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Recent developments in Ramberg–Bäcklund and episulfone chemistry

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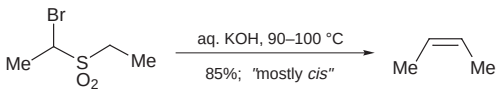
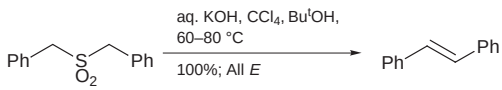
A brief historical review of the Ramberg–Bäcklund rearrangement is presented along with a summary of its applications to the synthesis of bioactive target molecules. Recent developments in this area originating from the author's laboratories, mostly from the past five years, are reviewed. These include: (i) the isolation of episulfones from the Ramberg–Bäcklund rearrangement, (ii) the preparation of episulfones by the oxidation of episulfides, (iii) the generation and synthetic applications of episulfone α-anions, (iv) the epoxy-Ramberg–Bäcklund rearrangement, (v) the tandem conjugate addition-Ramberg–Bäcklund rearrangement, and (vi) utilisation of the Ramberg–Bäcklund rearrangement in natural product synthesis and related areas, including recent applications for the synthesis of *C*-glycosides.

(*a*) Introduction

Since its discovery in 1940,[1] the Ramberg–Bäcklund rearrangement, the base-mediated conversion of α-halogenated sulfones into regio-defined alkenes (Scheme 1), has attracted a considerable amount of interest from both synthetic and mechanistic viewpoints.[2] The development of the Meyers' modification (Scheme 2),[3] in which the sulfone undergoes *in situ* halogenation-Ramberg–Bäcklund rearrangement, has further extended the synthetic utility of this process.



Scheme 1



Scheme 2

The strengths of the procedure from a synthetic perspective are: (i) the ease with which the requisite sulfones can be constructed and the conjunctive nature of the sequences, (ii) the unambiguous location of the resulting alkene moiety and the applicability of the procedure to all alkene substitution patterns including tetrasubstituted variants, (iii) the efficiency with which strained alkenes (*e.g.* cyclobutenes, unsaturated cyclophanes)[2,3] can be prepared, (iv) the applicability of the procedure to conjugated polyene synthesis, either by using allylic sulfones[2] or *via* the vinylogous[4] and Michael-induced[5] variants of the Ramberg–Bäcklund rearrangement. Predictably high stereocontrol is not a feature of the Ramberg–Bäcklund rearrangement, but in general *Z*-alkenes predominate when mild bases are employed, whereas stronger bases favour *E*-alkenes.[2]

The utility of the Ramberg–Bäcklund rearrangement can be seen from applications to the synthesis of natural products and related analogues. Recent examples from other groups, shown in Fig. 1, include a formal total synthesis of brassinolide,[6] the total syntheses of (+)-solamin,[7] (+)-eremantholide A[8] and (−)-conduritol E derivatives,[9] the preparation of enediyne[10] and ciguatoxin[11] analogues, and the synthesis of an advanced intermediate to the *C*-aryl glycoside chrysomycin A.[12]

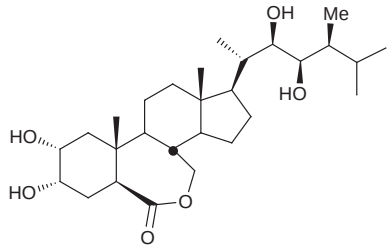
In terms of the mechanism of the Ramberg–Bäcklund reaction, considerable progress was made in the 1950s and 1960s.[2] Elegant studies by Bordwell, Neureiter, Paquette and others have resulted in the general acceptance of the mechanistic sequence illustrated in Scheme 3. Indirect support was obtained for the intermediacy of episulfones (thiirane 1,1-dioxides): they were prepared by other procedures (*e.g. via* addition of diazoalkanes to sulfenes[13]) and then it was established that they gave alkenes under the conditions normally employed for the Ramberg–Bäcklund rearrangement.[14]

My interest in synthetic and mechanistic aspects of the Ramberg–Bäcklund rearrangement was stimulated by Dr D. Neville Jones, my Ph.D. supervisor. Although a considerable amount of research had already been carried out by that time, I became convinced that the full potential of the process had yet to be realised. However, it was a number of years before the opportunity arose to make any personal contributions to this area of chemistry. This article summarises these recent contributions and includes some, as yet, unpublished results.

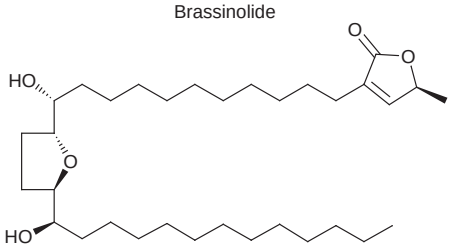
(*b*) The isolation of episulfones from α-halo sulfones

As part of a programme to synthesise novel sulfur-containing analogues of thromboxane A_2,[15] Richard Batten, Guy Casy, Vinod Kansal, Simon Lane, Stephen Quick, Alan Sutherland and Stamatis Vassiliou developed a number of procedures to prepare substituted thianes.[15,16] This presented an opportunity to explore some novel Ramberg–Bäcklund chemistry, investigating the utility of the rearrangement for the conversion of

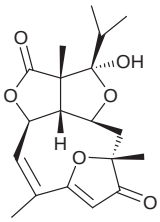
Richard Taylor graduated from the University of Sheffield and then carried out his PhD under the supervision of Dr D. Neville Jones working in the area of thiasteroid synthesis. After postdoctoral periods with Dr Ian T. Harrison (Syntex Research, Palo Alto; prostaglandin synthesis) and Professor Franz Sondheimer, University College London; annulene synthesis), he was appointed to a lectureship at the Open University in Milton Keynes (1975–1979). A move to the University of East Anglia, Norwich, followed and in 1993 he was appointed to a Chair of Organic Chemistry at the University of York. His research interests centre on the synthesis of bioactive natural products and related compounds, and the development of new synthetic methodology utilising organometallic and organosulfur chemistry. His awards include the Royal Society of Chemistry's Hickinbottom Fellowship for independent creativity in experimental organic chemistry (1985–1987) and the Royal Society of Chemistry's Tilden Medal and Lectureship (1999/2000). He is currently UK Regional Editor of the international journal Tetrahedron and a member of the Executive Board of Tetrahedron Publications.



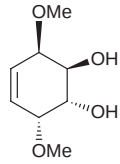
Brassinolide



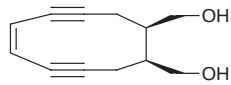
Solamin



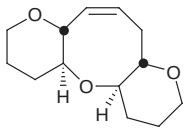
Eremantholide A



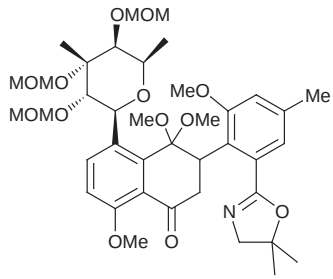
1,4-Dimethyl conduritol E



Bioactive enediyne analogue

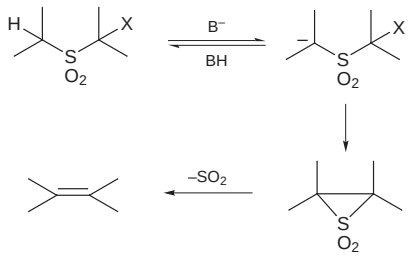


Ciguatoxin analogue



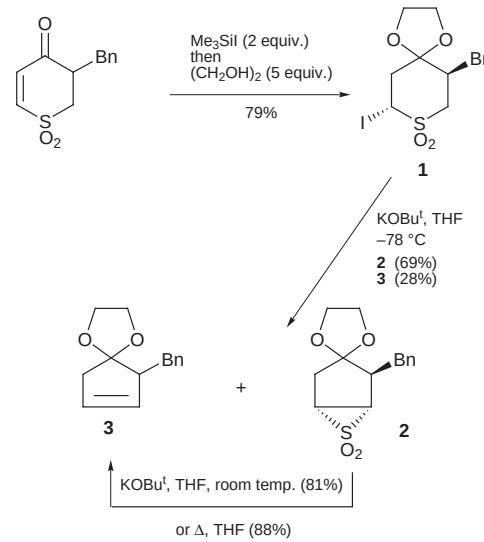
Chrysomycin A precursor

Fig. 1 Bioactive target molecules prepared using the Ramberg–Bäcklund rearrangement.



