolytic oxidative radical cyclisation of either spiroketal iodohydrin **23a** or **23b** in the presence of iodobenzene diacetate and iodine produced a 1.7 : 1 ratio of bis-spiroketals **24a** and **24b**. Bis-spiroketal **24a** possesses the correct absolute stereochemistry present in deoxy-(*O*-8)-*epi*-17-salinomycin **21** and thus was considered a suitable intermediate for the synthesis of aldehyde **25** to which the pyran moiety could be appended (Scheme 10). However, despite considerable efforts, displacement of iodide in bis-spiroketal **24a** resulted in concomitant silyl group cleavage at C9, curtailing efforts towards the synthesis of aldehyde **25**.[26] In



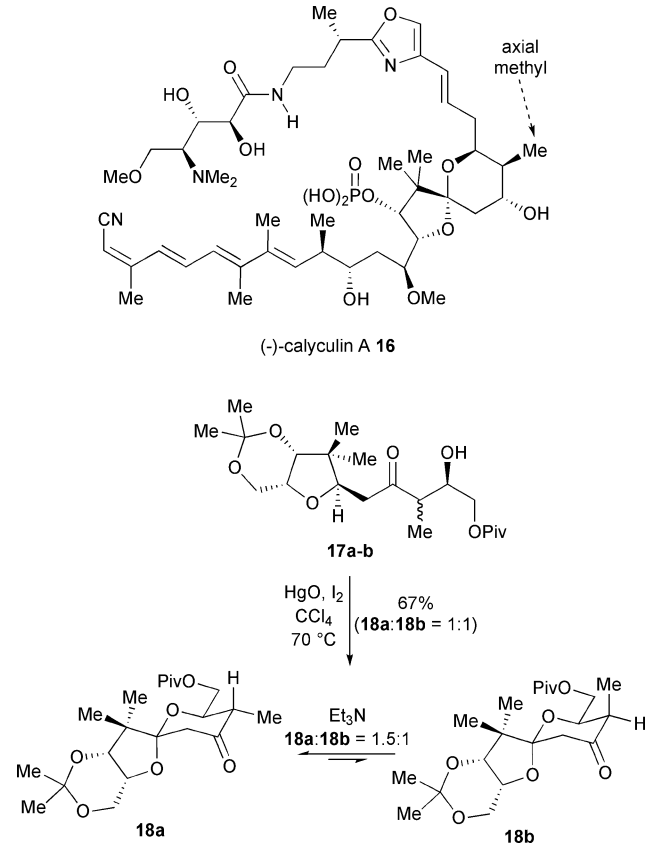
Scheme 7 Electrochemical oxidative cyclisation by Markó.[15]



Scheme 8 Synthesis of spiroketal **15** during the total synthesis of avermectin A_{1a} **13** by Danishefsky.[17a–b]

order to circumvent this problem, an alternative protecting group strategy was sought.

Having established a suitable route that employed an acetate at C2 during the synthesis of a model bis-spiroketal,[26] an investigation into the synthesis of the bis-spiroketal moiety of CP44,161 **22** was conducted.[27a–b] Thus, the 1 : 1 mixture of diastereomeric hydroxyspiroketals **26a-b** and **27a-b** were subjected to a photolytic oxidative cyclisation in the presence of iodobenzene diacetate



Scheme 9 (–)-Calyculin A **16** and synthesis of spiroketals **18a-b** by Trost.[19]

