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A Fascination with 1,2-Diacetals

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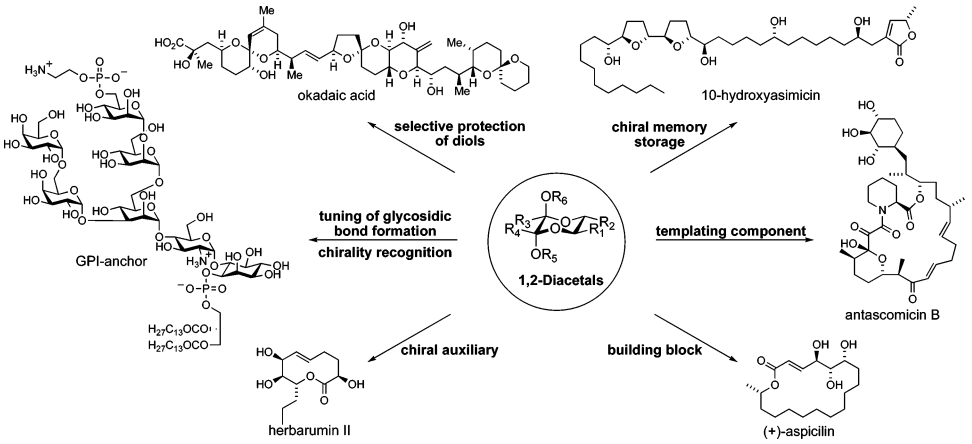

1,2-Diacetals are readily prepared, rigid structural motifs that provide a wide range of opportunities for applications in natural product assembly. These uses encompass selective 1,2-diol or α-hydroxy acid protection, enantiotopic recognition and desymmetrization methods, chiral memory applications, and reactivity control in oligosaccharide synthesis, as well as functioning as templating components, chiral auxiliaries, and building blocks. 1,2-Diacetals are often more stable and lead to products with enhanced crystallinity compared to their five-ring acetonide counterparts. Many 1,2-diacetals have favorable NMR parameters, which facilitate structural assignment, particularly during asymmetric reaction processes.

I. Introduction

In this Perspective, we look back to the early development of 1,2-diacetals[1] and their application to complex natural product synthesis and then move forward to today's challenges and problems. In doing so, we will embrace a wide diversity of synthesis opportunities, especially those that define ways to control or introduce polyoxygen functionality into organic molecules. Given that 1,2-diacetals have been known since 1938,[2] it is surprising that they have not been usefully employed in synthesis programs until relatively recent times, yet this is the case. In general terms, we will describe opportunities that arise by using 1,2-diacetals such as the dispiroketal motif **1**[3] or more simply defined as **2** (Figure 1).

For these structures, one can anticipate considerable control coming from predictable anomeric (or exo-anomeric) effects, the favored equatorial substituent placement, and other torsional effects, which can be expressed through chemical reactivity differences or facially selective reaction processes. The ability to store chiral information in the acetal units, or being able to tune substituents for later elaboration and even assist in their later deprotection, adds further value to these systems. Unfortunately, in a paper of this type we cannot cover all of the chemistry of 1,2-diacetals. We will therefore focus on completed

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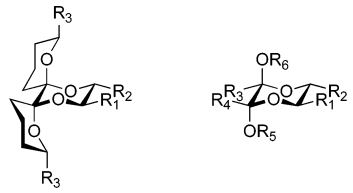


FIGURE 1. Dispiroketals (**1**) and 1,2-diacetals (**2**) motifs.

natural product syntheses that have exploited the methods successfully, mainly with examples from our own laboratories, but we will also include key contributions from other groups. For a detailed discussion of the development of the methods using 1,2-diacetals, readers are encouraged to consult the reviews[1,3] and recent work describing new aspects of 1,2 diacetal chemistry.[4−15] General methods for preparing dispiroketals and other 1,2-diacetals and their various uses emerge as the paper unfolds.

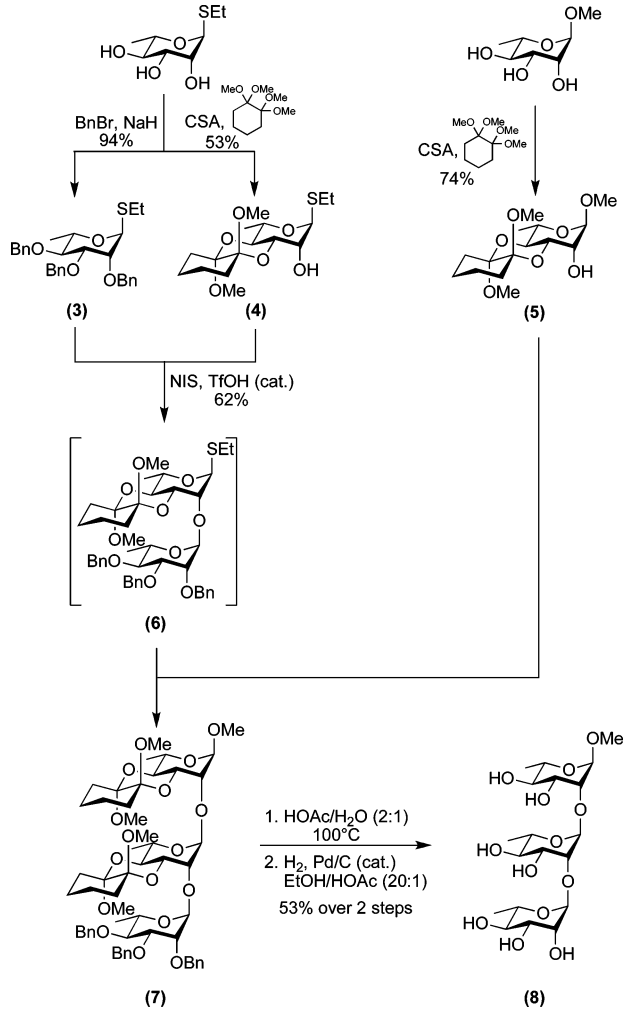
II. General Discussion and Natural Product Syntheses

