The Ramberg-Bäcklund Reaction 70 Years On

Joanne E. Harvey* and Mark J. Bartlett

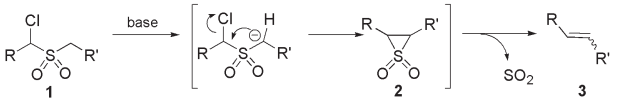
School of Chemical and Physical Sciences, Victoria University, PO Box 600, Wellington 6140
(e-mail: *joanne.harvey@vuw.ac.nz*)

Introduction

Ten years ago, on a train between Warsaw and Krakow, I (JEH) learned about the Ramberg-Bäcklund reaction (RBR). At the time, I was a PhD student at the Australian National University, and my informant was Margaret Brimble, then at the University of Sydney. We had both attended the ICOS-13 conference in Warsaw. Subsequently, I spent three years as a post-doctoral fellow with Richard Taylor in York whose studies have pioneered many of the recent synthetic applications of the RBR. Now, 70 years after the initial disclosure of this reaction and with the Victoria University Organic Synthesis group beginning to apply the RBR in some of its synthetic endeavours, it seemed appropriate to provide some context for this fascinating and useful reaction in the modern setting. There have been many excellent reviews previously published on the Ramberg-Bäcklund reaction.[1] Our article focuses on recent applications (2005-2010) of the RBR in synthetic approaches to natural products and other bioactive molecules.

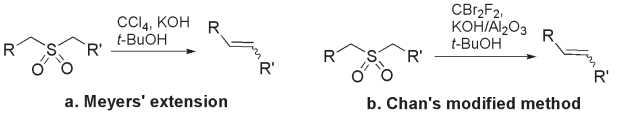
Background

In 1940, Swedish chemist Ludwig Ramberg and his student Birger Bäcklund published a method for transforming α-halosulfones into alkenes (Scheme 1).[2] Subsequent mechanistic investigations indicated that abstraction of a proton from the non-halogenated α-centre of **1** leads to formation of an episulfone **2**, which extrudes sulfur dioxide to provide the product alkene **3**.[3] The intermediacy of an episulfone was confirmed by Sutherland and Taylor through the isolation of an episulfone from a low-temperature RBR and its subsequent transformation to an alkene.[4]



Scheme 1

The utility of this reaction was greatly augmented by Meyers' development of a one-pot chlorination/RBR sequence, which overall converts a sulfone into an alkene using carbon tetrachloride, potassium hydroxide, water and *t*-butanol (Scheme 2a)[5] however, the formation of dichlorocarbene as a by-product of the reaction can lead to undesired reactivity in some instances.[1] There have been several variations of the one-pot halogenation/RBR, notably that by Chan in which the halogen source is dibromodifluoromethane and the KOH is adsorbed on an alumina support (Scheme 2b).[6] The starting sulfones can be prepared in a multitude of different ways.[1,7] One popular method involves oxidation of a thioether, which in turn may be generated by nucleophilic substitution of a halide (or similar leaving group) on one substrate by a thiol. This overall sequence has the potential to represent a major disconnection in a convergent synthetic strategy.



Scheme 2

The RBR has become a versatile method for preparation of alkene π bonds within a variety of structural motifs, including strained cyclic systems.[1] The position of an alkene prepared by the RBR is unambiguous, as required in modern target-oriented synthetic chemistry. Furthermore, SO_2 extrusion as a method for forming complex alkenes is more atom-economic[8] than several of the common alternative strategies, such as the popular Wittig and Horner-Wadsworth-Emmons reactions, and the Julia-Kocienski reaction.[9] Despite the fact that the alkene geometry cannot be predicted with certainty in all cases,[1] the utility of the RBR is amply demonstrated by its application in the synthesis of targets as diverse as dendrimers[10] and cyclophanes.[1] It has been used to provide key connections in synthetic routes to constituents of most natural product classes,[1] from alkaloids[11] and terpene derivatives[12] to enediynes[1] and complex polycycles.

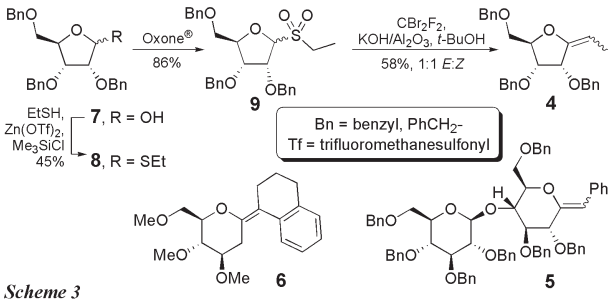
Synthesis of Targets Containing Modified Carbohydrates

A vast number of carbohydrates and their analogues have been synthesized using the RBR, with the Taylor and Franck groups making tremendous contributions to the field. Numerous other players have made valuable advances and diversified the applications of this chemistry.[13]

exo-*Glycals*

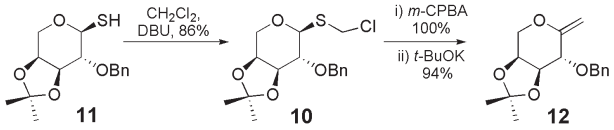
exo-Glycals are unsaturated carbohydrates with an exocyclic π bond at the anomeric site.[14] They have attracted attention as synthetic targets, in part because they can be transformed into a wide range of *C*-glycosides (*vide infra*) but also because of their potential use as glycosidase inhibitors.[15] The RBR is particularly versatile and allows for the synthesis of more highly substituted variants than other methods.[13] For instance, the Taylor group has prepared a number of diverse *exo*-glycals such as furanose **4** and disaccharide **5** (Scheme 3),[16] while Franck *et al*. have synthesized a variety that includes tricycle **6**.[17] The synthesis (shown for **4**) involves the ready conversion of a suitably protected sugar **7** into a thioglycoside **8** that is oxidized by one of a range of oxidants[16–18] to sulfone **9**. This undergoes halogenation/RBR to *exo*-glycal **4**.