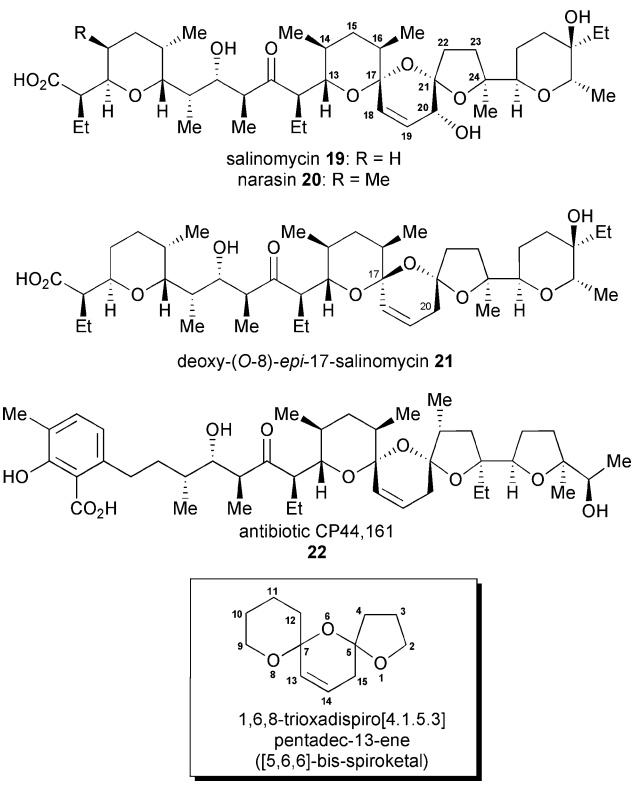
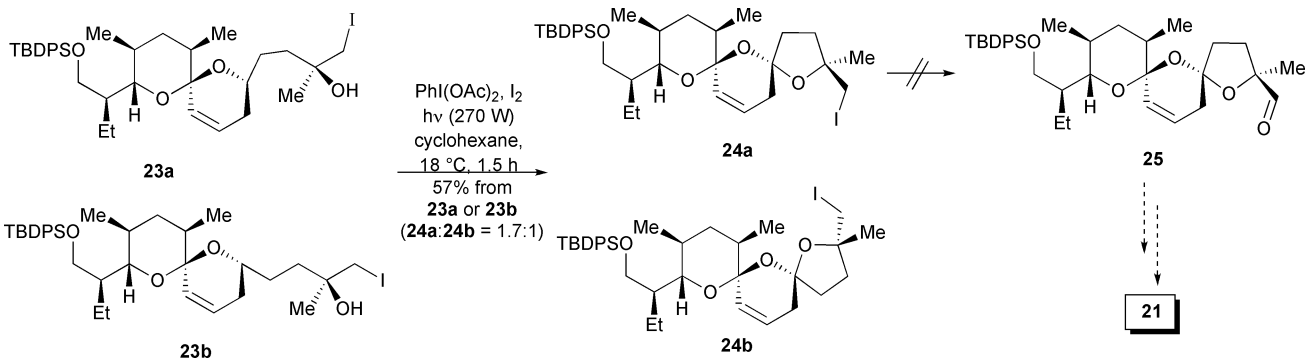
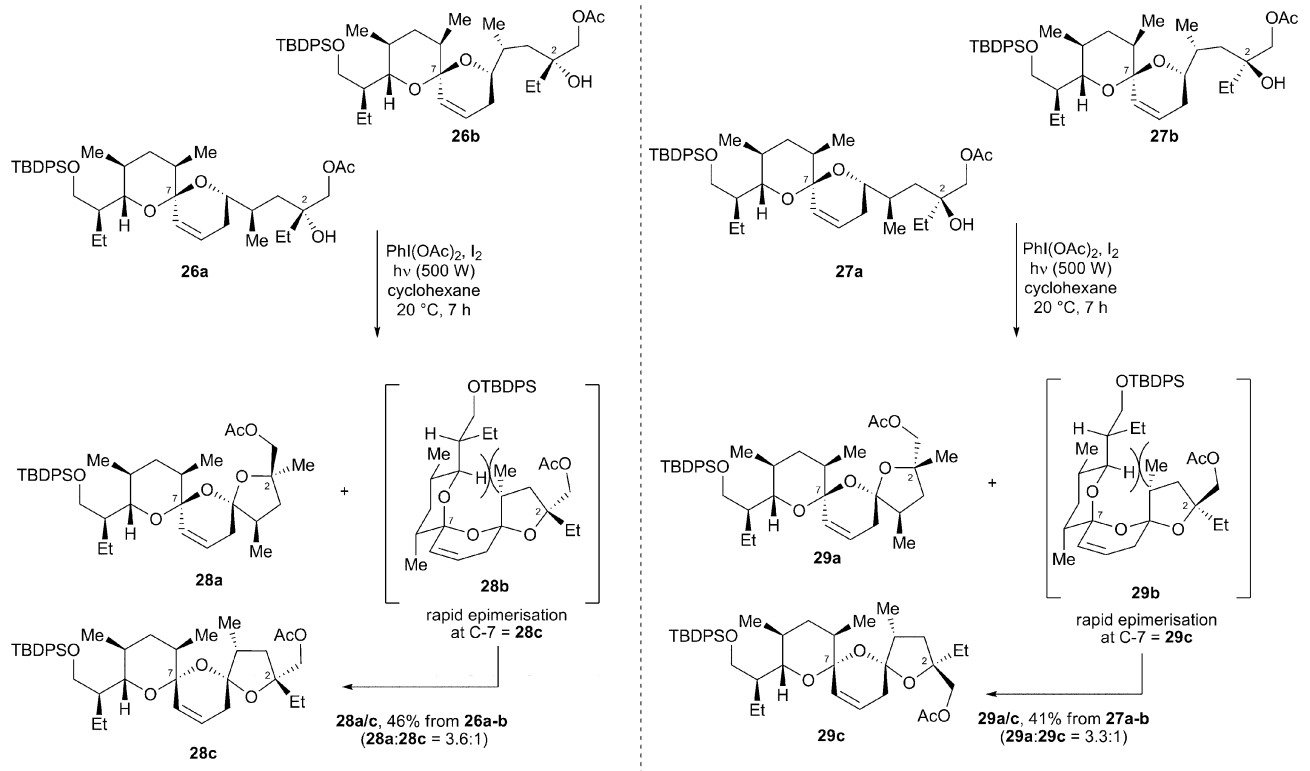


Fig. 1 Salinomycin **19**, narasin **20**, deoxy-(*O*-8)-*epi*-17-salinomycin **21** and CP44,161 **22** with a shared [5,6,6]-bis-spiroketal motif.



Scheme 10 Synthesis of bis-spiroketals **24a** and **24b**[25] and failed conversion to aldehyde **25** by Brimble.[26]



Scheme 11 Synthesis of bis-spiroketals **28a/c** and **29a/c** by Brimble.[27a–b]

and iodine delivering their respective bis-spiroketals **28** and **29**. In each case, *cis* bis-spiroketals **28a** and **29a** were produced as the major diastereomer. *Trans* bis-spiroketals **28b** and **29b** were not observed as they underwent rapid epimerisation at C7 to form *cis* bis-spiroketals **28c** and **29c** respectively. Bis-spiroketal **29c** has the correct stereochemistry at C2 and the same absolute stereochemistry found in both salinomycin **19** and antibiotic CP44,161 **22** (Scheme 11).