The main driver for the profitable development of 1,2-diacetals arose from the desire to solve problems in the carbohydrate area and, in particular, oligosaccharide synthesis. Although protecting groups have traditionally played crucial roles in the synthesis of carbohydrates, and will continue to do so, many problems still exist. For example, syntheses tend to be very extended owing to the multiple steps that are often necessary to deliver appropriately protected coupling partners. Also, there is a general lack of appreciation for the effect of protecting groups on glycosidic bond coupling reactions, both in terms of the rate and anomeric control, and that the final global deprotection steps often lead to low yields or contaminated products.[16]

Carbohydrate chemists have grown up with considerable specialist knowledge and have established a toolbox of methods that can be applied to particular problems. We wanted to find a new general solution to the selective protection of 1,2-diequatorial diols, preferably in the presence of further unprotected hydroxyl groups. We also wanted to be able to do this in an asymmetric fashion, by either exploiting inherent chirality or by using enantiotopic differentiation methods. We anticipated that the fusion of a diacetal to a diol group of a sugar derivative would impart considerable rigidity to the system and should provide a tunable element to control reactivity during the oligosaccharide coupling process.[17−20] These methods could also shorten considerably some of the more convoluted, multistep processes common to classical oligosaccharide assembly.[21] We were able to achieve all of these goals. Here, however, we will simply illustrate in a few examples how the methods can be applied and then consummate this knowledge in a synthesis of a highly complex oligosaccharide, the glycophosphatidylinositol GPI anchor of *Trapanosoma brucei*, the African parasite responsible for human sleeping sickness.

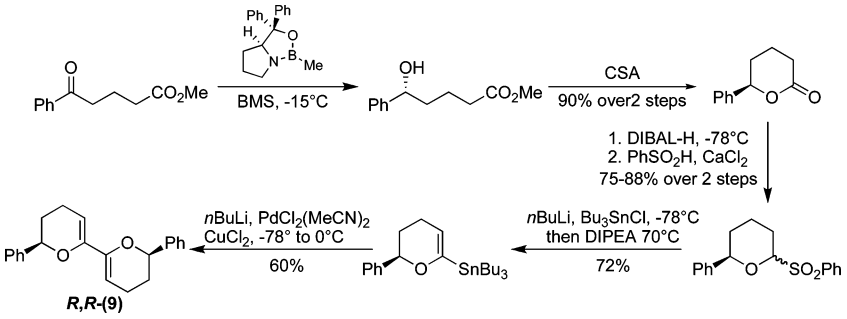
The first example demonstrates two key aspects of 1,2-diacetal chemistry, namely, selective diequatorial diol protection and subsequent reactivity control arising during glycosidation to give a trisaccharide derivative in a single reaction pot.[22] The particular trisaccharide we prepared is thought to be the binding epitope of the polysaccharide antigen of group B *Streptococci*. Here, the required carbohydrate building blocks **3**−**5** are derived from *S*-ethyl-α-L-rhamnose and methyl-α-L-rhamnose, respectively. In particular, the key steps show that both rhamnose derivatives react with 1,1,2,2-tetramethoxycyclohexane in the presence of camphorsulfonic acid and trimethyl orthoformate in methanol to give the corresponding cyclohexane 1,2-diacetals CDA **4** and **5** in a selective manner (Scheme 1).[23] The next important feature to notice is that the two building blocks **3** and **4** have the same activatable thioethyl leaving group. However, owing to the torsional strain imparted by the CDA protection in **4**, one can expect this to be less reactive than the more flexible derivative **3** during the glycosidation process, and therefore, upon reaction with *N*-iodosuccinimide and triflic acid, the glycosyl donor **3** couples selectively with the acceptor **4** to give an intermediate disaccharide **6**.

SCHEME 1. Access to Epitope 8

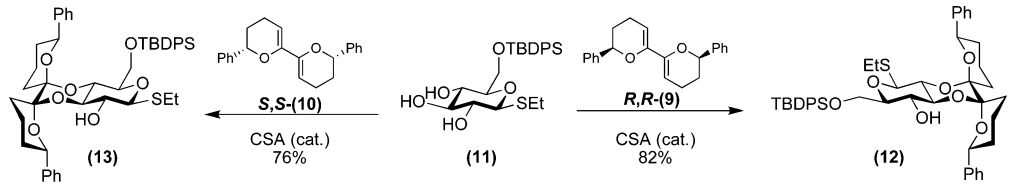


The disaccharide **6** was not isolated, but since it still contained an SEt group, albeit less reactive, it could be activated as the second glycosyl donor which then goes on to couple with the third acceptor **5** to give the trisaccharide derivative **7**, in a single reaction pot. Final deprotection afforded the epitope **8** (Scheme 1). These principles of reactivity tuning during glycosidation using 1,2-diacetal fusion have turned out to be very general and applicable to a wide range of substrates to achieve one-pot oligosaccharide assembly.[17−20] It should be noted that no cleavage of the trisaccharide occurs during the final CDA removal by hydrolysis using acetic acid/H_2O. This is an important feature of the reaction, especially for the preparation of more complex systems[21] as will be seen later.

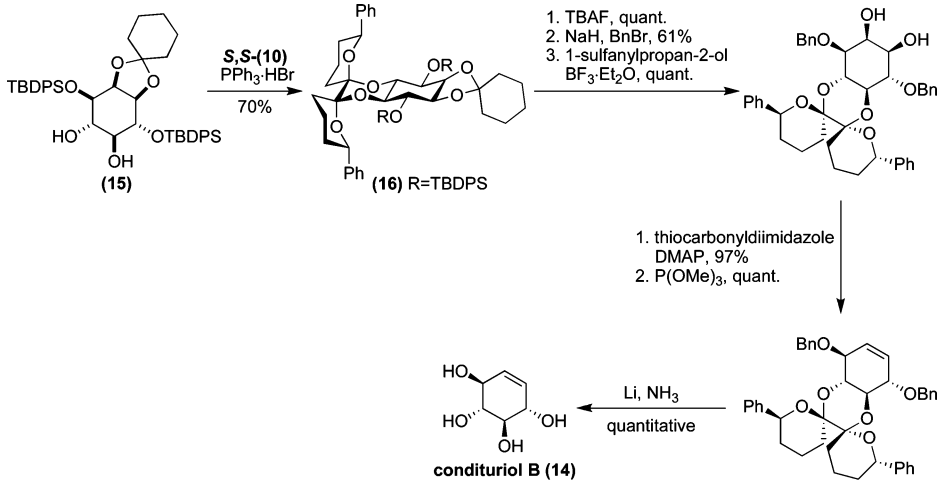
SCHEME 2. Preparation of the (*R*,*R*)-Diphenyl-Substituted Dihydropyran