A related method for the synthesis of methylidene *exo*-glycals has recently been reported;[19] (chloromethyl)thiogl ycosides, such as **10** (Scheme 4), are oxidized and using a



Scheme 3

classic (one-step) RBR. The thioglycosides are prepared from the appropriate glycosyl thiols, *e.g.* **11**, by reaction with CH_2Cl_2 in the presence of base. Oxidation with *m*-chloroperoxybenzoic acid provides access to sulfones that give the *exo*-glycals **12** when treated with base.

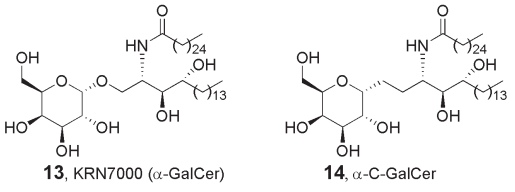


Scheme 4

C-*Glycosides*

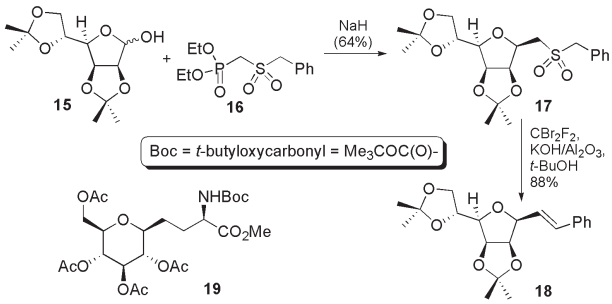
C-Glycosides are carbohydrate analogues in which the exocyclic oxygen of the anomeric acetal is replaced by carbon. The *C*-analogues tend to be more resistant to hydrolysis, which can enhance their efficacy as enzyme inhibitors and in binding to other biological molecules.

The Taylor and Franck groups have prepared a number of *C*-glycosides from *exo*-glycals using the RBR,[13,17,20] including an analogue of the potent immunostimulant KRN7000 (α-GalCer; **13**).[21] In fact, the *C*-linked analogue **14** stimulates increased production of certain cytokines involved in the immune response, and shows more pronounced anti-tumour effects in mice. The synthesis of **14** and discovery of its bioactivity has encouraged the design of ever more potent *C*-glycoside agents for adjuvant immunotherapy in humans. This discovery validated the ideas of using *C*-linked analogues of natural glycosides to achieve increased binding affinity for biological targets and thus obtain greater efficacy against many diseases.[22]



13, KRN7000 (α-GalCer) **14**, α-C-GalCer

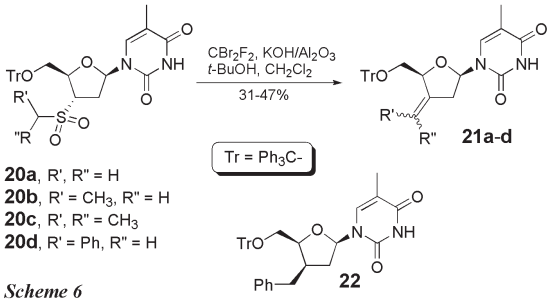
A direct route to unsaturated *C*-glycosides using the RBR has been developed by Taylor's group.[13] This is illustrated by the example of Scheme 5 that involves the Horner-Wadsworth-Emmons reaction of reducing sugar **15** with sulfonyl phosphonate **16**. Spontaneous conjugate addition of the resulting hydroxyl group to the resulting *α,β*-unsaturated sulfone gives ring-closed **17** that undergoes halogenation/RBR to *C*-glycoside **18**. This sequence can be achieved in a single pot,[13] on unprotected carbohydrates,[23] and with more complex phosphonates, making it a highly efficient route to *C*-glycosides, *C*-disaccharides, and *C*-linked glycosyl amino acids, such as **19**.[13] While the example of Scheme 5 displays excellent stereoselectivity in the conjugate addition step by providing only β-pseudo-anomer **18**, mixtures of isomers can arise. Recent research shows that, in some cases, stereoselectivity can be controlled by altering the temperature for the conjugate addition.[24]



Scheme 5

Thymidine analogues

A series of thymidine analogues with potential drug applications have recently been prepared in moderate yields using the RBR (Scheme 6).[25] Under Chan's conditions, 3′-deoxy-3′-sulfonylated thymidines **20a–d** provided the exocyclic methylidene products **21a–d** in 31–47% yield. For **21b**, an isomeric mixture of alkenes was formed, whereas **21d** was the sole isomer that gave the 3′-deoxy-3′-benzylthymidine **22**, a putative analogue of the anti-HIV drug AZT, on hydrogenation.[25]



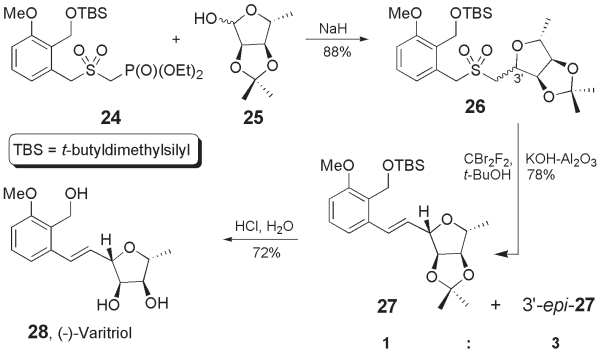
Scheme 6

Varitriol

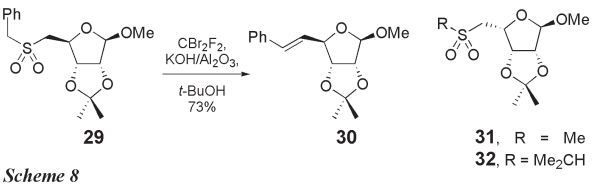
(+)-Varitriol was isolated from the fungus *Emericella variecolor* and is cytotoxic towards several cancer cell lines. A RBR-based synthesis of the unnatural enantiomer from D-ribose has been achieved by the Taylor group (Scheme 7).[26] The sulfonyl phosphonate **24** was prepared from methyl 2-methoxy-6-methylbenzoate in five steps. Coupling of this Horner-Wadsworth-Emmons reagent with D-ribose-derived **25** provided sulfone **26** as a mixture of 3′-isomers. RBR under Chan's conditions then provided the desired isomer of product **27** and its 3′-epimer, which were separately converted to the enantiomer of the natural product (**28**) and its 3′-epimer in a 1:3 ratio; the proportion of the desired isomer was improved to 1:1.3 by performing the HWE/RBR sequence as a single-pot process in THF with no added t-butanol. This indicates that tinkering with the reaction conditions may augment stereoselectivity. This synthesis provides a means to access both the natural product and a stereoisomeric analogue.