Ciguatoxin CTX3C

Ciguatoxin CTX3C **30** is the principle polycyclic ether neurotoxin responsible for ciguatera fish poisoning (Fig. 2).[28]

Building on from previous model work,[29] the spiroketal containing the IJKLM portion **32** was synthesised from alcohol **31** using a photolytic oxidative cyclisation in the presence iodobenzene diacetate and iodine. The 1 : 1 mixture of spiroketals produced underwent acid-catalysed equilibration delivering spiroketal **32**

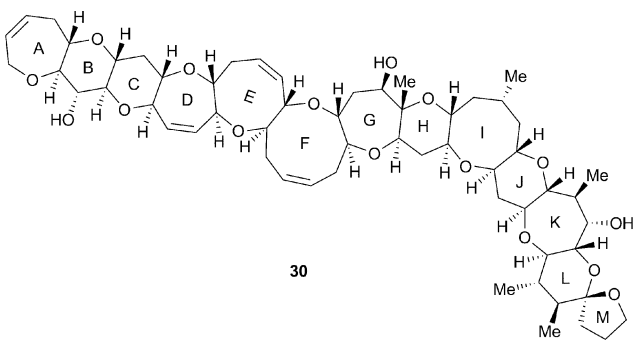
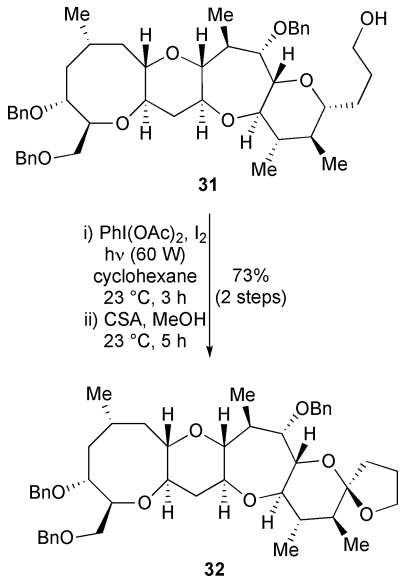


Fig. 2 Ciguatoxin CTX3C **30**.

exclusively which possesses the correct configuration present in ciguatoxin CTX3C **30** (Scheme 12).[30]



Scheme 12 Synthesis of pentacyclic IJKLM fragment **32** of ciguatoxin CTX3C by Fujiwara.[30]

Spirolides B and D

Our own laboratory reported the synthesis of the bis-spiroketal fragments related to the marine biotoxins,[31] spirolides B **33** and D **34** using iterative oxidative radical cyclisations. Extending a successful synthesis of a racemic model unsaturated 5,5,6-bis-spiroketal,[32] the oxidative radical cyclisation was extended to a stereoselective synthesis. Thus, irradiation of either pair of 1 : 1 inseparable diastereomeric alcohols **35a–b** or **35c–d** in the presence of iodobenzene diacetate and iodine delivered 1 : 1 mixtures of diastereomeric spiroketals **36a-b** and **36c-d** respectively. Silyl group cleavage from all four diastereomeric spiroketals **36a–d** (1 : 1 : 1 : 1) gave the four spiroketal alcohols **37a-d** (1 : 1 : 1 : 1) which underwent a second oxidative cyclisation. A 1 : 1 : 1 : 1 mixture of diastereomeric bis-spiroketals **38a–d** was obtained which underwent acid-catalysed equilibration to produce bis-spiroketal **38b** (18%) which was separable from an inseparable mixture of bis-spiroketals **38a** and **38c** (3.3 : 1, 68%). The bis-spiroketal **38a** possesses the same absolute stereochemistry present in spirolides B and D. Although bis-spiroketals **38a** and **38c** were further elaborated to bis-spiroketals **39a** and **39c** respectively, introduction of a synthetic handle at C22 proved troublesome (Scheme 13).[33a–b]

Extending this work further,[34a–b] the synthesis of the fully functionalized bis-spiroketal **40** was achieved. Oxidative cyclisation of a 1 : 1 mixture of diastereomeric alcohols **41** using iodobenzene diacetate and iodine furnished a 1 : 1 mixture of two diastereomeric spiroketals **42** which underwent silyl ether deprotection to give alcohols **43**. A second oxidative radical cyclisation of alcohols **43** afforded bis-spiroketals **44a–d** as a 1 : 1 : 1 : 1 mixture of diastereomers. The 1 : 1 : 1 : 1 mixture of diastereomeric spiroketals **44a–d** was treated with *m*-CPBA, effecting concomitant epoxidation and equilibration remarkably resulting in one diastereomer **45**. Further elaboration gave bis-spiroketal **40**, a diastereomer of the bis-spiroketal fragment present in spirolides B and D (Scheme 14).

Bistramide C

Bistramide C **46** is a bioactive cyclic polyether which exhibits potent *in vitro* inhibition against numerous tumour cell lines.[35] Wipf and co-workers carried out a total synthesis of a stereoisomer of bistramide C using an oxidative cyclisation and subsequently assigned the configuration of the natural product.[36] This assignment was later confirmed through total synthesis that also involved a photolytic oxidative radical spiroketalisation.[37] Thus, alcohol **47** underwent the key photolytic oxidative cyclisation in the presence of iodobenzene diacetate and iodine followed by reductive removal of the pivaloate to afford a 3.8 : 1 mixture of spiroketal **48** and iodospiroketal **49**. Iodospiroketal **49** was treated with azobisisobutyronitrile and tributyltin hydride to produce spiroketal **48** which was used as an intermediate in the total synthesis of (+)-bistramide C **46** (Scheme 15).