Scheme 3

thiane dioxides into cyclopentenoid natural products [see section (*f*)].[17] As part of this study, Alan Sutherland carried out the Ramberg–Bäcklund rearrangement of α-iodo sulfone **1** at low temperature. Surprisingly, because these reactions were generally very clean, two products were obtained (Scheme 4). The expected cyclopentene **3** was accompanied by a major crystalline by-product (69% yield) which no longer contained an iodide group, but neither did it possess alkenyl protons or carbons in its NMR spectra. We eventually concluded that the mystery by-product had to be the episulfone **2** (this finally being confirmed by X-ray crystallography). Episulfone **2** was stable



Scheme 4

for months on storage at −18 °C but, as expected, gave cyclopentene **3** on thermolysis or treatment with base. This was the first time that an episulfone had been isolated from an α-halo sulfone under the conditions of the Ramberg–Bäcklund reaction and it provided unambiguous proof of its intermediacy in the rearrangement process.[18]

After the initial discovery, the reaction conditions conditions were optimised and Alan Sutherland, Stephen Jeffery, Simon Pyke, Wendy Loughlin, Richard Ewin and Carlos Morales prepared the 'parent' episulfone **4** and a range of stable, functionalized analogues from α-halo sulfones in high yields (Fig. 2).[19,20] All of the compounds have been fully characterised and X-ray crystal structures were obtained on compounds **2** and **5**. It is not essential to use α-iodo sulfones in this process: episulfone **5** was also prepared from the corresponding α-bromo (74%) and α-chloro (85%) sulfones.

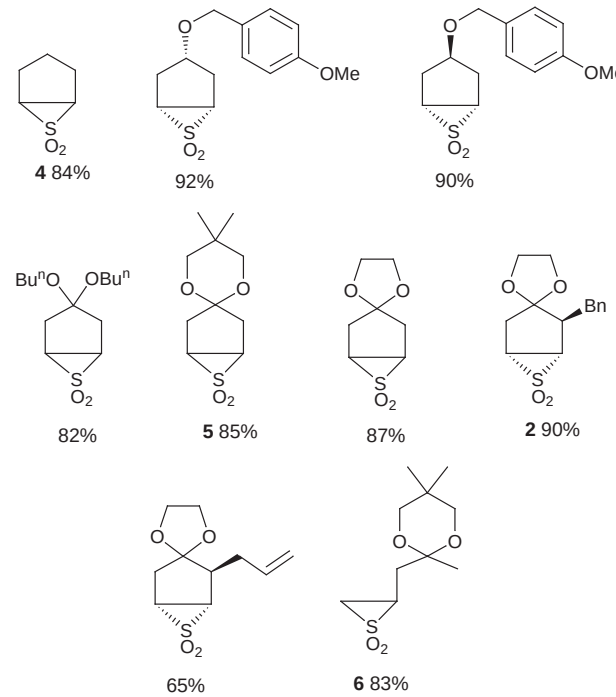


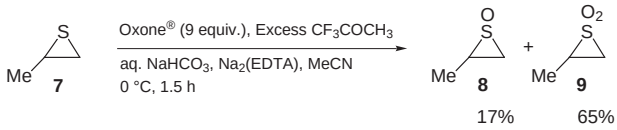
Fig. 2 Episulfones prepared from α-iodo sulfones (isolated yields shown).

Although most of the episulfone isolation programme was carried out using thiane dioxides, we believe that this procedure

for episulfone preparation is likely to be widely applicable: this is illustrated by the efficient conversion of an acyclic α-iodo sulfone into episulfone **6**.[20] In addition, Simpkins recently reported the preparation of 1-ethyl-2-methylepisulfone from the corresponding acyclic α-iodo sulfone using a similar procedure.[21]

(*c*) Preparation of episulfones by the oxidation of episulfides

Having disproved one widely accepted belief concerning episulfones—that they cannot be prepared from α-halo sulfones—we turned our attention to another. A wide range of organic sulfides, both acyclic and cyclic, are readily oxidised to give the corresponding sulfoxides and sulfones. Episulfides (thiiranes), however, have proved anomalous: under controlled conditions they can be oxidised to episulfoxides but, despite many attempts,[22] there were no authenticated[23] reports of episulfones being prepared from either episulfides or episulfoxides by an oxidative pathway. Given the accessibility of episulfides, we decided to reinvestigate their oxidation. The choice of oxidant was prompted by the recent report[24] that methyl(trifluoromethyl)dioxirane (TFDO) converts sulfides directly into sulfones *via* sulfurane intermediates, and does not proceed by way of sulfoxides. Such a procedure seemed to be ideally suited to the preparation of episulfones from episulfides, particularly as a convenient *in situ* method for preparing TFDO from Oxone® ($KHSO_5$ triple salt) and 1,1,1-trifluoroacetone has been described by Yang *et al.*[25] Paul Johnson therefore investigated the oxidation of propene episulfide **7** under these conditions (Scheme 5). This particular episulfide was chosen because it is commercially available and gives a reasonably stable and well characterised episulfoxide **8**.[26]



Scheme 5

To our delight, and somewhat surprisingly in view of previous studies, treatment of propene episulfide **7** with Oxone®/trifluoroacetone under Yang's conditions gave the corresponding episulfone **9** in 65% isolated yield, together with 17% of episulfoxide **8**, after chromatography. Having made this discovery, we went on to demonstrate that a range of episulfones can be prepared by the Oxone®/trifluoroacetone oxidative procedure (Fig. 3).[27]

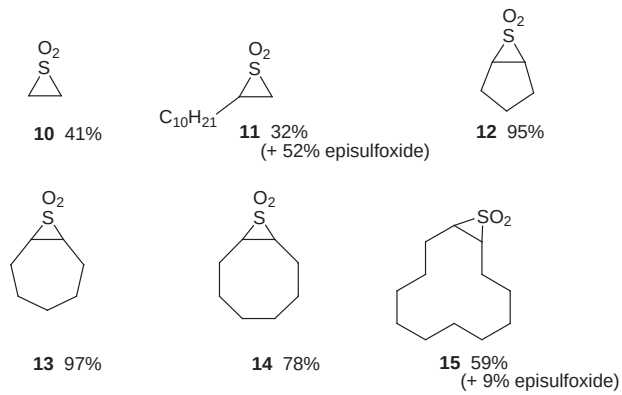
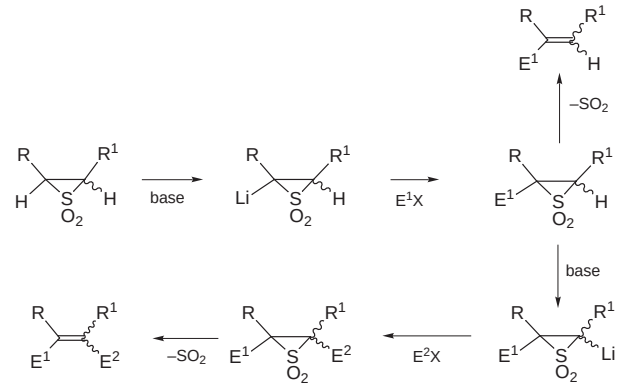


Fig. 3 Oxone®/trifluoroacetone preparation of episulfones **10–15**.

The ease with which bicyclic episulfones can be obtained is particularly noteworthy as the standard diazoalkane/sulfene methodology is not readily applicable to such systems. It should be noted that a preliminary study using 'isolated' TFDO, which readily oxidises a range of sulfides to sulfones,[24] has revealed that it converts episulfides into episulfoxides in good yield but that, surprisingly, episulfones are not formed in any significant amount. More research is needed, but it seems likely that the active oxidant in the Oxone®/trifluoroacetone mixture which promotes episulfone production is not TFDO but some other peroxidic species.