The related RBR of unsubstituted benzyl sulfone **29** gave alkene **30** in good yield as expected (Scheme 8).[27] How-

ever, the corresponding methyl and isopropyl sulfones did not undergo reaction but epimerized to **31** and **32** instead.



Scheme 7

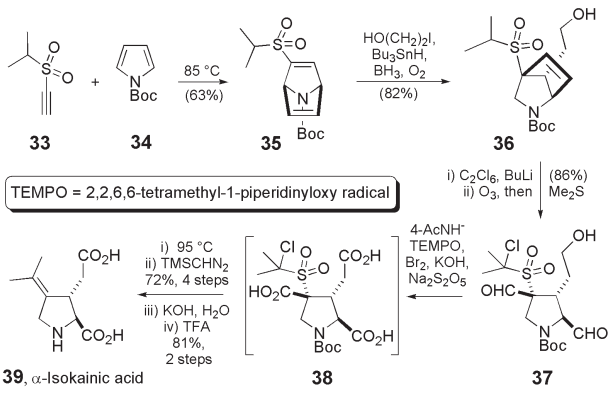


Scheme 8

Synthesis of Amino Acids

(+)-α-Isokainic acid

Kainoids are non-proteinogenic amino acids that have important roles as neurotransmitters in the mammalian nervous system. In a recent synthesis of (±)-α-isokainic acid (**39**),[28] a decarboxylative RBR is part of the sequence that forms the exocyclic alkene (Scheme 9). The key steps involve [4+2] cycloaddition of **33** and **34**, followed by radical-based conjugate addition of 2-iodoethanol to the unsaturated sulfone of **35** and consequent rearrangement of the bicyclic framework to the 2-azabicycle **36**. α-Chlorination and ozonolysis provided **37** that was isolated as a mixture of cyclic hemiacetals. Without purification, **37** was oxidized to triacid intermediate **38** that underwent decarboxylation and RBR. Subsequent methylation of the carboxylic acid moieties, purification, saponification and cleavage of the *N*-protecting group gave natural product **39**.



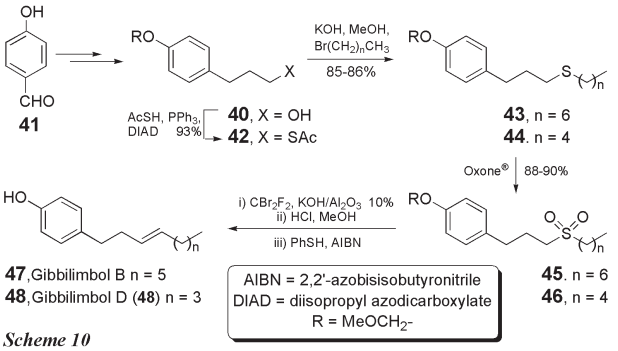
Scheme 9

Synthesis of Aromatic Natural Products

The RBR lends itself particularly well to the synthesis of natural products containing aromatic rings because of the ease with which benzylic sites undergo halogenation and proton abstraction. Nonetheless, this section includes examples where reaction occurs at non-benzylic positions.

Gibbilimbols B and D

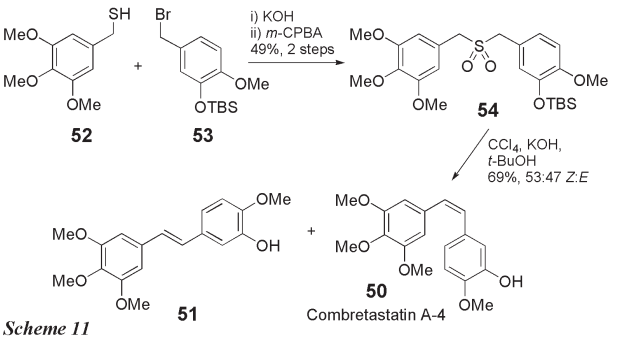
The leaves and juices from the bark of the Papua New Guinean shrub *Piper gibbilimbum* have been used as antiseptics to treat skin and internal ailments, and also some forms of cancer. Extraction of the leaves yields a family of natural products, the gibbilimbols, which display moderate anti-cancer and antibacterial activity.[29] A recent synthesis of gibbilimbols B and D (Scheme 10) was based upon the RBR.[30] The sulfone starting material was generated by Mitsunobu reaction of alcohol **40** [prepared from *p*-hydroxybenzaldehyde (**41**)] with thioacetic acid, followed by acetate deprotection of **42** and substitution of the appropriate alkyl bromide (1-bromoheptane or 1-bromopentane) by the resulting thiolate. Oxidation of thioethers **43** and **44** using Oxone® led to sulfones **45** and **46**. The RBR was sluggish, giving only 10% conversion and requiring recycling of the sulfone for further iterations. Adding to the poor reactivity was the fact that the products were generated as *ca*. 1:1 mixtures of *E*/*Z*-alkenes. However, after MOM deprotection, the (*Z*)-isomers underwent radical-induced isomerization to the thermodynamically favoured (*E*)-isomers **47** and **48**.