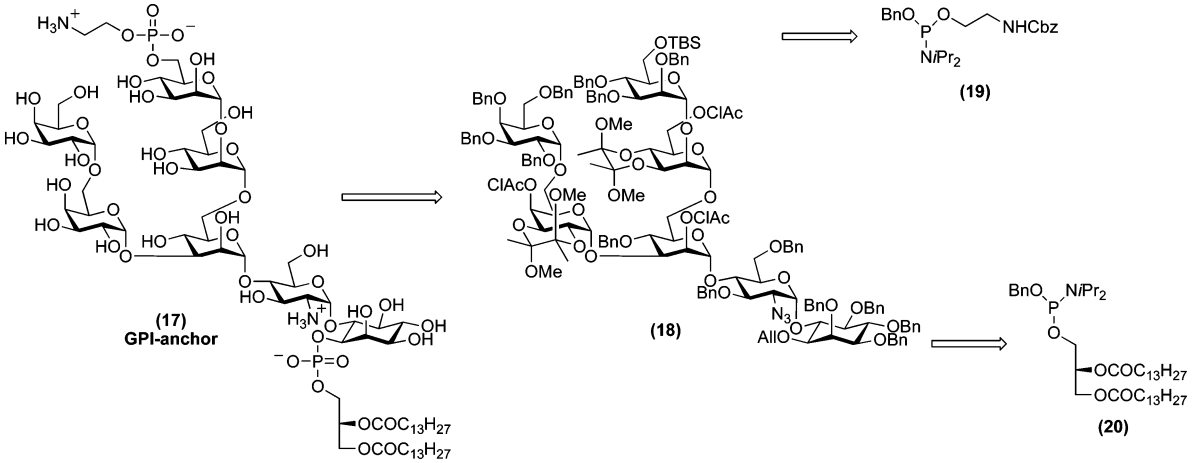
SCHEME 3. Chirality Recognition in the Formation of Dispiroketals



SCHEME 4. Synthesis of Conduritol B



SCHEME 5. GPI Anchor



The next exploitable aspect of 1,2-diacetals makes use of the principles of chirality matching and mismatching through the use of the operating anomeric effects in chiral dispiroketals.[24,25] One of the many examples of these concepts utilizes diphenyl-substituted dihydropyrans **9** and the corresponding enantiomer **10**.[26] These are prepared by various methods, although the route shown in Scheme 2 is very effective in producing the *R,R′* isomer **9**. The *S,S′*-**10** isomer can be prepared similarly.

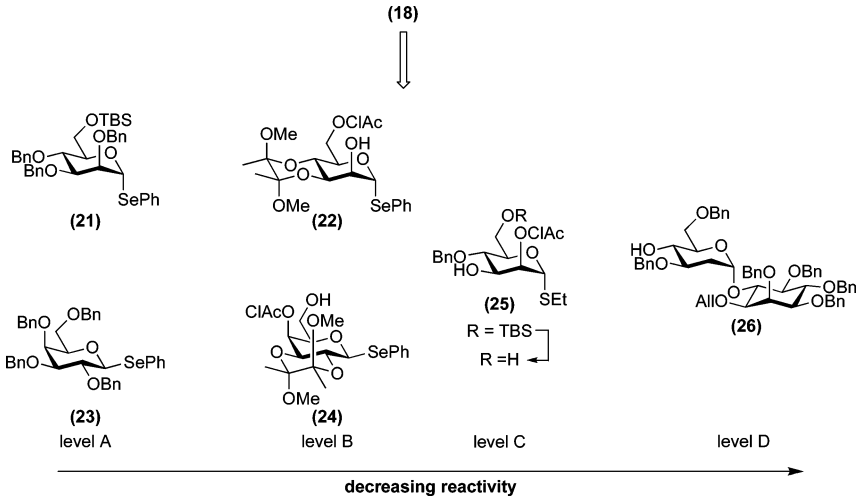
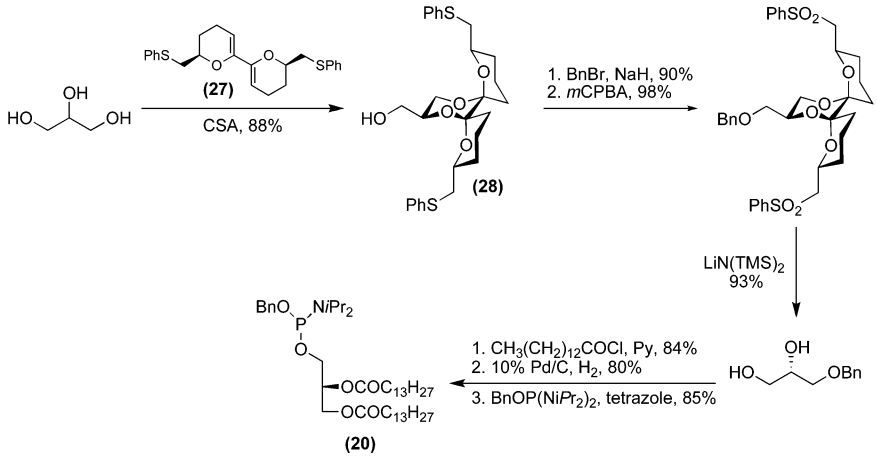
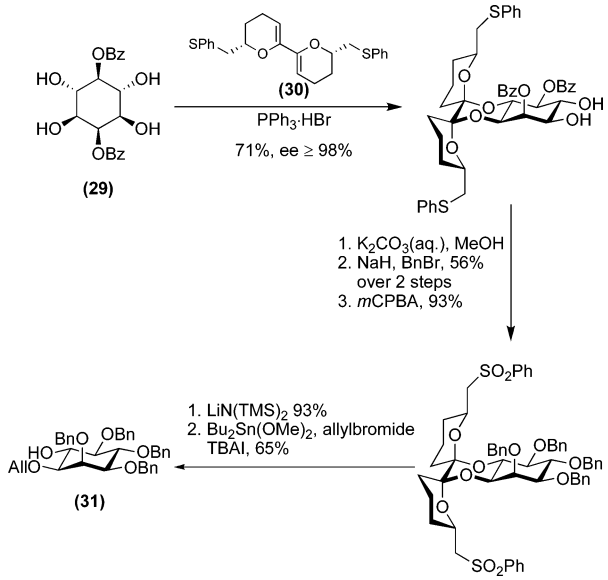


FIGURE 2. Reactivity of the building blocks.