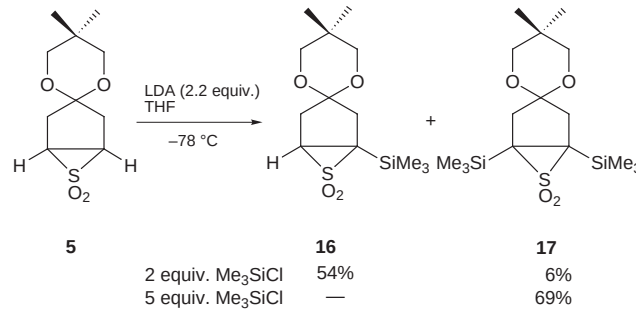
(*d*) The generation and synthetic applications of episulfone α-anions

With straightforward routes now available for episulfone preparation we decided to investigate their synthetic applications. Simon Pyke therefore set out to generate α-sulfonyl anions from episulfones and examine their trapping reactions with electrophiles. We thought that this methodology could provide a useful new procedure for the stereocontrolled synthesis of alkenes with a range of substitution patterns: this is illustrated in Scheme 6 for the production of tri- and tetrasubstituted alkenes.



Scheme 6

In order to establish the viability of this proposal we chose to study the deprotonation-trapping of episulfone **5** due to its accessibility, stability, and the fact that stereoisomeric alkylated episulfones and alkenes are not possible, therefore simplifying product analysis. Extensive experimentation with a range of bases and electrophiles gave only trace amounts of the required adducts (as the alkenes).[28] Wendy Loughlin then achieved success using an *in situ* trapping approach in which the electrophilic trapping agent is premixed with the substrate before the addition of the base (Scheme 7). Using this



Scheme 7

procedure, with trimethylsilyl chloride as the electrophile, we could produce good yields of mono- or di-silyl adducts, **16** or **17** respectively, depending on the excess of electrophilic trapping agent. Andy Graham prepared a good quality crystal of disilylated episulfone **17** and its structure was confirmed by

Madeleine Moore and Giles Wilson using X-ray crystallography: this is the first reported X-ray structure of a tetrasubstituted episulfone and the long carbon–carbon episulfone bond length (1.686 Å) is particularly noteworthy.[29]

Using similar procedures, Wendy Loughlin and Andy Graham prepared a range of silyl and stannyl episulfone adducts (Fig. 4), most as relatively stable, fully characterised crystalline solids.[29] Carbon-based electrophiles were also employed successfully, although the yields of the adducts were rather low. Complementary research on episulfone α-anions has recently been described by Simpkins *et. al.*,[21,30] and they have shown that *C*-alkylation and hydroxyalkylation can be performed much more efficiently by use of the Bu^t-P$_4$-phosphazene base.

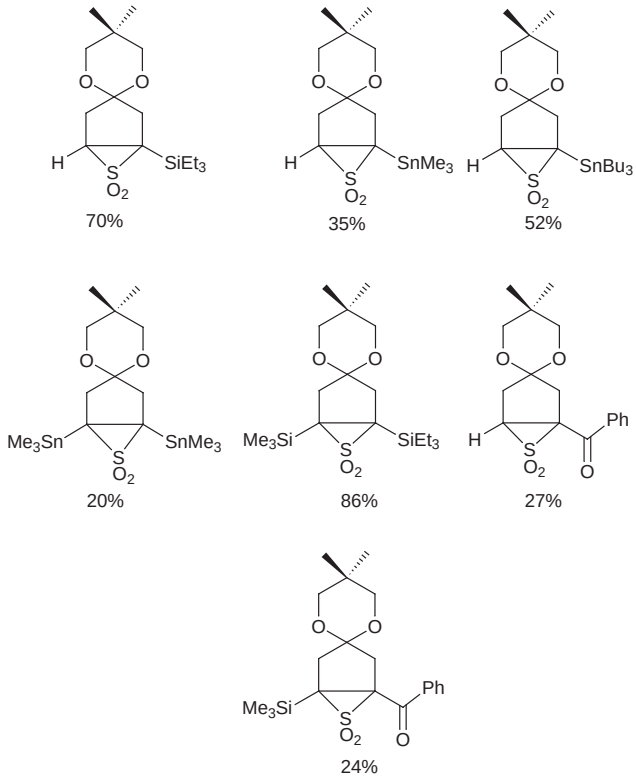
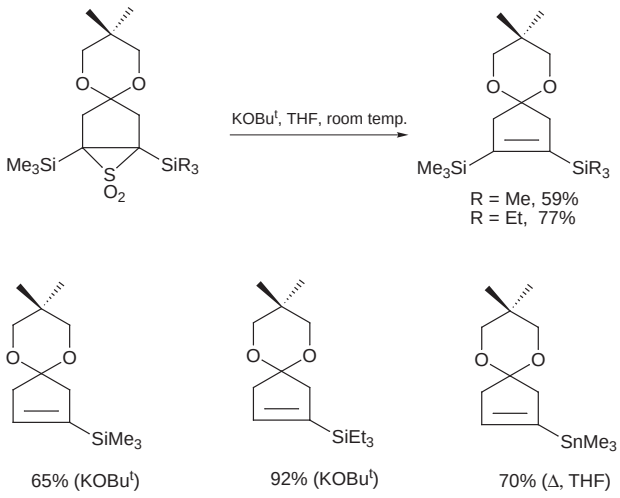


Fig. 4 Episulfones prepared from episulfone α-anions (isolated yields shown).

The functionalized episulfones were efficiently converted into novel 1,2-bis(silyl)alkenes, vinylsilanes and vinylstannanes by treatment with potassium *tert*-butoxide or thermolysis (Scheme 8).



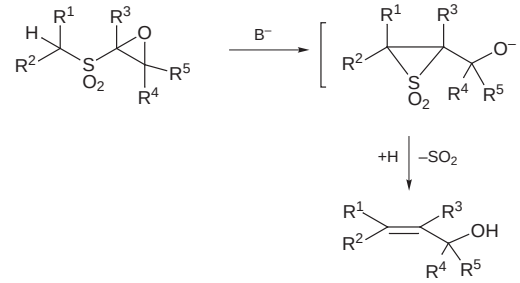
Scheme 8

(*e*) New variants of the Ramberg–Bäcklund rearrangement

More recently, we have developed two novel variants of the Ramberg–Bäcklund rearrangement.

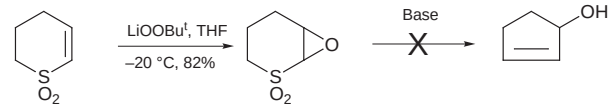
(*i*) The epoxy-Ramberg–Bäcklund reaction

The first of these variants was suggested in discussion with Mark Gamble. We envisaged a new variant of the Ramberg–Bäcklund rearrangement in which the leaving group is incorporated into a three membered ring (Scheme 9). A major advantage of this new variant compared to the traditional Ramberg–Bäcklund rearrangement is that alkene formation is accompanied by the introduction of allylic functionality. Thus, the epoxy-Ramberg–Bäcklund reaction would provide a new method for the synthesis of allylic alcohols from readily available sulfonyl oxiranes.



Scheme 9

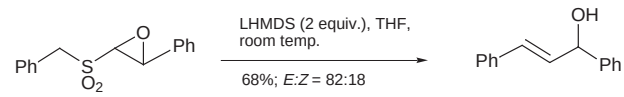
Initial studies to establish the viability of this idea were carried out by Arne Grumann, who had what we believed to be the ideal starting material, **18**, to hand (Scheme 10). Thus, the required epoxide **19** was easily prepared but, despite a considerable amount of effort, we were unable to devise conditions to effect the ring contraction to give cyclopentenol.



18 **19**

Scheme 10

We reasoned that the spirocyclic intermediate required for this transformation would be just too strained when starting with a bicyclic epoxide. When Paul Evans started his research in this area we therefore investigated an acyclic system (Scheme 11).



Scheme 11

We were delighted to observe the success of this new process and Paul Evans and Paul Johnson have since applied it to a range of substrates (Fig. 5).[31,32] As can be seen, the epoxy-Ramberg–Bäcklund reaction can be employed to prepare mono-, di- and tri-substituted alkenes, is often high yielding and can exhibit a high degree of stereoselectivity.

We are currently optimising this epoxy-Ramberg–Bäcklund reaction, exploring the thiirane and aziridine variants, and optimising a tandem epoxidation-epoxy-Ramberg–Bäcklund procedure (Scheme 12). We are also utilising the methodology for the synthesis of natural products such as sphingosine.