Scheme 10

Combretastatin A-4

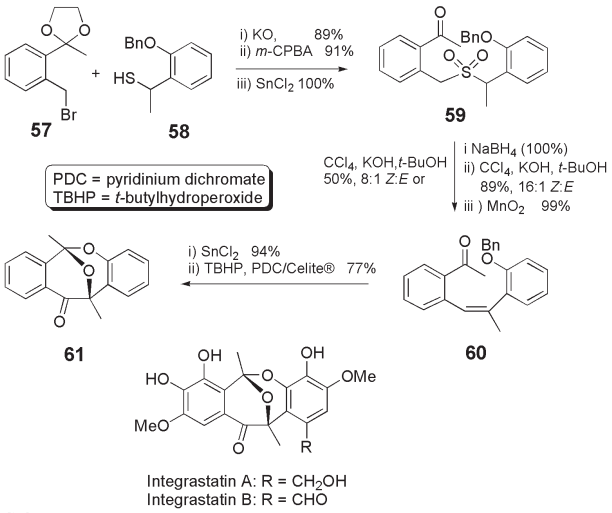
A series of stilbenes was generated using the RBR with interesting *E*/*Z* stereoselectivity gained by varying the reaction conditions.[31] These results include the synthesis of the anti-cancer agent combretastatin A-4 (**50**) and its (*E*)-isomer **51** (Scheme 11). Combretastatin A-4, from the bark of the African bush willow tree *Combretum caffrum*, binds tubulin and causes tumour cell necrosis.[32] Coupling of thiol **52** with benzylic bromide **53** and oxidation of the resultant thioether provided sulfone **54**. Subjection to a variety of RBR conditions gave mixtures of (*E*)- and (*Z*)-alkenes. Interestingly, Meyers' conditions gave significantly higher proportions of the desired (*Z*)-alkene **50** than those of either Chan or Franck (which uses $C_2Br_2F_4$ as the halogen source).



Scheme 11

Integrastatin nucleus

Integrastatins A and B, isolated in 2002, are potential HIV inhibitors.[33] Their bridged tetracyclic framework encompasses a high degree of oxygenation and was generated using a RBR as a key part of the strategy.[34] Coupling of the benzylic bromide **57** and thiol **58** (Scheme 12), followed by thioether oxidation and acetal hydrolysis gave sulfone **59**, which underwent RBR using Meyers' conditions to provide the (*Z*)-stilbene **60**. However, a higher yield and better (*Z*)-selectivity came from a reduction, RBR, and oxidation sequence. Improved (*Z*)-selectivity in the RBR of sulfones containing appropriately positioned benzylic hydroxyl groups, *viz*. the reduced form of **59**, likely comes from intramolecular promotion of SO_2 extrusion by the adjacent alkoxide.[35] Lewis acid-promoted benzyl ether deprotection and acetal formation was followed by benzylic oxidation to provide the tetracyclic core of the integrastatins in the form of structure **61** (Scheme 12).



Scheme 12

Synthesis of Polyenes

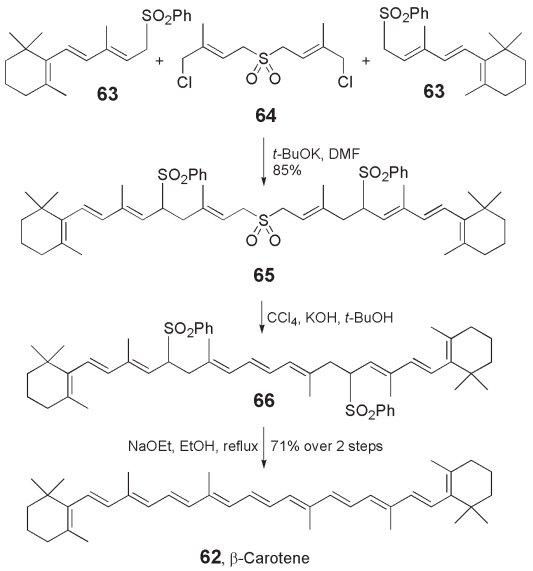
The RBR provides a useful method for preparing polyenes.[1,36] The precursor sulfones (or thioethers) are effectively *protected* alkenes, as they can be converted into the target alkenes but in the meantime lack many of the undesirable reactivity properties of a polyene, making them useful intermediates for chemical manipulations.

Carotenoids

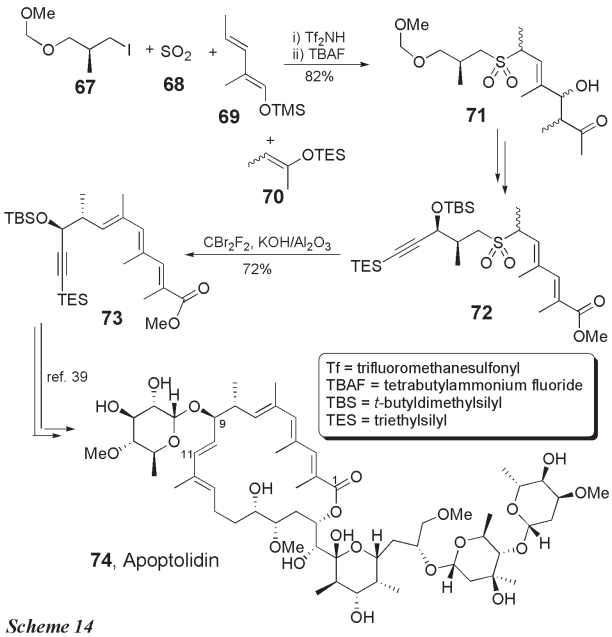
A number of carotenoids have been generated through use of dual sulfone chemistry, in which the RBR is a key player.[37] Amongst the products obtained have been β-carotene (**62**) and its oxidized counterparts canthaxanthin, astaxanthin, and astacene. The synthetic strategy, shown in Scheme 13 for β-carotene, involves coupling of sulfone α-anions (derived from **63**) with sulfone-containing dichloride **64** to produce trisulfone **65**. The chain-embedded sulfone then partakes in a RBR to form conjugated triene **66**; subsequent base-promoted dehydrosulfonation provides the fully conjugated carotenoid **62**.