(+)-Spirolaxine methyl ether

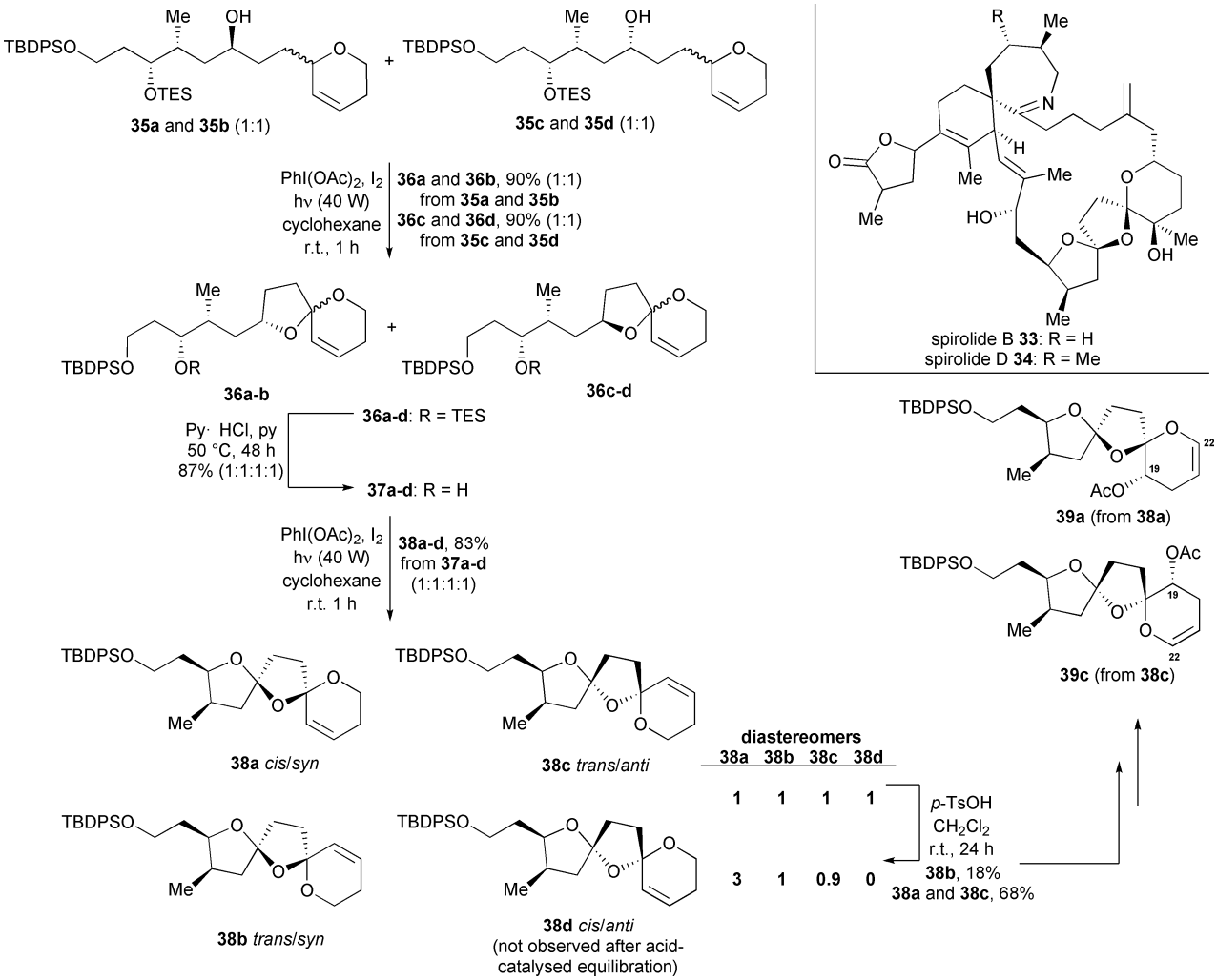
Dallavalle[38] reported the total synthesis of the anti-*Helicobacter pylori* agent (+)-spirolaxine methyl ether **50**[39] in which spiroketalisation was achieved using an oxidative cyclisation. Upon irradiation in the presence of mercuric oxide and iodine, alcohol **51** underwent oxidative radical cyclisation affording spiroketal **52** as a single diastereomer, a key intermediate in the total synthesis of (+)-spirolaxine methyl ether **50** (Scheme 16).