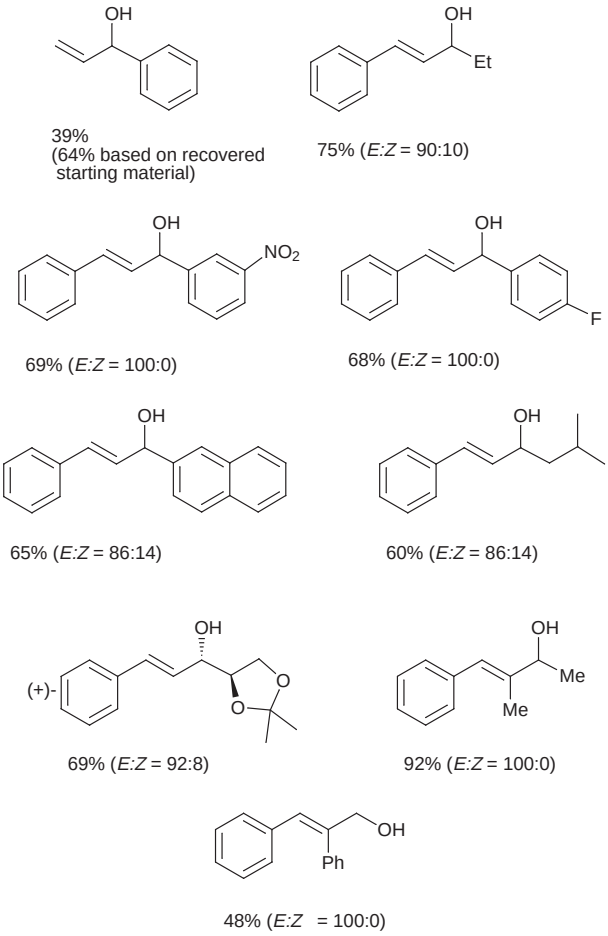
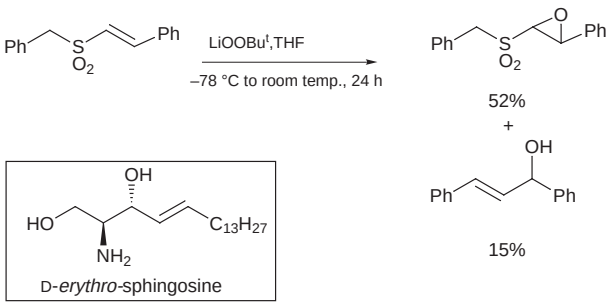


Fig. 5 Products of the epoxy-Ramberg–Bäcklund rearrangement (using LiOBu^t in THF; isolated yields shown).

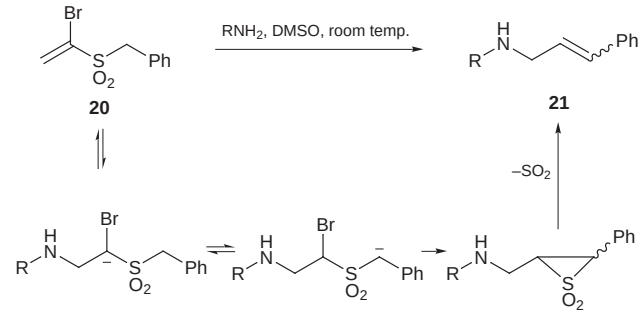


Scheme 12

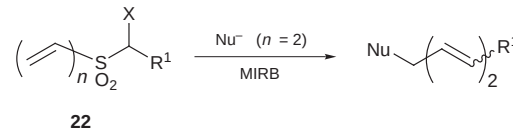
(*ii*) Tandem conjugate addition-Ramberg–Bäcklund rearrangements

Serendipity played a major part in the discovery of the second variant of the Ramberg–Bäcklund rearrangement. Paul Evans was attempting to prepare sulfonyl aziridines to study the feasibility of the aziridine-Ramberg–Bäcklund rearrangement. However, treatment of bromovinyl sulfone **20** with amines did not produce the corresponding aziridines, as expected,[33] but generated allylamines **21** instead (Scheme 13).

We presume that this process proceeds by the sequence shown in Scheme 13, *i.e.* conjugate addition to bromovinyl sulfone **20** followed by α-sulfonyl anion equilibration and Ramberg–Bäcklund rearrangement. This process is related to the Michael-induced Ramberg–Bäcklund (MIRB) reaction shown in Scheme 14.[5] The MIRB process is of limited utility, however, due to the apparent requirement for a dienyl sulfone (**22**, n = 2); similar reactions involving vinyl sulfones (n = 1) are unknown.

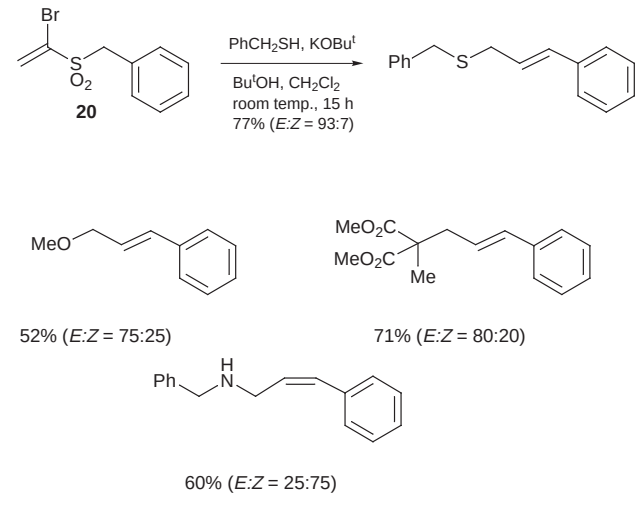


Scheme 13



Scheme 14

The novel tandem conjugate addition Ramberg–Bäcklund sequence was investigated with several other nucleophiles (Scheme 15).[34] We believe that this is a generally useful procedure as bromovinyl sulfones are readily prepared from the corresponding vinyl sulfones by a bromination–dehydrobromination sequence and they are excellent Michael acceptors. Thus, thiolates, alkoxides, amines and malonates all gave successful addition-rearrangements. The stereochemical outcome of the these reactions reflects the basicity of the reaction medium: with amines as nucleophiles/bases, *cis*-isomers predominate, whereas the more basic conditions employed in the other processes favoured formation of the *trans*-alkenes.



Scheme 15

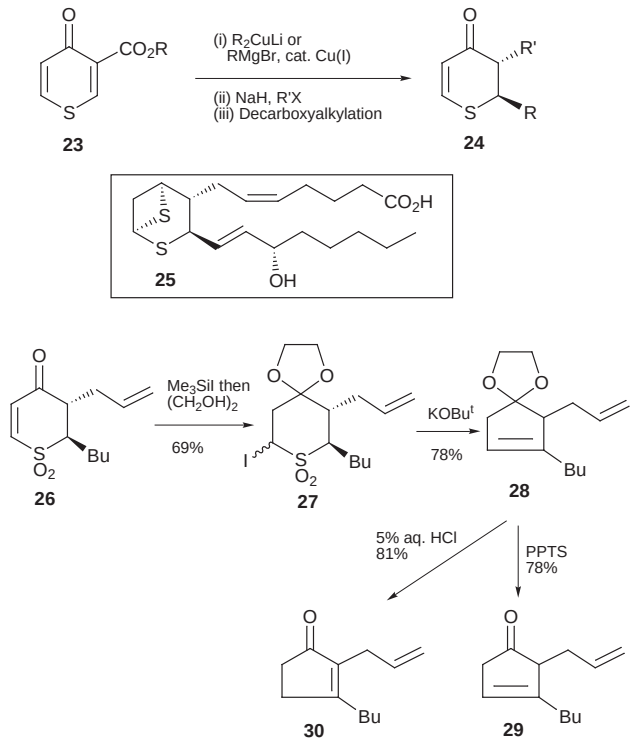
(*f*) Applications of the Ramberg–Bäcklund rearrangement in natural product and bioactive target molecule synthesis

We have utilised the Ramberg–Bäcklund rearrangement for the synthesis of a number of natural products and related compounds of biological interest.