Apoptolidin (formal synthesis)

A formal total synthesis of the cytotoxic agent, apoptolidin, was realized[38] through use of Ramberg-Bäcklund technology to generate a key intermediate from a previous route.[39] The four components, **67–70**, were coupled in a one-pot reaction by electrophilic conjugate addition of sulfur dioxide (**68**) to enol ether **69**, attack of enol ether **70** on the resulting intermediate, and, upon addition of iodide **67** and a desilylating agent, formation of sulfone **71** (Scheme 14). A series of transformations yielded alkyne **72** that underwent a RBR using Chan's conditions to produce Nicolaou's apoptolidin fragment **73**, constituting the C1-C11 portion of the natural product **74**.



Scheme 13



Scheme 14

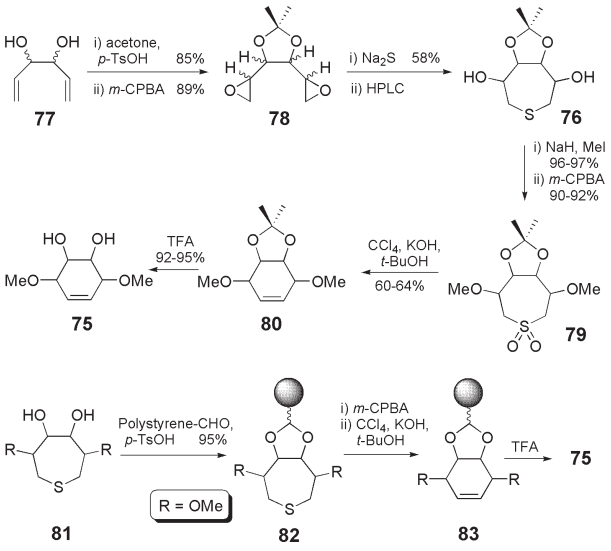
Ring Formations by the RBR in the Synthesis of Cyclic Natural Products

The Ramberg-Bäcklund reaction is finding an important role in the synthesis of medium-to-large ring compounds.[40] Its efficacy in forming cyclic compounds can be attributed to the fact that it operates as part of a two-step process: ring closure (often by nucleophilic attack of a thiol on a halide) forms an (n+1) cycle and is followed (not necessarily immediately) by the RBR which causes ring contraction to the target cyclic compound with ring size n. This sequence can provide benefits over other methods that involve direct ring closure because, in com-

parison to the desired *n* ring system, the formation of a larger (*n*+1) ring system typically reduces the amount of ring strain that must be overcome in the cyclization step. Furthermore, thiols are very reactive nucleophiles as a result of their polarizability, electron density and basicity,[41] meaning that they are well suited to cyclization reactions with large activation barriers. The recent examples presented here are in order of increasing ring size produced in the RBR.

Conduritols

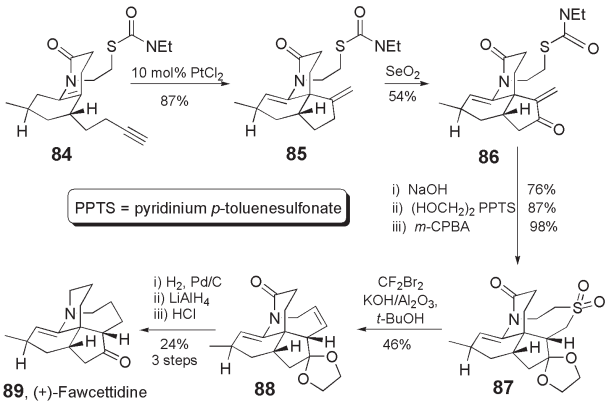
The conduritols are a family of stereoisomeric unsaturated cyclitols, which have shown biological activity as glycosidase inhibitors.[42] Conduritol was isolated from the bark of the vine *Marsdenia condurango* in 1908, but its structure and stereochemistry was not determined until 30 years later. The biogenesis of the natural conduritols has been traced back to D-glucose and D-galactose. Syntheses of ***all ten*** stereoisomeric conduritols (as the dimethyl analogues **75**) have been achieved through oxidation and RBR of thiepane isomers **76** (Scheme 15).[43] Thus, a mixture of stereoisomeric allylic diols **77** were protected and epoxidized to give **78**, which reacted with sodium sulfide in a double substitution reaction to afford the stereoisomeric thiepanes **76**. The ten separated (HPLC) thiepanes **76** were then methylated and oxidized to the corresponding sulfones **79**. RBR under Meyers' conditions then afforded cyclohexenes **80**, and deprotection gave products **75**. Notably, the chemistry was demonstrated to work equally well on solid supports. Thus, a polystyrene-CHO resin was appended to the thiepanes **81** to give acetals **82**. After oxidation, the RBR was carried out to provide alkenes **83**, which, after removal from the resin, led to two conduritol isomers **75**.



Scheme 15

Fawcettidine

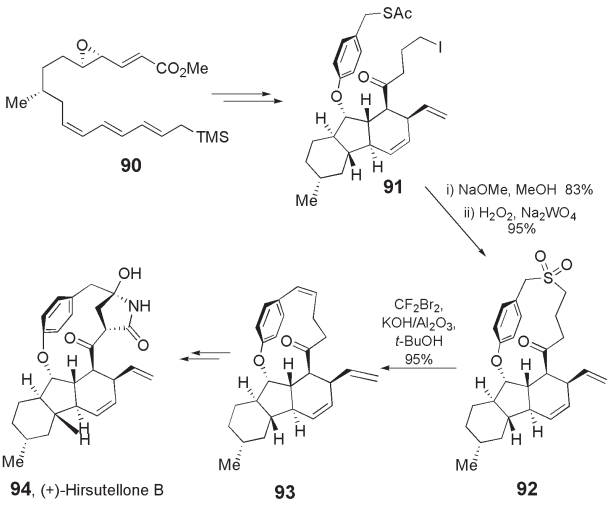
Fawcettidine contains a complex tetracyclic ring system and is a member of the *Lycopodium* family of alkaloids, some of which inhibit acetylcholine esterase, a promising target for the treatment of Alzheimer's disease. The seminal total synthesis of (+)-fawcettidine by Kozak and Dake employed the RBR in an elegant late-stage construction of the seven-membered ring.[44] Bicyclic alkyne **84** (Scheme 16), prepared from the monoterpenoid chiral pool reagent (*R*)-(+)-pulegone, underwent a Pt(II)-catalyzed annulation to form tricycle **85**. This was followed by allylic oxidation to **86** using selenium dioxide. The thiocarbamate protecting group was cleaved under basic conditions, and conjugate addition of the resulting thiolate occurred spontaneously. Ketone protection as a cyclic ketal and thioether oxidation gave sulfone **87**. RBR of this using Chan's procedure successfully produced the desired tetracyclic product **88**, which was hydrogenated, the amide group reduced to an amine, and the ketone revealed to afford the natural product **89**.