SCHEME 6. Desymmetrization of Glycerol



SCHEME 7. Desymmetrization of *myo*-Inositol

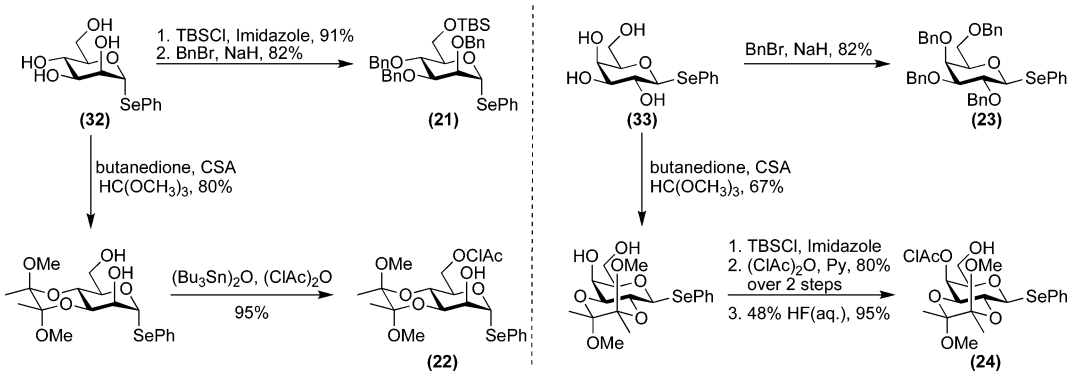


The phenyl substituents in these dihydropyrans not only control the next spirocyclization event, they facilitate later removal by hydrogenolysis. The best illustration of how these chiral bis-dihydropyrans function in a selective manner occurs in the example whereby the *S*-ethyl glucose derivative **11** was reacted with *R*,*R*′-**9**, the only product isolated was the 2,3-protected dispiroketal **12**, while with the enantiomer *S*,*S*′-**10** only the 3,4-protected dispiroketal isomer **13** was observed (Scheme 3).[27] No mixed products were detected since these would involve serious steric clashes, owing to the loss of anomeric effects and placement of phenyl group side chains in axial positions.

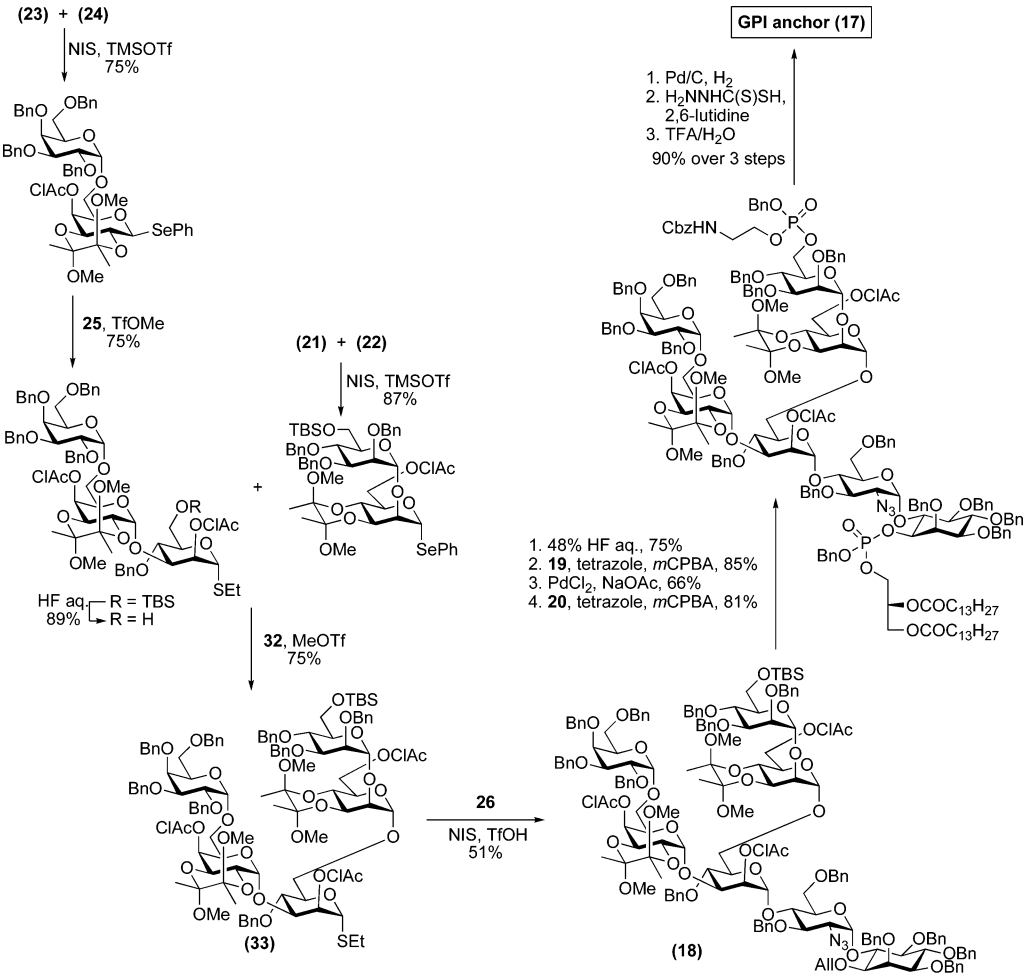
From these results, it is clear that there is a chirality recognition between particular diequatorial diol pair and the chiral dihydropyran. This effect leads to the most thermodynamically favored product being formed whereby the phenyl substituents prefer diequatorial dispositions and there is maximum anomeric control at the newly formed spiroketal centers.