(*i*) Cyclopentene-based natural products and related compounds

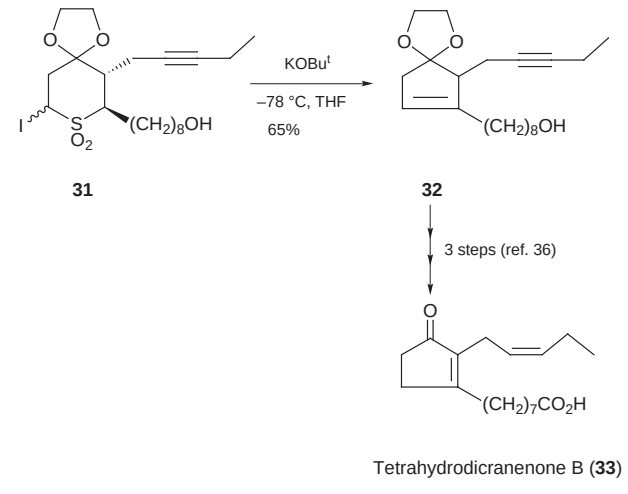
As referred to earlier, Guy Casy, Simon Lane and Stephen Quick developed a general organocopper-based route to convert

3-alkoxycarbonylthiin-4-ones **23** into 2,3-disubstituted 2,3-dihydrothiin-4-ones **24** as part of a programme to prepare thiathromboxane A_2 (**25**) and novel thiathromboxane analogues (Scheme 16).[15,16] We envisaged utilising the Ramberg–Bäcklund rearrangement to convert the sulfones derived from these 2,3-disubstituted 2,3-dihydrothiin-4-ones into 2,3-disubstituted cyclopentenones as shown in Scheme 16. We wrote to Professor Leo Paquette outlining our ideas. Receiving an encouraging response, Guy Casy prepared dioxide **26** by oxidation of the corresponding sulfide and introduced the iodide substituent with concomitant ketone protection giving adduct **27**. Ramberg–Bäcklund rearrangement proceeded smoothly to produce cyclopentene **28** which was converted into either the non-conjugated cyclopentenone **29**, or its conjugated isomer **30**, by acidic hydrolysis.[17] Matsuyama's group reported the use of the Ramberg–Bäcklund rearrangement to prepare cyclopentenes at about the same time.[35]



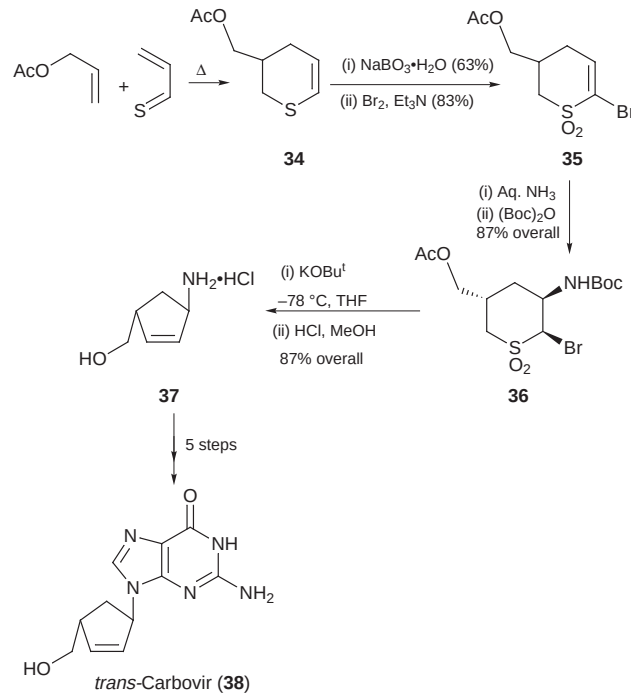
Scheme 16

Guy Casy went on to utilise this mild Ramberg–Bäcklund route to cyclopentenes as part of a formal total synthesis of the naturally occurring antibacterial agent tetrahydrodicranenone B (**33**), as shown in Scheme 17.[17] α-Iodo sulfone **31**, prepared using similar organocopper methodology to that shown in Scheme 16, underwent Ramberg–Bäcklund rearrangement to give cyclopentene **32** which can be converted into tetrahydrodicranenone B in three efficient steps using the chemistry developed by Moody, Roberts and Toczek.[36]



Scheme 17

Arne Grumann later employed a similar Ramberg–Bäcklund ring contraction, this time on α-bromo sulfone **36**, as the key step in the first synthesis of *trans*-carbovir **38** (Scheme 18).[37] *cis*-Carbovir is a fraudulent nucleoside which acts as a potent inhibitor of HIV reverse transcriptase. The 5-substituted unsaturated thiane **34** was prepared from thioacrolein *via* a hetero-Diels–Alder process. An important subsequent step involved conjugate addition of ammonia to unsaturated sulfone **35** to produce α-bromo sulfone **36** in an efficient and stereoselective manner. The use of α-bromo-α,β-unsaturated sulfones as precursors to Ramberg–Bäcklund substrates should be generally useful methodology (see also Scheme 15). Ramberg–Bäcklund reaction of **36** followed by deprotection gave amine hydrochloride **37** which was elaborated using the Traube method to complete the synthesis of *trans*-carbovir.[37]

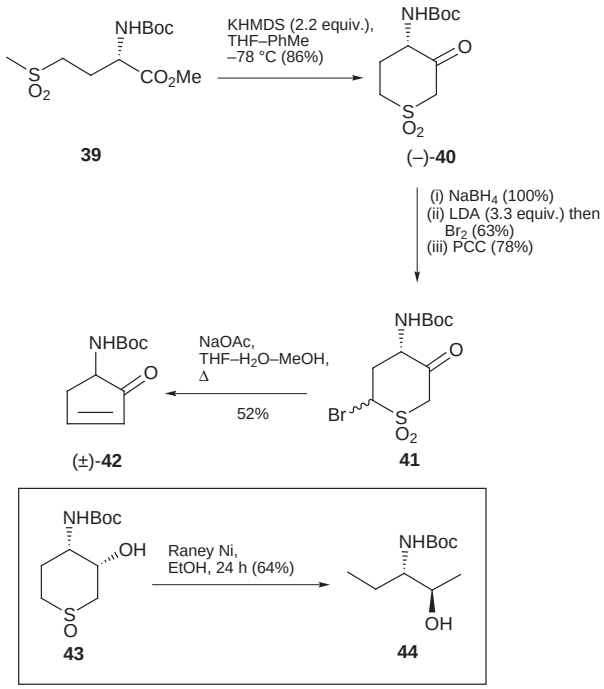


Scheme 18

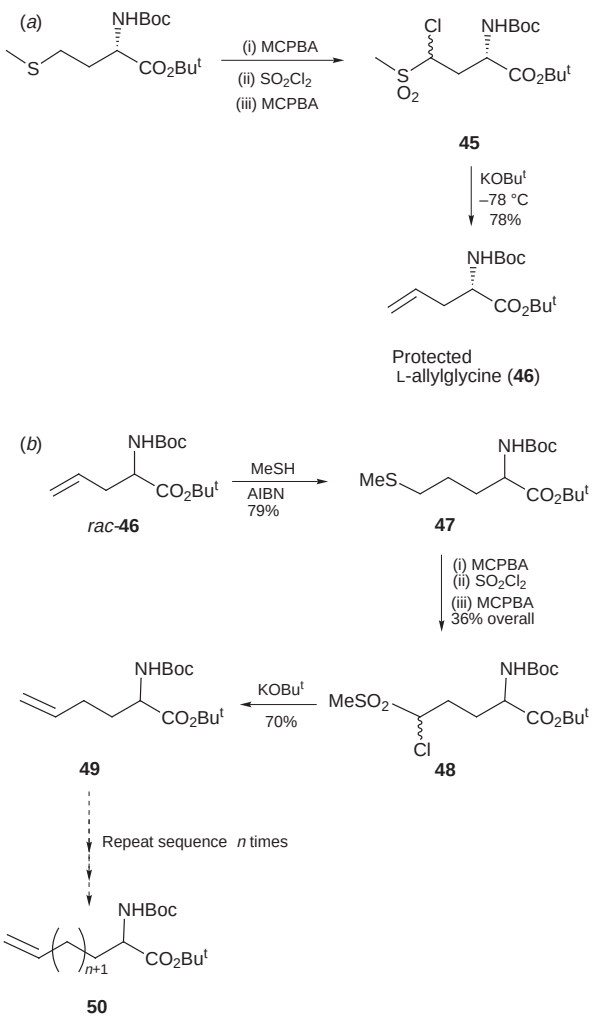
About this time we became interested in synthetic applications of amino acids. Mark Gamble first prepared amino cyclopentanes using glutamic acid-derived sulfones.[38] He then studied the cyclisation reactions of methionine-derived sulfones such as **39** (Scheme 19). The cyclisation to produce the enantiomerically pure thiane dioxide **40** proceeded in high yield and the product was subsequently elaborated to give α-bromo sulfone **41**. This compound underwent Ramberg–Bäcklund rearrangement to give the protected amino cyclopentenone **42**, unfortunately in racemic form.[39] Attempts to desulfurise the cyclic sulfones in this sequence were unsuccessful but Tim Ockendon and Peter O'Brien found that the sulfoxides corresponding to **39** also underwent cyclisation, and Raney nickel desulfurisation of intermediates such as **43** provided a method for preparing protected *anti*-1,2-amino alcohols like **44**.[39]