Scheme 16

Hirsutellone

Hirsutellone B is a fungal secondary metabolite that displays exciting antimicrobial activity against *Mycobacterium tuberculosis*, the causative pathogen of tuberculosis. In the seminal total synthesis of (+)-hirsutellone B, Nicolaou and co-workers used a RBR to form a highly strained, 13-membered *p*-cyclophane ether.[45] The fused tricyclic system was generated by an elegant intramolecular epoxide opening/Diels-Alder cascade reaction of epoxide **90** (Scheme 17), itself prepared by chain extension of (+)-citronellal. While the cascade reaction proceeded in a modest 50% yield, the desired [6.5.6] tricycle was obtained as a single stereoisomer! A series of transformations led to the iodothioacetate **91**, which underwent deacetylation and immediate cyclization with base. The resulting 14-membered thioether was oxidized to the corresponding sulfone **92** using hydrogen peroxide and so-

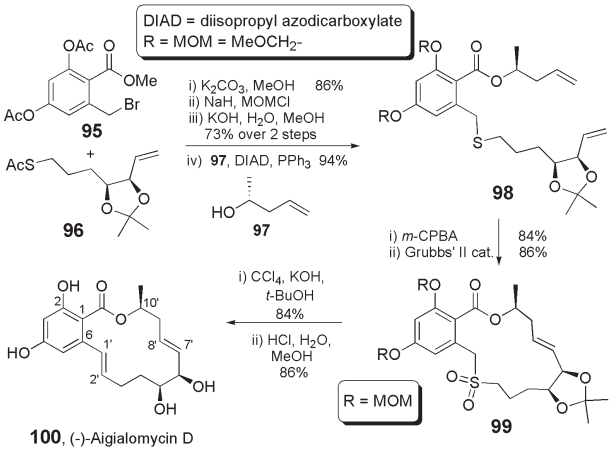


Scheme 17

dium tungstate. The RBR was performed using the Chan protocol and produced the desired 13-membered ring **93** in 95% yield, suitably functionalized for conversion to the natural product **94**.

Aigialomycin D

The family of resorcylic acid lactone natural products is synthetically sought after for the myriad of biological activities engendered by its components.[46] (-)-Aigialomycin D, isolated[47] in 2002, displays moderate anti-malarial and anti-cancer properties, inhibiting kinases CDK1, CDK5 and GSK3. Last year, our team published a synthetic route to this macrocyclic natural product, **100**, that relies upon a ring-closing metathesis/RBR sequence to form the 1,7-diene (Scheme 18).[48] The methyl orsellinate-derived benzyl bromide **95** underwent nucleophilic substitution by a D-ribose-derived thiol formed by deacetylation of **96**. After protection of the thus-formed phenolic groups and ester hydrolysis, a Mitsunobu reaction of the resulting acid with homoallylic alcohol **97** allowed installation of the branched ester within **98**. Oxidation of the thioether preceded the RCM step in order to avoid unwanted complexation of Grubbs' second generation catalyst by the thioether. The sulfone **99** represents a masked alkene, necessary to avoid a competing RCM process to a cyclohexene by-product, as seen in other routes.[49] A high-yielding and completely *E*-stereoselective RBR using Meyers' conditions afforded protected aigialomycin D, which was transformed efficiently to the natural product **100**.



Scheme 18

Concluding Remarks

The past 70 years have seen the RBR progress from a mechanistically interesting observation to part of the synthetic chemist's toolbox of versatile and widely applied transformations. We have endeavoured here to demonstrate the diversity of uses for the RBR in recent times and to showcase the considerable potential that this reaction holds for future synthetic efforts.

Acknowledgements

We thank Victoria University for a PhD Scholarship (MB) and the Tertiary Education Commission (Bright Futures) for support of our work. We are very grateful to Prof. Richard Taylor for assistance with this article.