Ritterazines and cephalostatins

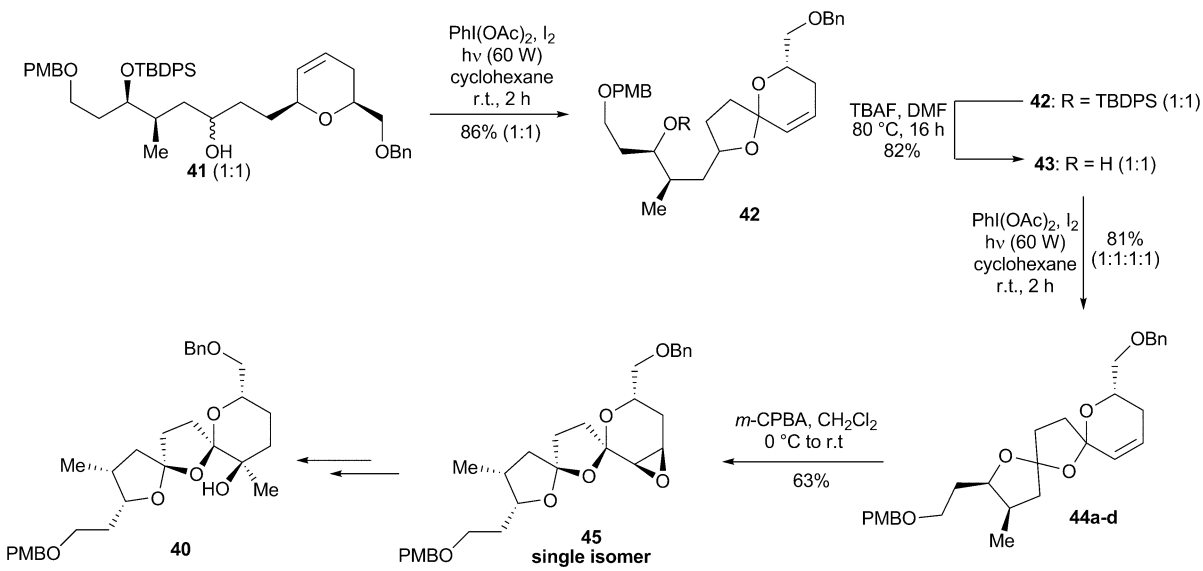
The ritterazines[40] and cephalostatins[41] comprise a family of 45 trisdecacyclic bis-steroidal pyrazines that display potent cytotoxicity against human tumors, ranking among the most potent anticancer agents ever tested by the NCI.[42] Selected members of this family that contain spiroketal moieties are shown in Fig. 3.

Based on extensive model work,[43] Fuchs reported the total synthesis of ritterazine M **53** using a photolytic oxidative radical cyclisation of alcohol **58** with iodobenzene diacetate and iodine giving [5,6]-spiroketals **59a-b** in a 5.5 : 1 ratio and excellent yield.[44] Spiroketal **59a** was subsequently used for the total synthesis and structure reassignment of ritterazine M **53** (Scheme 17).

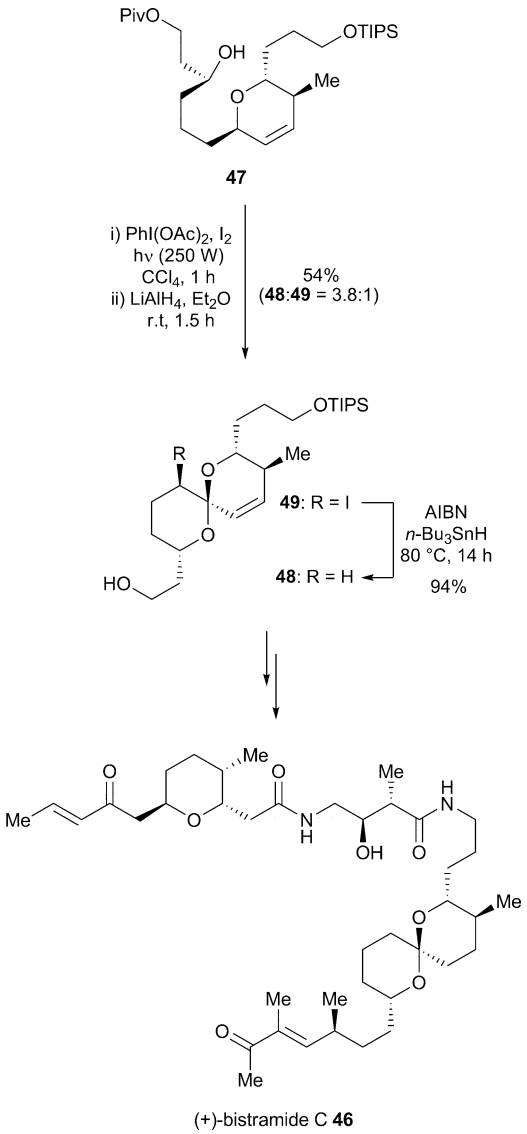
Due to their scarcity from nature and unknown mechanism of action, several studies towards the synthesis of analogues of the ritterazines and the cephalostatins have been reported, several of which employed the oxidative radical spiroketalisation. Suárez synthesized a series of C22 and C25 stereoisomers of cephalostatin and upon probing the acid stability of the spiroketal products, it was discovered that compounds with the greatest acid-catalysed reactivity possessed the natural stereochemistry.[45a,b] Also using this methodology, Fuchs reported the synthesis of a series of [5,5]-spiroketal analogues of cephalostatin[46] and Shair reported the synthesis of the 'northern' halves of ritterazines B (**54**), F (**55**), G (**56**), and H, which ultimately led to the



Scheme 13 Structures of spirolides B **33** and D **34**, synthesis of bis-spiroketals **39a/c** by Brimble.[33a–b] *cis/trans* denotes the arrangement of the both terminal ring oxygen atoms across the central ring; *syn/anti* denotes the arrangement of the central ring oxygen and the substituents attached to the outer THF ring.