These concepts can be utilized in a variety of ways; however, the synthesis of one of the least accessible natural product conduritols,[28,29] namely conduritol B **14**, is a good example since it employs the chiral bisdihydropyran *S*,*S*′-**10** as a resolving agent. Here, the racemic protected polyol derivative **15** (available readily from *myo*-inositol) reacts selectively, using the same principles as above, to give the enantiopure dispiroketal product **16** as the only product.[30] This was transformed to conduritol B **14** in a number of straightforward steps. The dispiroketal was then removed quantitatively in the last step by hydrogenolysis, using sodium in ammonia to cleave the benzylic bond and correspondingly leads to deprotection (Scheme 4).

SCHEME 8. Synthesis of Building Blocks 21−24



SCHEME 9. Coupling of the Units and Synthesis of GPI Anchor

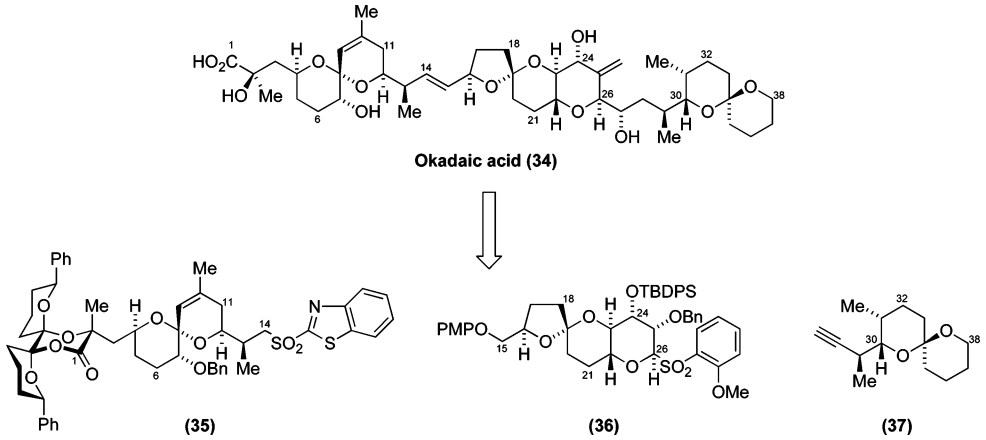


The stage was set to take on a much greater challenge: the total synthesis of the glycosylphosphatidylinositol GPI anchor **17**. In our plan for making the GPI anchor **17**, the coupling of three major components was envisaged (Scheme 5).[31] First, an appropriately protected carbohydrate core **18** had to be constructed, which would then be coupled with a phosphorylated ethanolamine derivative **19** and finally assembled by additional coupling with a phosphorylated glycerol unit **20**, containing the two fatty acid side chains.

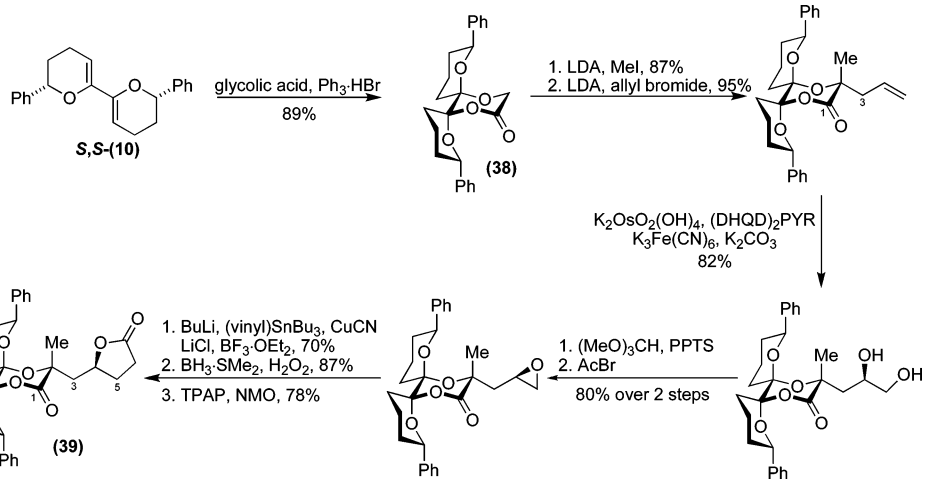
To construct the carbohydrate core **18** efficiently, six building blocks **21**−**26** were designed which exploited the reactivity tuning principles discussed earlier using 1,2-diacetals. The mannose-derived phenylselenide **21** and the galactose selenide **23** were expected to be the most reactive glycosyl donors, while the two butane diacetal (BDA) protected derivatives **22** and **24** should be less reactive owing to torsional constraints, and these selenides in turn should both be less reactive than the ethylthio mannose building block **25**. Compound **26** would be the remaining glucosamine inositol disaccharide fragment functioning as the final glycosyl acceptor (Figure 2).

Before discussing the preparation of these carbohydrate coupling fragments, the syntheses of a further two further chiral components are required, both of which use spiroketals in their formation. To access the enantiopure glycerol side chain