References

1. Taylor, R. J. K.; Casy, G. *Org. React.* **2003**, *62*, 357–475; Taylor, R. J. K. *Chem. Commun.* **1999**, 217–227; Clough, J. M. *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, pp 861–886; Paquette, L. A. *Org. React.* **1977**, *25,* 1–71.
2. Ramberg, L.; Bäcklund, B. *Ark. Kemi. Mineral. Geol.* **1940**, *27*, 1–50 (*Chem. Abstr.* **1940**, *34*, 4725).
3. Bordwell, F. G.; Cooper, G. D. *J. Am. Chem. Soc.* **1951**, *73*, 5187–5190; Bordwell, F. G.; Doomes, E. *J. Org. Chem.* **1974**, *39*, 2526–2531.
4. Jeffery, S. M.; Sutherland, A. G.; Pyke, S. M.; Powell, A. K.; Taylor, R. J. K. *JCS Perkin Trans. I* **1993**, 2317–2327.
5. Meyers, C. Y.; Malte, A. M.; Matthews, W. S. *J. Am. Chem. Soc.* **1969**, *91*, 7510–7512.
6. Chan, T.-L.; Fong, S.; Li, Y.; Man, T.-O.; Poon, C.-D. *Chem. Commun.* **1994**, 1771–1772.
7. Yao, Q. *Org. Lett.* **2002**, *4*, 427–430 and refs. cited; Block, E.; Jeon, H. R.; Putman, D.; Zhang, S.-Z. *Phosphorus, Sulfur & Silicon* **2005**, *180*, 1197–1202.
8. Trost, B. M. *Science* **1991**, *254*, 1471–1477.
9. Aïssa, C. *Eur. J. Org. Chem.* **2009**, 1831–1844 and refs. cited.
10. Chow, H.-F.; Ng, M.-K.; Leung, C.-W.; Wang, G.-X. *J. Am. Chem. Soc.* **2004**, *126*, 12907–12915.
11. Li, Y.; Zhang, Y.; Wang, X. L.; Huang, Z.; Cao, X. P. *Chin. Chem. Lett.* **2004**, *15*, 631–634.
12. Oh, S.; Jeong, I. H.; Shin, W.-S.; Lee, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3683–3686.
13. Taylor, R. J. K.; McAllister, G. D.; Franck, R. W. *Carbohydr. Res.* **2006**, *341*, 1298–1311.
14. Taillefumier, C.; Chapleur, Y. *Chem. Rev.* **2004**, *104*, 263–292.
15. Lin, C.-H.; Lin, H-C.; Yang, W.-B. *Curr. Top. Med. Chem.* **2005**, *5*, 1431–1457.
16. Griffin, F. K.; Paterson, D. E.; Murphy, P. V.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2002**, 1305–1322.
17. Belica, P. S.; Franck, R. W. *Tetrahedron Lett.* **1998**, *39*, 8225–8228.
18. Morais, G. R.; Humphrey, A. J.; Falconer, R. A. *Tetrahedron* **2008**, *64*, 7426–7431.
19. Zhu, X.; Jin, Y.; Wickham, J. *J. Org. Chem.* **2007**, *72*, 2670–2673.
20. Pasetto, P.; Franck, R. W. *J. Org. Chem.* **2003**, *68*, 8042–8045; Paterson, D. E.; Griffin, F. K.; Alcaraz, M.-L.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2002**, 1323–1336.
21. Franck, R. W.; Tsuji, M. *Acc. Chem. Res.*, **2006**, *39*, 692–701.
22. See, for example: Li, X.; Chen, G.; Garcia-Navarro, R.; Franck, R. W.; Tsuji, M. *Immunology* **2009**, *127*, 216–225.
23. Jeanmart, S.; Taylor, R. J. K. *Tetrahedron Lett.* **2005**, *46*, 9043–9048.
24. Aucagne, V.; Tatibouët, A.; Rollin, P. *Tetrahedron Lett.* **2008**, *49*, 4750–4753.
25. Pal, T. K.; Pathak, T. *Synlett* **2008**, 2263–2266.
26. McAllister, G. D.; Robinson, J. E.; Taylor, R. J. K. *Tetrahedron* **2007**, *63*, 12123–12130.
27. Pal, T. K.; Pathak, T. *Carbohydr. Res.* **2008**, *343*, 2826–2829.
28. Hodgson, D. M.; Hachisu, S.; Andrews, M. D. *Synlett* **2005**, 1267–1270.
29. Orjala, J.; Mian, P; Rali, T.; Sticher, O. *J. Nat. Prod.* **1998**, *61,* 939–941.
30. Wang, T.; Zhou, L.; Cao, X. P. *Chin. Chem. Lett.* **2009**, *20*, 147–149.
31. Robinson, J. E.; Taylor, R. J. K *Chem. Commun.* **2007**, 1617–1619.
32. Malcontenti-Wilson, C.; Muralidharan, V.; Skinner, S., *et al.*. *Clin. Can. Res.* **2001**, *7*, 1052–1060.
33. Singh, S. B.; Zink, D. L.; Quamina, D. S.; Pelaez, F. *et al., Tetrahedron Lett.* **2002**, *43*, 2351–2354.
34. Foot, J. S.; Giblin, G. M. P.; Taylor, R. J. K. *Org. Lett.* **2003**, *5*, 4441–4444.
35. Foot, J. S.; Giblin, G. M. P.; Whitwood, A. C.; Taylor, R. J. K. *Org. Biomol. Chem.* **2005**, *3*, 756–763.

36. Cao, X. P. *Acta Chim. Sin.* **2000**, *58*, 112–117.

37. Choi, S.; Koo, S. *J. Org. Chem.* **2005**, *70*, 3328–3331; Jeong, Y. C.; Ji, M.; Lee, J. S.; Yang, J.-D., *et al. Tetrahedron*, **2004**, *60*, 10181–10185; Ji, M.; Choi, H.; Jeong, Y. C.; Jin, J., *et al. Helv. Chim. Acta* **2003**, *86*, 2620–2628.

38. Bouchez, L. C.; Vogel, P. *Chem. Eur. J.* **2005**, *11*, 4609–4620.

39. Nicolaou, K. C.; Fylaktakidou, K. C.; Monenschein, H.; Li, Y.; Weyershausen, B., *et al. J. Am. Chem. Soc.* **2003**, *125*, 15433–15442; Nicolaou, K. C.; Li, Y.; Sugita, K.; Monenschein, H., *et al*. *J. Am. Chem. Soc.* **2003**, *125*, 15443–15454.

40. Nicolaou, K. C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E. J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866–4868; Mlinarić-Majerski, K.; Pavlović, D.; Marinić, Z. *Tetrahedron Lett.* **1996**, *37*, 4829–4832; Chan, T.-L.; Hung, C.-W.; Man, T.-O.; Leung, M.-K. *Chem. Commun.* **1994**, 1971–1972; Doomes, E.; McKnight, A. A. *J. Heterocycl. Chem.* **1995**, *32*, 1467–1471; McGee, D. I.; Beck, E. J. *Can. J. Chem.* **2000**, *78*, 1060–1066; Wei, C.; Mo, K.-F.; Chan, T.-L. *J. Org. Chem.* **2003**, *68*, 2948–2951.