(*ii*) Unsaturated amino acid synthesis

The interest in methionine chemistry referred to in the previous section provided the stimulus for Marcel Schaeffer to investigate the Ramberg–Bäcklund reactions of L-methionine-derived α-chloro sulfones [Scheme 20(*a*)]. He showed that



Scheme 19

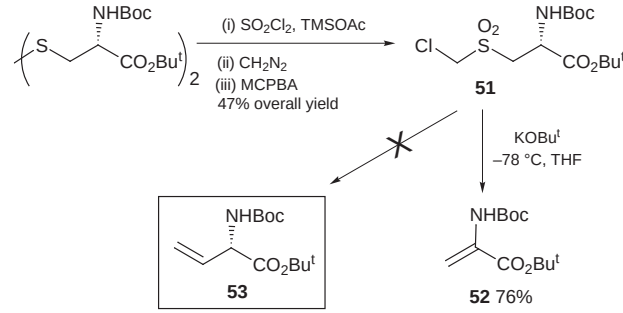


Scheme 20

chloro sulfone **45** underwent efficient conversion into allyl glycine derivative **46** and demonstrated, with Zhao-Xia Guo, that racemisation could be avoided by carrying out the reaction at −30 °C or lower.[40]

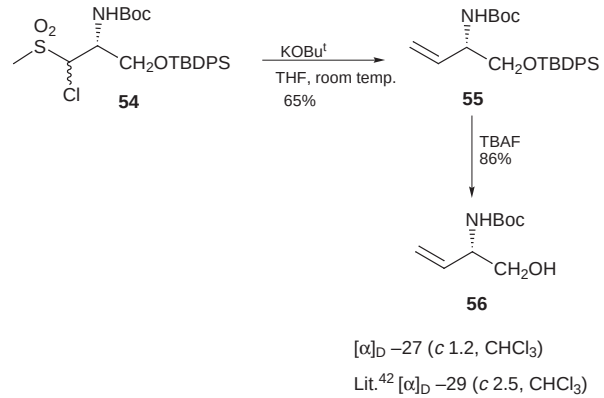
In unpublished and unoptimised work, Zhao-Xia Guo went on to demonstrate that this sequence could be employed in an iterative manner [Scheme 20(*b*)]. Thus, the radical addition of methanethiol to the protected allylglycine **46** gave sulfide **47** which was easily elaborated *via* α-chloro sulfone **48** to give butenyl glycine derivative **49**. In principle, this sequence could be employed to prepare the series of unsaturated amino acid derivatives **50** (n = 0,1,2 *etc*.).

In order to complete the sequence, Tim Ockendon attempted to prepare the corresponding vinyl glycine derivative **53** (Scheme 21). He utilised a modified version of the sulfinyl



Scheme 21

chloride procedure developed by Ottenheijm *et al*.[41] to prepare α-chloro sulfone **51** in a regioselective manner. Unfortunately, treatment of **51** under standard Ramberg–Bäcklund conditions gave 1,2-elimination, producing alkene **52**, and none of the required product **53** was observed. We were, however, able to prepare the corresponding vinyl glycinol **56** using Ramberg–Bäcklund methodology (Scheme 22). α-Chloro sulfone **54** was thus converted into alkene **55** which was desilylated to give the known[42] alcohol **56** in enantiomerically pure form.



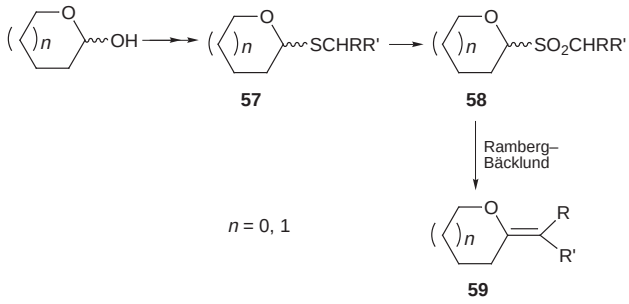
Scheme 22

(*iii*) *exo*-Glycal synthesis

As part of a project to design and synthesise novel analogues of sialyl Lewis^x,[43] Paul Murphy prepared a number of thioglycosides **57**. These compounds provided us with the opportunity to obtain the corresponding *S*-glycoside dioxides **58** and investigate their Ramberg–Bäcklund rearrangements (Scheme 23).

The sequence illustrated in Scheme 23 leads to *exo*-glycals **59**. The parent 1-*exo*-methylene compounds (**59**, R = R′ = H) have been used as glycosidase inhibitors[44] and are valuable synthetic intermediates.[45–51] Scheme 24 summarises synthetic applications of the glucose-derived *exo*-methylene compound **60**. The corresponding substituted *exo*-glycals **59** (R, R′ ≠ H) are also of considerable interest.[52]

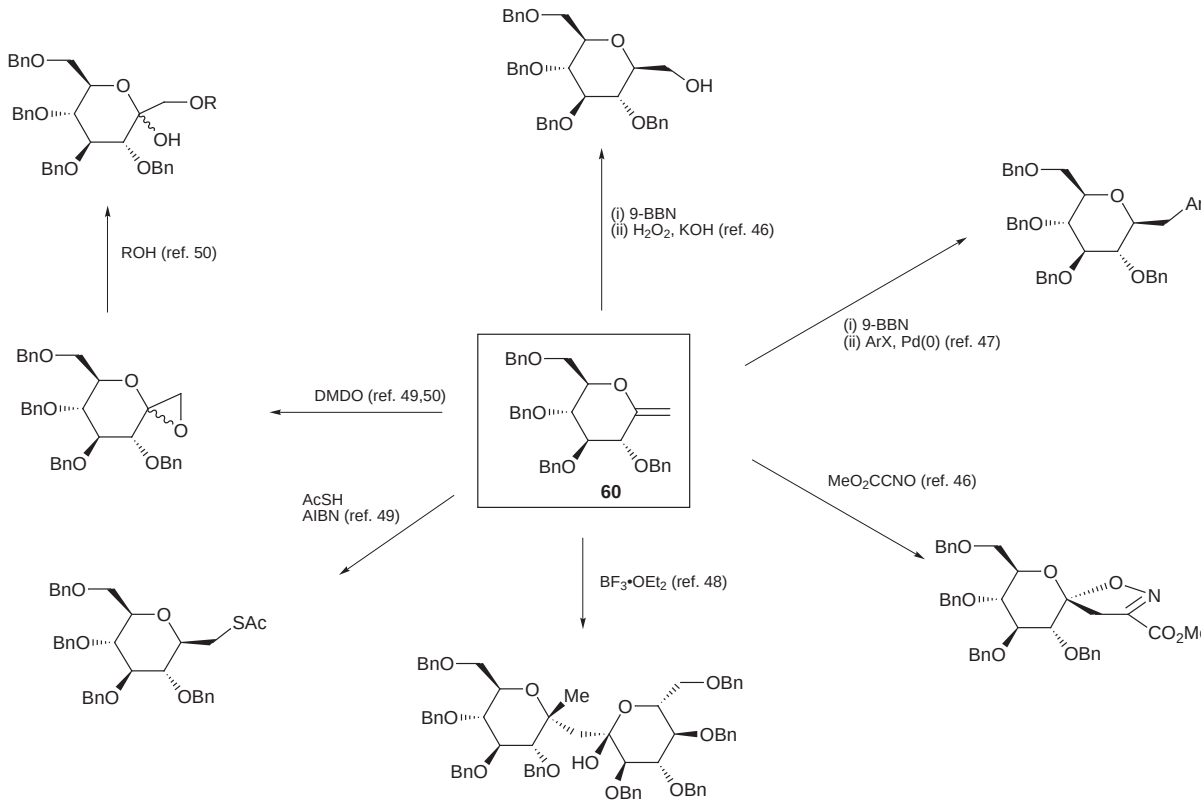
A number of procedures have been published for the preparation of *exo*-methylene glycals[44–51] but the method of