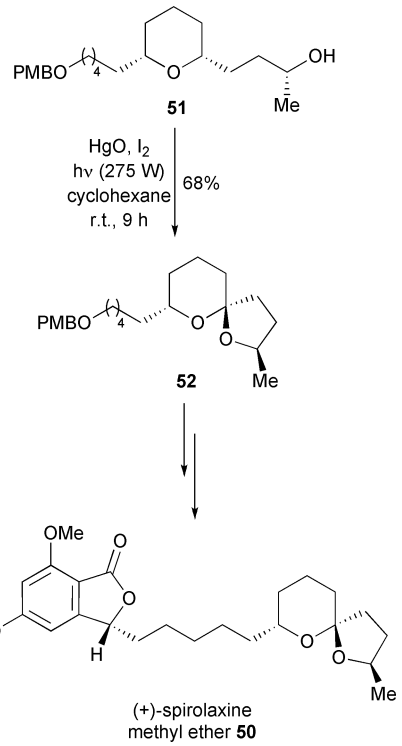


Scheme 14 Synthesis of bis-spiroketal **40** by Brimble.[34a–34b]



Scheme 15 Synthesis of (+)-bistramide C **46** by Wipf.[37]

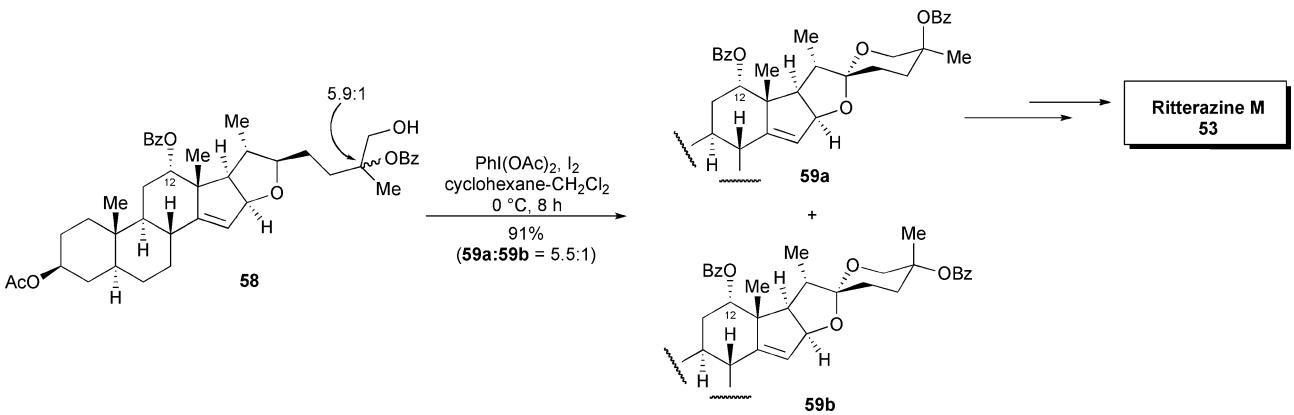
reassignment of the [5,5]-spiroketal moiety of ritterazines B and F.[47] These studies have proven the value of this mild spiroketalisation reaction in the remote functionalisation of steroid nuclei.



Scheme 16 Synthesis of (+)-spirolaxine methyl ether **50** by Dallavalle.[38]

Conclusions

The oxidative radical cyclisation provides an excellent method for the synthesis of spiroketals and this perspective article highlights the utility of this approach in the field of natural product synthesis. However, the broad importance of this methodology in organic synthesis, particularly in carbohydrate chemistry,[48a–c] should not be understated. It is envisaged that this method will continue to provide a valuable synthetic tool in complex molecule synthesis.



Scheme 17 Total synthesis of ritterazine M **53** by Fuchs.[43,44]

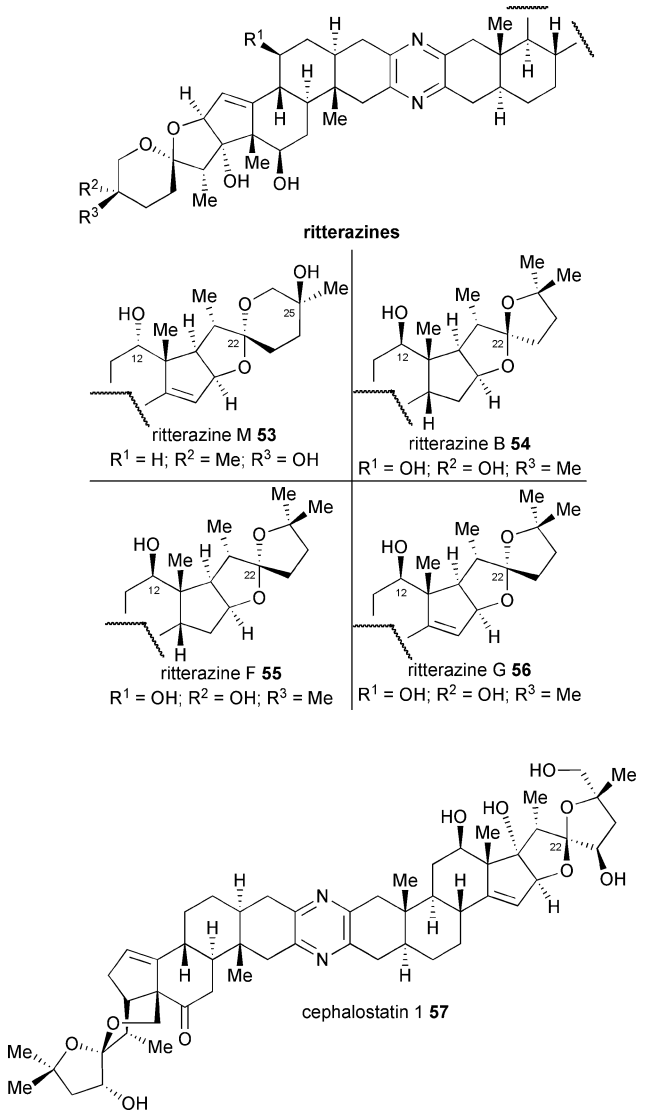


Fig. 3 Selected ritterazines and cephalostatin 1.