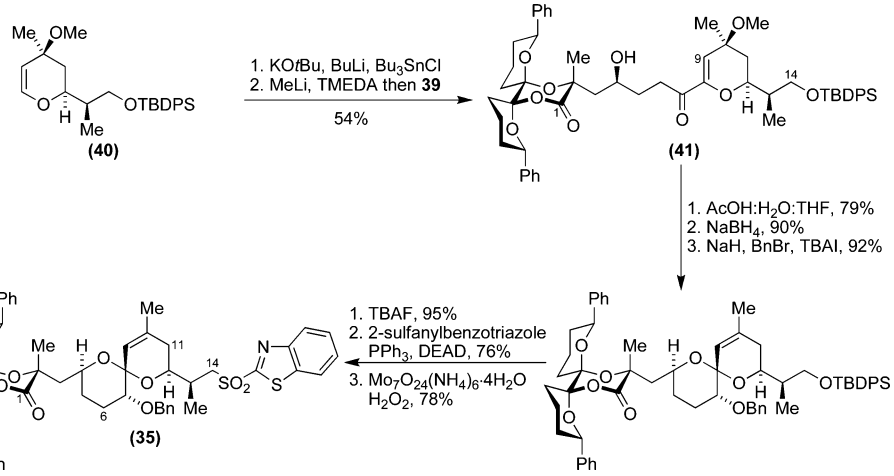
SCHEME 10. Okadaic Acid



SCHEME 11. Asymmetric Substituted Glycolic Acid Synthesis



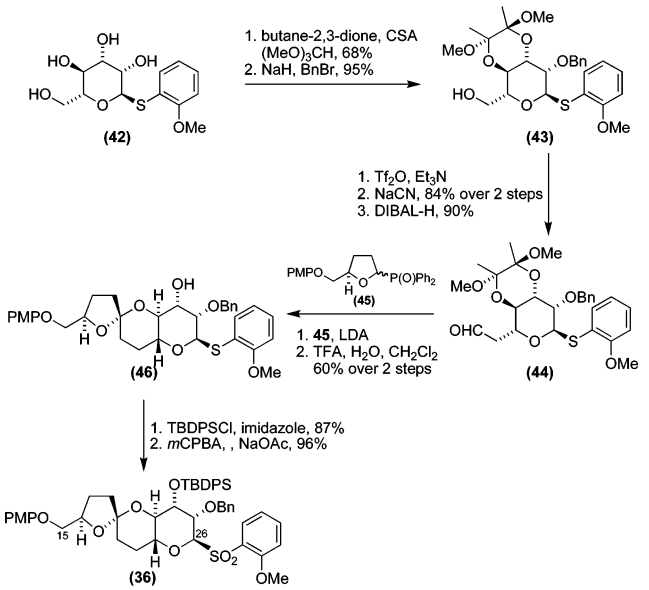
SCHEME 12. Synthesis of Dispiroketal Fragment 35



component **20**, an interesting desymmetrization protocol was developed. Here, glycerol itself was reacted with the bisphenylthio-substituted dihydropyran **27** to give the enantiopure dispiro-protected derivative **28** as a single product in 88% yield. Again, the chiral protecting bisdihydropyran **27** reacted with just one enantiotopic diol pair to give the product with maximum anomeric effects where the side chains CH_2OH and $PhSCH_2$ all adopt equatorial positions. The phenylthio groups[32,33] in **28** assist the later deprotection of the dispiroketal via oxidation and β-elimination to eventually afford the coupling compound **20** (Scheme 6).

Using similar principles, the protected inositol fragment **31** needed for the disaccharide unit **26** could now be obtained by enantiotopic diol discrimination from the prochiral inositol derivative **29**. Here, the enantiomeric bisdihydropyran **30** reacted under the usual conditions to give the expected dispiroketal product in excellent yield, which was then progressed to inositol **31** and eventually through to disaccharide **26** (Scheme 7).

SCHEME 13. Selective BDA Protection in the Synthesis of Fragment 36



For the preparation of the other key coupling partners, **21** and **22** in the manno series and **23** and **24** in the galacto series, common seleno starting materials can be batch split to deliver both reactive donors and detuned donors. For example, the unprotected manno-selenide **32** reacted selectively with butane-2,3-dione,[34,35] methyl orthoformate, and camphor sulfonic acid in methanol to give the corresponding butane-2,3-diacetal, which was then converted to **22** (Scheme 8). The remaining half of the material **32** went through to reactive donor **21**. Likewise, the galacto selenide **33** was transformed to the benzyl-protected donor **23** and the detuned BDA protected acceptor/donor **24** by a similar batch-splitting technique (Scheme 8).

With all of the coupling units prepared, their assembly and transformation to the GPI anchor proceeded well (Scheme 9). The BDA protecting groups functioned as predicted by tuning the glycosidic bond formation and facilitating removal at the end of the sequence by brief treatment with TFA/water without causing any disruption of other sensitive functional features.[36]

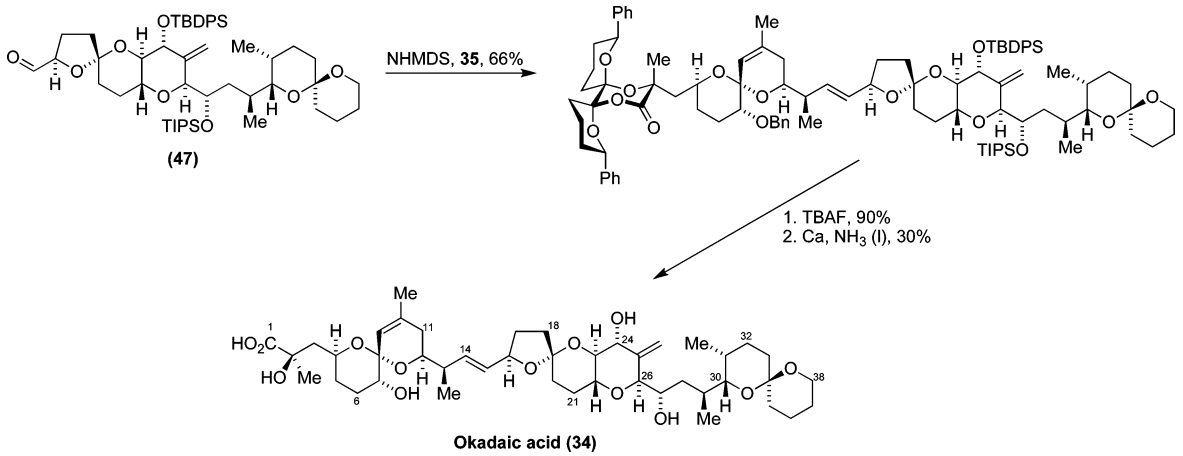
Another powerful demonstration of the 1,2-diacetal methodology is illustrated in our total synthesis of the protein phosphatase inhibitor, okadaic acid **34**.[37] It was envisaged that the synthesis of this complex natural product could arise by the coupling of three fragments, **35**−**37**. Two of these units, **35** and **36**, were designed to use 1,2-diacetals in their assembly (Scheme 10).

For fragment **35**, a new aspect of the dispiroketal chemistry comes into play. Here, the bisDHP *S*,*S*′-**10** was reacted with glycolic acid in the presence of $Ph_3P{\cdot}HBr$ to give the chiral glycolic acid derivative **38**, such that the dispiroketal unit is formed under anomeric/thermodynamic control. This arrangement facially and asymmetrically desymmetrizes the glycolate during subsequent alkylation reactions. In other words, compound **38** may be doubly asymmetrically alkylated through intermediate enolates to give exclusively only one product. Indeed, the chiral glycolate **38** served as a general substrate for asymmetric substituted glycolic acid synthesis.[38,39] Elaboration of alkylated product to the lactone **39** involved a series of straightforward steps (Scheme 11).