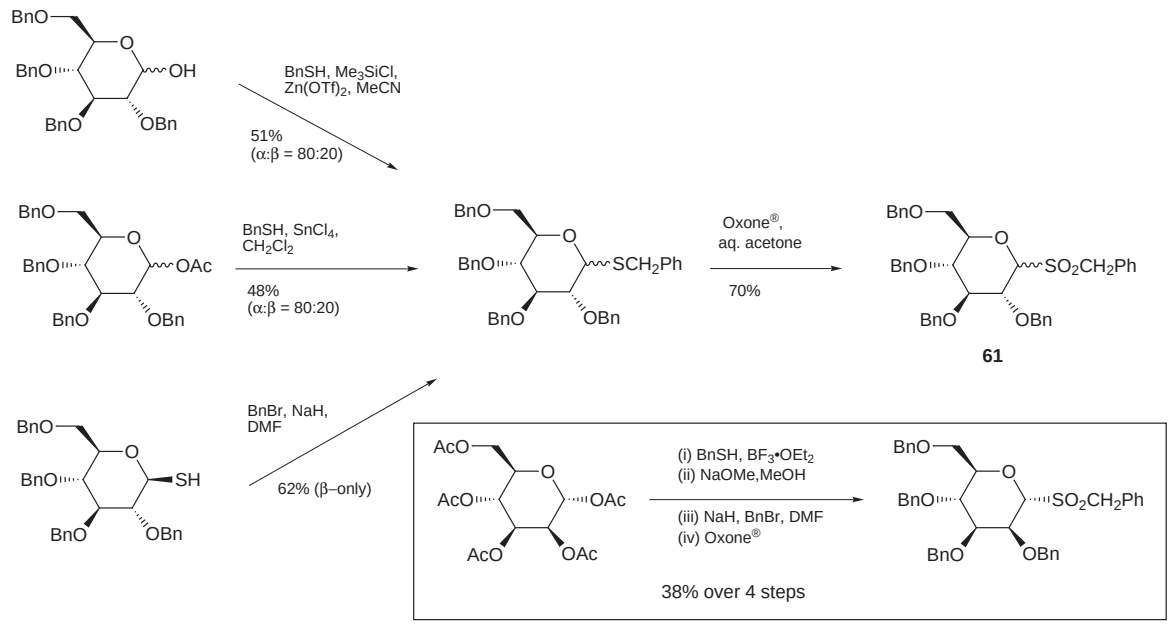
Scheme 23

choice would appear to be methylenation of the corresponding lactones using dicyclopentadienyl(dimethyl)titanium (or the Tebbe reagent).[47,51] There is no general method to prepare substituted *exo*-glycals **59** (R, R′ ≠ H), however.[53] Paul Murphy, Frank Griffin and Duncan Paterson therefore set out to explore the Ramberg–Bäcklund route to *exo*-glycals.[54,55] Scheme 25 summarises some of the procedures used to prepare the *S*-glycosides[56] and thus the sulfones needed for the Meyers' variant of the Ramberg–Bäcklund rearrangement.[3] Similar procedures were used to prepare related glucose-derived sulfones and *S*-glycoside dioxides derived from other sugars.

We were delighted to observe that the required transformations to produce *exo*-glycals proceeded efficiently using

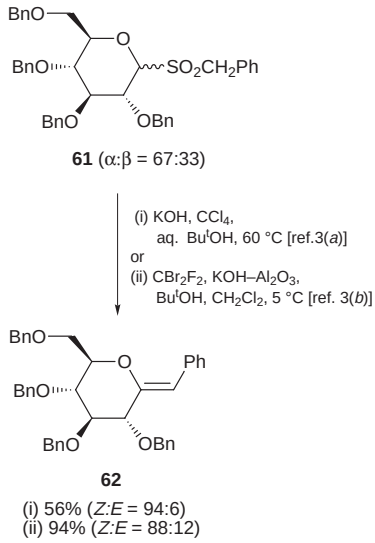


Scheme 24



Scheme 25

Meyers' original conditions[3a] (CCl_4, KOH) and the modified conditions (CBr_2F_2, KOH, Al_2O_3) recently reported by Chan *et al*.[3b] This is shown in Scheme 26 for the glucose derived benzyl sulfone **61**: phenyl glycal **62** was produced in reasonable yield using the Meyers' conditions and excellent yield by the Chan procedure, the *Z*-product predominating in both cases.



Scheme 26

We then proceeded to prepare a range of *exo*-glycals using this Ramberg–Bäcklund methodology (Fig. 6). As can be seen, the glucose-derived methylene compound **63a** was prepared, as were the phenyl, methyl and ethyl substituted alkenes **63b–d** (all with the *Z*-alkene predominating). Although unoptimised, galactose, mannose, xylose, fucose and ribose derived alkenes **63e–i** were equally accessible. Tetrasubstituted alkenes **63j–l** were also prepared by this methodology, although in these cases the required transformation was only observed using the Meyers' conditions. Further work is needed to optimise these yields, but the availability of highly hindered glycals, particularly adamantene derivative **63l**, is noteworthy.

The ease with which anomeric carbanions eliminate C-2 alkoxides to give *endo*-glycals has been a longstanding problem in *C*-glycoside synthesis until recently.[57] It should be noted that the Ramberg–Bäcklund methodology is compatible with 2-alkoxy substituents. Investigations are therefore underway to probe the mechanisms of these reactions.[54]

As mentioned, *exo*-glycals have proved to be valuable glycosidase inhibitors[44,52] but for our methodology to be of use in this area it is important to be able to remove the hydroxy group protection without reducing or hydrolysing the enol ether moiety. Benzyl protection is not suitable for this purpose and Duncan Paterson has explored the compatibility of other protecting groups with the Ramberg–Bäcklund conditions (Scheme 27). Sulfone **64**, protected by *tert*-butyldimethylsilyl (TBDMS) groups, was therefore prepared. Ramberg–Bäcklund rearrangement of **64** proceeded smoothly and desilylation was accomplished using tetrabutylammonium fluoride (TBAF). This two step sequence produced the unprotected enol ether **65** (which was acetylated for characterisation purposes).

We have also investigated synthetic applications of these novel *exo*-glycals. As shown in Scheme 28, Marie-Lyne Alcaraz utilised the *Z*-phenyl derivative **62** in a formal synthesis of the *C*-glycoside **68**, recently reported as a new β-glycosidase inhibitor by Schmidt and Dietrich.[58] Thus, hydroboration using borane–THF followed by oxidation gave a separable 25 : 75 mixture of α- and β-alcohols **66** and **67** in 65% overall yield. Schmidt and Dietrich converted alcohol **67** into enzyme inhibitor **68** in five high yielding steps.[58] The advantage of our new procedure is the brevity of the synthetic route: Schmidt and