References

1 For general reviews on the synthesis and biological properties of spiroketals, see:(*a*) B. Rama Raju and A. K. Saikia, *Molecules*, 2008, **13**, 1942–2038; (*b*) T. K. Mead and B. N. Brewer, *Curr. Org. Chem.*, 2003, **7**, 227–256; (*c*) M. A. Brimble and D. P. Furkert, *Curr. Org. Chem.*, 2003, **7**, 1461–1484; (*d*) M. F. Jacobs and W. Kitching, *Curr. Org. Chem*, 1998, **2**, 395–436.

2 For reviews regarding non-anomeric spiroketals, see:(*a*) J. E. Aho, P. M. Pikho and T. K. Rissa, *Chem. Rev.*, 2005, **105**, 4406–4440; (*b*) S. Favre, P. Vogel and S. Gerber-Lemaire, *Molecules*, 2008, **13**, 2570–2600; (*c*) M. A. Rizzacasa and A. Pollex, *Org. Biomol. Chem.*, 2009, **7**, 1053–1059.

3 V. M. Mićović, S. Stojčić, M. Bralović, S. Mladenović, D. Jeremić and M. Stefanović, *Tetrahedron*, 1969, **25**, 985–993.

4 A. G. González, C. G. Francisco, R. Freire, R. Hernández, J. A. Salazar and E. Suárez, *Tetrahedron Lett.*, 1976, **17**, 2725–2728.

5 C. G. Francisco, R. Freire, R. Hernández, M. C. Medina and E. Suárez, *Tetrahedron Lett.*, 1983, **24**, 4621–4624.

6 J. L. Courtneidge, J. Lusztyk and D. Pagé, *Tetrahedron Lett.*, 1994, **35**, 1003–1006.

7 G. Majetich and K. Wheless, *Tetrahedron*, 1995, **51**, 7095–7129.

8 C. G. Francisco, R. Freire, A. J. Herrera, I. Peréz-Martín and E. Suárez, *Org. Lett.*, 2002, **4**, 1959–1961.

9 C. G. Francisco, A. J. Herrera, A. R. Kennedy, D. Melián and E. Suárez, *Angew. Chem., Int. Ed.*, 2002, **41**, 856–858.

10 I. T. Kay and E. G. Williams, *Tetrahedron Lett.*, 1983, **24**, 5915–5918.

11 I. T. Kay and D. Bartholomew, *Tetrahedron Lett.*, 1984, **25**, 2035–2038.

12 (*a*) J. I. Concepción, C. G. Francisco, R. Hernández, J. A. Salazar and E. Suárez, *Tetrahedron Lett.*, 1984, **25**, 1953–1956; (*b*) P. de Armas, J. I. Concepción, C. G. Francisco, R. Hernández, J. A. Salazar and E. Suárez, *J. Chem. Soc., Perkin Trans. 1*, 1989, 405–411.

13 (*a*) J. de Pascual Teresa, J. G. Urones, A. Montaña and P. Basabe, *Tetrahedron Lett.*, 1985, **26**, 5717–5720; (*b*) J. G. Urones, P. Basabe, I. S. Marcos, D. D. Martín, M. J. Sexmero, M. H. Peral and H. B. Broughton, *Tetrahedron*, 1992, **48**, 10389–10398.

14 J. I. Concepción, C. G. Francisco, R. Freire, R. Hernández, J. A. Salazar and E. Suárez, *J. Org. Chem.*, 1986, **51**, 402–404.

15 I. E. Markó, *Tetrahedron Lett.*, 2000, **41**, 4383–4387.

16 R. W. Burg, B. M. Miller, E. E. Baker, J. Birnbaum, S. A. Currie, R. Hartman, Y.-L. Kong, R. L. Monaghan, G. Olson, I. Putter, J. B. Tunac, H. Wallick, E. O. Stapley, R. Ōiwa and S. Ōmura, *Antimcrob. Agents. Chemother.*, 1979, **15**, 361–367.

17 (*a*) S. J. Danishefsky, D. M. Armistead, F. E. Wincott, H. G. Selnick and R. Hungate, *J. Am. Chem. Soc.*, 1987, **109**, 8117–8119; (*b*) S. J. Danishefsky, D. M. Armistead, F. E. Wincott, H. G. Selnick and R. Hungate, *J. Am. Chem. Soc.*, 1989, **111**, 2967–2980.

18 S. Matsunaga and N. Fusetani, *Tetrahedron Lett.*, 1991, **32**, 5605–5606 and references therein.

19 B. M. Trost and J. A. Flygare, *Tetrahedron Lett.*, 1994, **35**, 4059–4062.

20 H. Kinashi, N. Ōtake, H. Yonehara, S. Sato and Y. Saito, *Tetrahedron Lett.*, 1973, **14**, 4955–4958.

21 J. L. Occolowitz, D. H. Berg, M. Debono and R. L. Hamill, *Biol. Mass Spectrom.*, 1976, **3**, 272–277.

22 J. W. Westley, J. F. Blount, R. H. Evans, Jr. and C.-M. Liu, *J. Antibiot.*, 1977, **30**, 610–612.

23 J. Tone, R. Shibatawa, M. Maeda, K. Inoue, S. Nishiyama, M. Ishiguro, W. P. Cullen, J. B. Routien, L. R. Chappell, C. E. Moppett, M. T. Jefferson, and W. D. Celmer, 18th Intersociety Conference on Antimicrobial Agents Chemotherapy, Atlanta, Ga, Oct. 2–4, 1978.