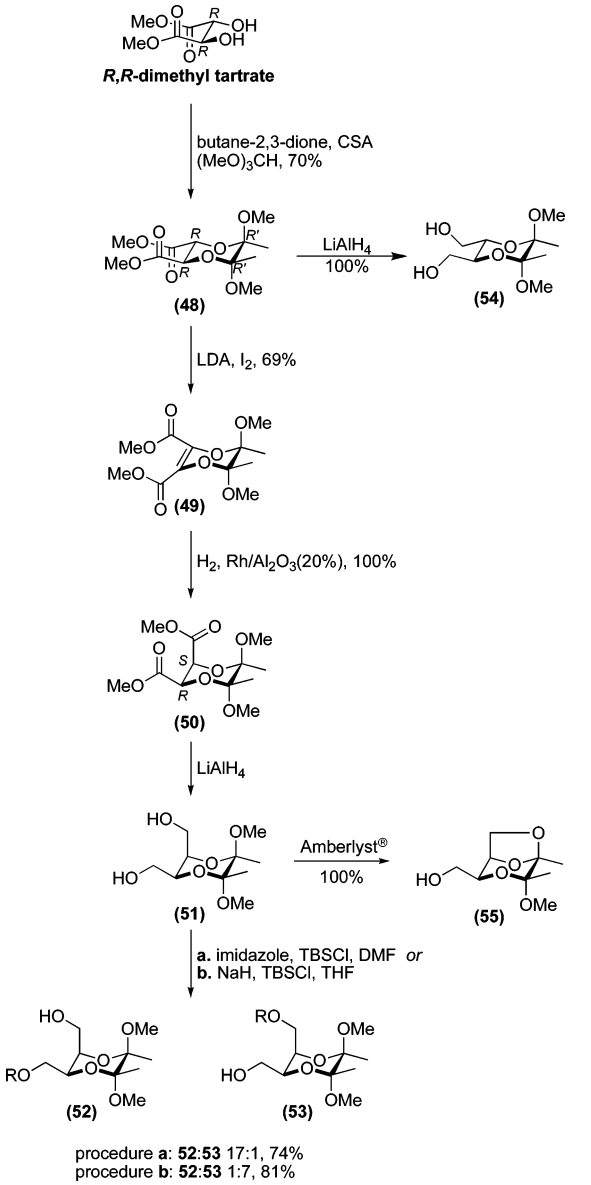
To convert lactone **39** into the first coupling partner **35**, further reactions were necessary. These additionally demonstrated the robust nature of the diphenyl substituted dispiroketal appendage. Moreover, the route employed a new spiroketalization process that deserves comment. The corresponding vinyl anion generated from the glycal **40** underwent C-acylation with lactone **39** to give compound **41**. This in turn underwent a designed acid-catalyzed spirocyclization under isomerizing conditions that ejected the C-10 methoxy group in compound **41** to give the corresponding desired unsaturated spiroketal. This was readily transformed to the sulfone **35**, making it suitable for further coupling via the Julia−Kocienski method (Scheme 12).

The second fragment **36** came together also using both BDA chemistry and a new spiroketal forming reaction. First, the *o*-methoxythiomannose derivative **42** reacted selectively with butane-2,3-dione under the usual conditions[34] to form a single BDA-protected product **43** after further selective reaction with benzyl bromide. The 3,4-diequatorial diol arrangement of mannose was selectively recognized over the other unprotected hydroxyl groups, thus eliminating the usual multistep protecting group sequence that would have been necessary to unveil this protecting group pattern. Compound **43** was readily homologated and converted to the aldehyde **44** ready for the next interesting "all-in-one" spirocyclization event. Here, the aldehyde underwent Horner−Wittig coupling with the diphenylphosphinoxide **45** giving an intermediate enol−ether that was

SCHEME 14. Synthesis of Okadaic Acid



SCHEME 15. Access to Enantiopure Diol Building Blocks

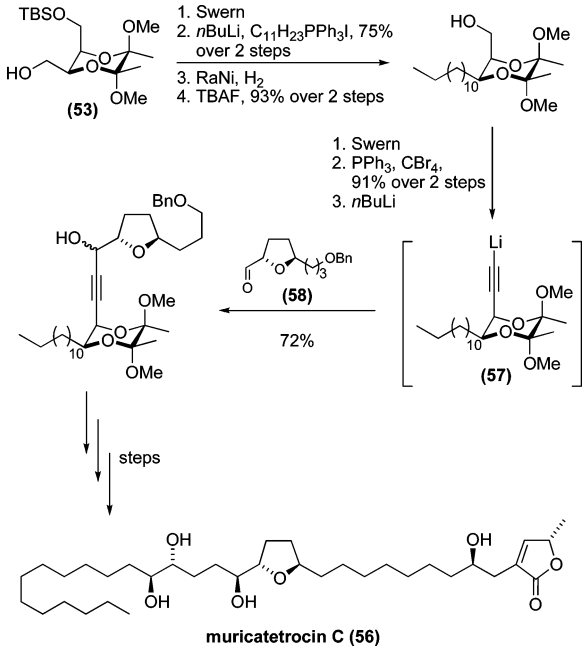


not isolated since we anticipated in the next step that BDA removal under acid-catalyzed conditions would simultaneously effect spiroketalization to give **46**.[40,41] Following this pleasing outcome, **46** was then readily converted to the sulfone **36**, the second coupling partner (Scheme 13).

Coupling of **36** with the final fragment **37** and further functional group manipulation gave aldehyde **47**, which was the last component necessary for ultimate fragment fusion with **35** and onto the natural product Okadaic acid **34**. The last step of this synthesis involved simultaneous removal of the diphenyl dispiroketal together with the hindered benzyl group at C-7, using calcium in ammonia at −33 °C (Scheme 14).