41. Edwards, J. O.; Pearson, R. G. *J. Am. Chem. Soc.* **1962**, *84*, 16–24.

42. Balci, M.; Sütbeyaz, Y.; Seçen, H. *Tetrahedron* **1990**, *46*, 3715–3742.

43. Cerè, V.; Minzoni, M.; Pollicino, S.; Ricci, A., *et al*. *J. Comb. Chem.* **2006**, *8*, 74–78; Cerè, V.; Peri, F.; Pollicino, S.; Ricci, A. *et al*. *J. Org. Chem.* **2005**, *70*, 664–669.

44. Kozak, J. A.; Dake, G. R. *Angew. Chem. Int. Ed.* **2008**, *47*, 4221–4223.

45. Nicolaou, K. C.; Sarlah, D.; Wu, T. R.; Zhan, W. *Angew. Chem. Int. Ed.* **2009**, *48*, 6870–6874.

46. Winssinger, N.; Barluenga, S. *Chem. Comm.* **2007**, 22–36.

47. Isaka, M.; Suyarnsestakorn, C.; Tanticharoen, M.; Kongsaeree, P.; Thebtaranonth, Y. *J. Org. Chem.* **2002**, *67,* 1561–1566.

48. Baird, L. J.; Timmer, M. S. M.; Teesdale-Spittle, P. H.; Harvey, J. E. *J. Org. Chem.* **2009**, *74*, 2271–2277.

49. Barluenga, S.; Dakas, P.-Y.; Ferandin, Y.; Meijer, L.; Winssinger, N. *Angew. Chem. Int. Ed.* **2006**, *45,* 3951–3954; Bajwa, N.; Jennings, M. P. *Tetrahedron Lett.* **2008**, *49,* 390–393.

Obituary: Raymund Marshall Golding AO (1935-2009)

Prof R. M. Golding MSc (NZ), PhD (Canterbury), DSc (NSW) died at his Mooloolah home in Queensland on 21 November 2009 after an illness of some months. He was a Fellow of NZIC (1966) and its 1967 Easterfield Medal recipient. He had distinguished scientific and academic careers on both sides of the Tasman.

Ray was born at Westport on 17 June 1935 to parents who were teachers in the Buller area. He received his secondary schooling at Auckland Grammar (1949-53), and attended Auckland University (1954-57) gaining MSc (Chemistry, 1st Class). He became a Scientific Officer in the Dominion Laboratory (later Chemistry Division, DSIR) in 1958 and then, in 1960 he took up a NZ National Research Fellowship at Cambridge University gaining his PhD in 1963. On return to DSIR he was appointed head of a new Theoretical Chemistry Section and he set about putting each of three relatively new spin resonance techniques, NMR, ESR and Mössbauer spectroscopy on a sound theoretical footing. The latter technique, introduced to NZ by the late Prof James Duncan, was the catalyst for a fruitful Golding-Duncan collaboration during the 60s. During this period Ray also completed his first book *Applied Wave Mechanics* (van Nostrand, 1969) which resulted, largely, from a two-year post-graduate lecture series given during 1964 and 1965 at VUW.

In 1968 he applied successfully for the vacant chair in Physical and Theoretical Chemistry at the University of New South Wales, a position that he held until 1978 whilst maintaining his contacts with NZ science and academia. David Rae (AU and DSIR) joined his staff as lecturer and the writer was a Teaching Fellow in his department (1969-71). Other postdoctorals/Visiting Fellows included Margaret Halton and Gary Burns (VUW), Barrie Peake (UC, later Otago) and Helen Bergen (Massey). In 1978, Ray became Pro-Vice-Chancellor at UNSW, a position that he held until 1986. In this capacity he was largely responsible for setting up the Australian Defence Force Academy in Canberra. In 1986, he became Vice-Chancellor at James Cook University in Townsville, a position that he held until his retirement in 1996. During his tenure at James Cook, the university doubled its student numbers, expanded its course offerings by a factor of three, became a multi-campus university with associated commercial companies, and doubled its assets. For services to education, science and the arts he was awarded Officer of the Order of Australia, General Division, in 1994.

As a scientist, Ray had an extraordinarily wide range of interests that did not cease when he moved into university administration. Together with one or two enthusiastic Research Fellows, he continued to work and publish in subjects that ranged from abstract group theory and quantum mechanics to medically-oriented publications and, until ill health intervened in mid-2009, effects of climate change. During his 10 years at James Cook he drafted 9 of 11 chapters of a new advanced text on quantum mechanics, a book eventually published in 2008. Ray's versatility is evident from his authoring of more than 120 research papers, a book chapter, and the following four books:

> *Applied Wave Mechanics*, van Nostrand: London, 1969; *Chemistry, Multistrand Senior Science for High School Students*, 1975; *The Goldings of Oakington* (A complete history and family tree of the Golding family of Oakington, Cambridgeshire from about 1650), 1992; and *Quantum Mechanics in Chemical Physics – an Exploration*, Common Ground Publishing, 2008.

Despite this full life, Ray was also Board Member/Director/Chairman of around 20 organisations from 1986. These include The Board of Senior School Studies NSW (1975-86), The Australian Festival of Chamber Music Pty. (1990-96), and The Australasian Marine Science Consortium (1984-2002). Apart from his FNZIC, he was a Fellow of the RACI, the Institute of Physics (UK), the Royal Society of Arts, the Australian Academy of Technological Sciences and Engineering, PACON International, and the Royal Astronomical Society.

Ray Golding always had time for colleagues, research fellows and students. He was never too busy to spend time carefully going through theory or discussing the detail of current research with them. Typically, he would set aside his Saturdays at UNSW and spend an hour or more with each student or research fellow in turn discussing progress, current stage of knowledge and future projections.

Following retirement from James Cook in 1996, Ray and wife Inge moved to a semi-rural property at Mooloolah, some 80 km north of Brisbane; *down on the farm* was the way Ray described it. At about this time, Ray was diagnosed with polymyositis, a rare degenerative muscular problem that affected his legs in particular. That hampered his movements to some extent but it did not stop him from cutting 2.5 Ha of lawn and generally tending to the *farm*, for some 12 years of retirement.

Ray is survived by wife Inge, two married daughters Tanya (Sydney) and Elke (Adelaide) and four grandchildren.

Craig Tennant