24 (*a*) M. A. Brimble, G. M. Williams, R. Baker and M. James, *Tetrahedron Lett.*, 1990, **31**, 3043–3046; (*b*) M. A. Brimble, G. M. Williams and R. Baker, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2221–2227.

25 M. A. Brimble and G. M. Williams, *J. Org. Chem.*, 1992, **57**, 5818–5822.

26 P. R. Allen, M. A. Brimble and F. A. Fares, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2403–2411.

27 (*a*) P. A. Allen, M. A. Brimble and H. Prabaharan, *Synlett*, 1999, 295–298; (*b*) P. R. Allen, M. A. Brimble and F. A. Fares, *J. Chem. Soc., Perkin Trans. 1*, 2001, 379–389.

28 M. Satake, M. Murata and T. Yasumoto, *Tetrahedron Lett.*, 1993, **34**, 1975–1978.

29 D. Domon, K. Fujiwara, Y. Ohtaniuchi, A. Takezawa, S. Takeda, H. Kawasaki, A. Murai, H. Kawai and T. Suzuki, *Tetrahedron Lett.*, 2005, **46**, 8279–8283.

30 D. Domon, K. Fujiwara, A. Murai, H. Kawai and T. Suzuki, *Tetrahedron Lett.*, 2005, **46**, 8285–8288.

31 T. Hu, J. M. Curtis, Y. Oshima, M. A. Quilliam, J. A. Walter, W. M. Watson-Wright and J. L. C. Wright, *J. Chem. Soc., Chem. Commun.*, 1995, 2159–2161.

32 V. Caprio, M. A. Brimble and D. P. Furkert, *Tetrahedron*, 2001, **57**, 4023–4034.

33 (*a*) D. P. Furkert and M. A. Brimble, *Org. Lett.*, 2002, **4**, 3655–3658; (*b*) M. A. Brimble and D. P. Furkert, *Org. Biomol. Chem.*, 2004, **2**, 3573–3583.

34 (*a*) K. Meilert and M. A. Brimble, *Org. Lett.*, 2005, **7**, 3497–3500; (*b*) K. Meilert and M. A. Brimble, *Org. Biomol. Chem.*, 2006, **4**, 2184–2192.

35 J.-F. Biard, C. Roussakis, J.-M. Kornprobst, D. Gouiffes-Barbin, J.-F. Verbist, P. Cotelle, M. P. Foster, C. M. Ireland and C. Debitus, *J. Nat. Prod.*, 1994, **57**, 1336–1345 and references therein.

36 P. Wipf, Y. Uto and S. Yoshimura, *Chem.–Eur. J.*, 2002, **8**, 1670–1681.

37 P. Wipf and T. D. Hopkins, *Chem. Commun.*, 2005, 3421–3423.

38 R. Nannei, S. Dallavalle, M. Lucio, A. Bava and G. Nasini, *J. Org. Chem.*, 2006, **71**, 6277–6280.

39 A. Arnone, G. Assante, G. Nasini and O. Vajna de Pava, *Phytochemistry*, 1990, **29**, 613–616.

40 S. Fukuzawa, S. Matsunaga and N. Fusetani, *Tetrahedron*, 1995, **51**, 6707–6716.

41 G. R. Pettit, M. Inoue, Y. Kamano, D. L. Herald, C. Arm, C. Dufresne, N. D. Christie, J. M. Schmidt, D. L. Doubek and T. S. Krupa, *J. Am. Chem. Soc.*, 1988, **110**, 2006–2007.
42 Reviews regarding the isolation, biological activity and synthesis of the cephalostatins and ritterazines are available(*a*) B. R. Moser, *J. Nat. Prod.*, 2008, **71**, 487–491; (*b*) S. Lee, T. G. LaCour and P. Fuchs, *Chem. Rev.*, 2009, **109**, 2275–2314.
43 S. Lee, T. G. LaCour, D. Lantrip and P. L. Fuchs, *Org. Lett.*, 2002, **4**, 313–316.
44 S. Lee and P. L. Fuchs, *Org. Lett.*, 2002, **4**, 317–318.
45 (*a*) C. Betancor, R. Freire, I. Pérez-Martín, T. Prangé and E. Suárez, *Org. Lett.*, 2002, **4**, 1295–1297; (*b*) C. Betancor, R. Freire, I. Pérez-Martín, T. Prangé and E. Suárez, *Tetrahedron*, 2005, **61**, 2803–2814.
46 J. S. Lee and P. L. Fuchs, *Org. Lett.*, 2003, **5**, 2247–2250.
47 S. T. Phillips and M. D. Shair, *J. Am. Chem. Soc.*, 2007, **129**, 6589–6598.
48 Recent examples(*a*) A. Martín, I. Pérez-Martín, L. M. Quintanal and E. Suárez, *Org. Lett.*, 2007, **9**, 1785–1788; (*b*) A. Martín, L. M. Quintanal and E. Suárez, *Tetrahedron Lett.*, 2007, **48**, 5507–5511; (*c*) C. G. Francisco, A. J. Herrera and E. Suárez, *J. Org. Chem.*, 2002, **67**, 7439–7445.