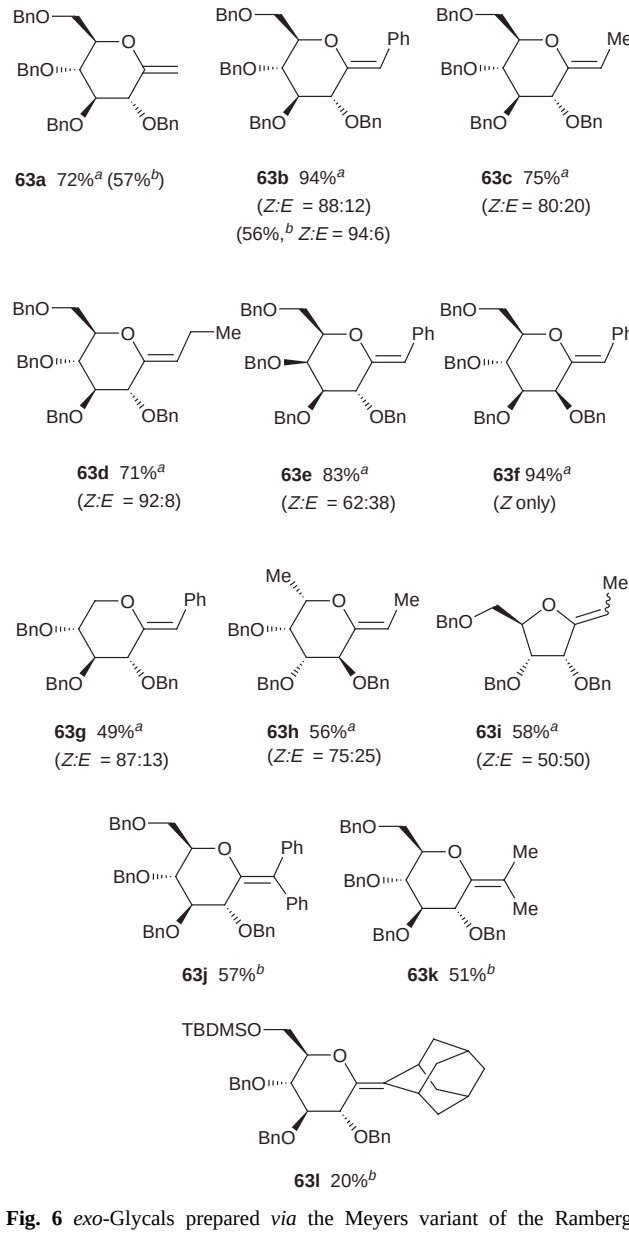
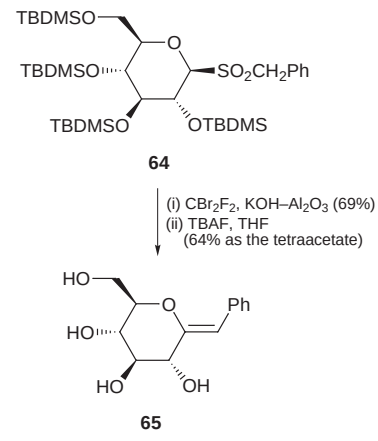


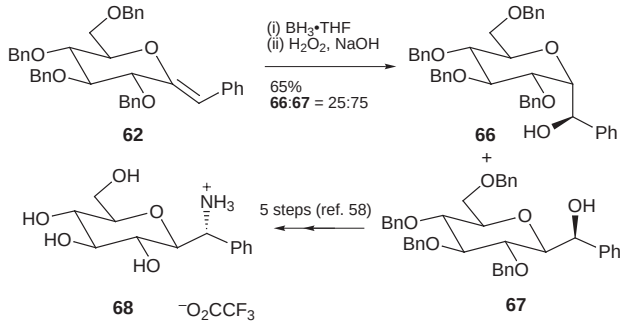
Fig. 6 *exo*-Glycals prepared *via* the Meyers variant of the Ramberg–Bäcklund rearangement. [a] Using CF_2Br_2 [ref. 3(*b*)]. [b] Using CCl_4 [ref. 3(*a*)].



Scheme 27

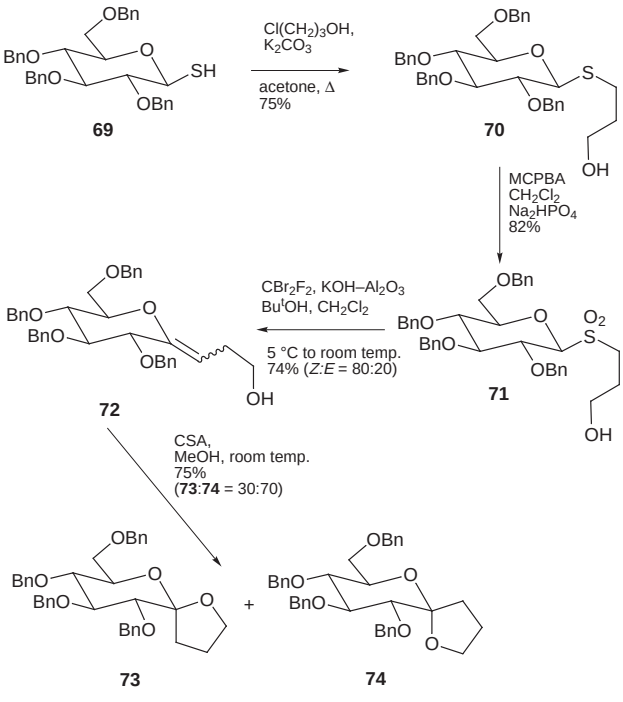
Dietrich required eight steps to prepare alcohol **67** from D-glucal.[58]

Frank Griffin employed this new methodology to prepare the spirocyclic sugars **73** and **74** (Scheme 29). These compounds,



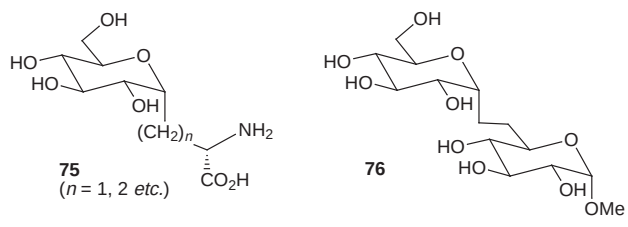
Scheme 28

which are simplified analogues of natural products such as papulacandin D,[59] have recently been prepared by a photolytic route.[60] In our new synthesis (Scheme 29), the benzylated thioglucose derivative **69**[56b] was alkylated giving sulfide **70** which was oxidised to sulfone **71**, both steps proceeding in good yield. The Ramberg–Bäcklund rearrangement proceeded smoothly on the unprotected alcohol **71** using Chan's CBr_2F_2 conditions[3b] giving *exo*-glycal **72** in 73% yield. Cyclisation was effected by treatment of enol ether **72** with camphorsulfonic acid (CSA) in methanol to produce a separable mixture of spiroacetals **73** and **74** (30 : 70) in 75% yield.



Scheme 29

We are currently optimising this Ramberg–Bäcklund methodology for *exo*-glycal synthesis, and exploring its applications for the synthesis of more complex *C*-glycosides and *C*-disaccharides. For example, routes to carba-glycopeptides[61] **75** and carba-disaccharides[62] such as methyl carba-isomaltoside **76** using the Ramberg–Bäcklund chemistry are currently being investigated.[63]



Summary

Major advances have been made in Ramberg–Bäcklund and episulfone chemistry over the past few years. Procedures have been developed which enable episulfones to be produced from α-halo sulfones or from episulfides by oxidation. Episulfone deprotonation-trapping reactions have been developed to provide a new method of preparing novel vinylsilanes and vinylstannanes, and new variants of the Ramberg–Bäcklund rearrangement have been discovered which produce functionalised products such as allylic alcohols and amines. Mild conditions have been developed for the classical Ramberg–Bäcklund rearrangement and applied to the synthesis of cyclopentene-based natural products and unsaturated amino acids. In addition, the Meyers' variant of the Ramberg–Bäcklund rearrangement has been utilised in a new route to *exo*-glycals commencing from *S*-glycoside dioxides. Ongoing work to further apply this new methodology, for example to the synthesis of sphingosines and novel *C*-disaccharides, promises further interesting and useful discoveries ahead.

Acknowledgements

This article is dedicated to Dr D. Neville Jones, who taught me all about the Ramberg–Bäcklund rearrangement (and many other things) and stimulated a life-long interest in organosulfur chemistry, and to Dr Ian Harrison, who extended this interest in organosulfur compounds and also introduced me to prostaglandins, thromboxanes and other arachidonic acid metabolites. Without the influence of these two outstanding teachers and scientists none of the research described in this article would have been possible.

I would like to pay tribute to the co-workers mentioned in the text for their practical skills, intellectual contributions and, in particular, for their enthusiasm when ploughing what has usually been a lone furrow alongside the organometallic and natural product teams. I would also like to thank the industrial collaborators and other group members for their contributions over the years and the EPSRC for financial support.

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