The next syntheses to be discussed required the development of alternative 1,2-diacetal building blocks that could be used in a modular fashion to introduce 1,2-diol units of any absolute configuration. This work employed the BDA derivatives of various tartrates which has been an area of interest for other groups who have also made significant contributions to the area.[42−46] In our own work,[47−50] we showed that D- or L-tartaric esters or acids directly react with butane-2,3-dione, CSA, and

SCHEME 16. Synthesis of Muricatetrocin C

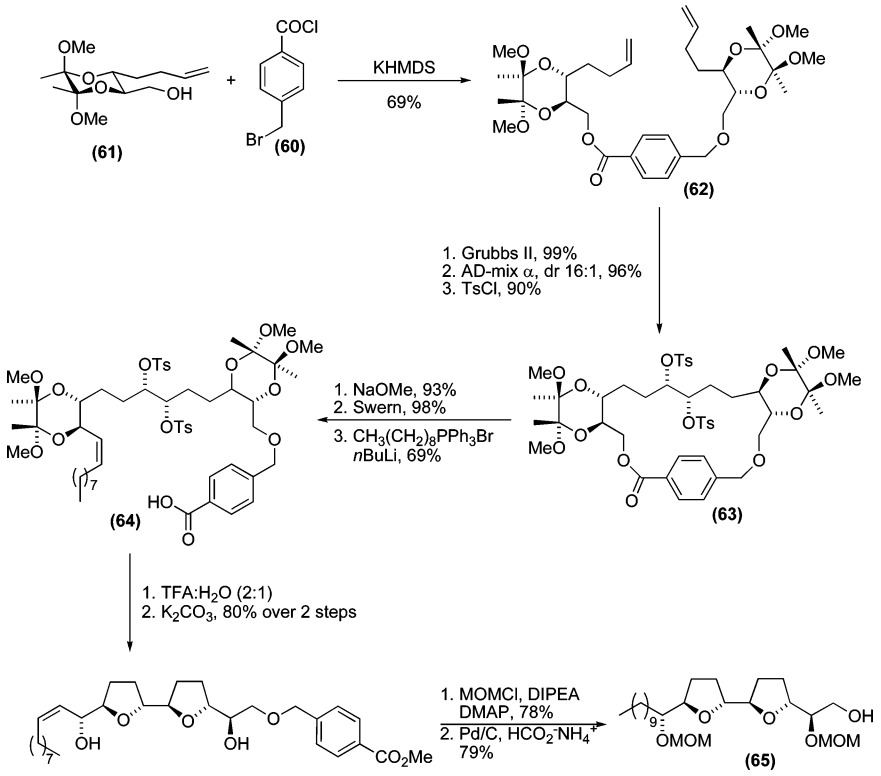


$HC(OMe)_3$ in methanol to give highly crystalline BDA derivatives. These should be contrasted with the more commonly used acetonide derivatives which are viscous oils, are difficult to weigh, and have long-term storage problems. For (*R*,*R*)-dimethyl tartrate, the BDA derivative **48** is formed in greater than 70% yield without chromatography. Importantly, the two initial ester-substituted stereogenic centers embed further chirality into the acetals. This concept can be used as a chiral memory storage effect, whereby after oxidation of **48** to **49**, followed by stereoselective return of hydrogen in a *cis*-fashion, an equally crystalline *meso*-tartrate derivative **50** can be obtained. Pure *meso*-tartrate derivatives are of course difficult to obtain by normal means, so this method has obvious applications in synthesis. For example, it should also be noticed that in **50** the two ester groups are now in two different spatial environments, i.e., axial and equatorial, and therefore should be chemically differentiable. Indeed, this turns out to be the case.[48] Also following reduction with $LiAlH_4$ the spatially differentiated diol **51** was obtained quantitatively. This can be selectively protected by *tert*-butyldimethylsilyl chloride and imidazole on the least hindered equatorial alcohol to give **52** in preference to **53** as an easily separated 17:1 mixture. If a metal hydride was used to effect proton removal prior to reaction with *tert*-butyldimethylsilyl chloride, then the ratio is reversed 7:1 in favor of **53** over **52** (Scheme 15).[49]

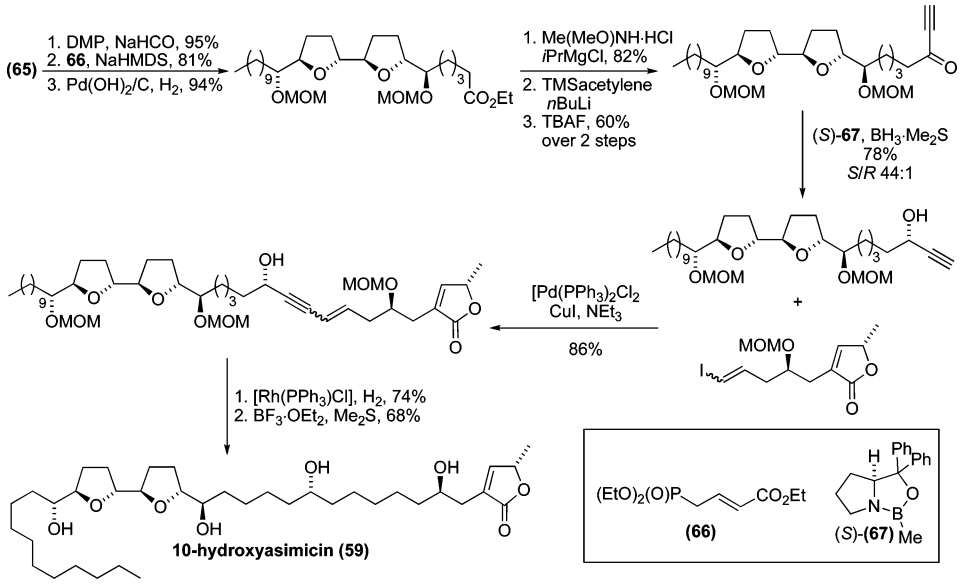
This is presumably due to additional metal chelation to other oxygen atoms of **53**, which are not readily accessible in the precursors to **52**. Reduction of **48** also leads to the diol **54**, which can be reacted to form useful monosubstituted derivatives. Alternatively, internal cyclization of **51** gave a triply protected compound **55**. In summary, from a simple tartrate precursor, a wide range of modular chiral building blocks becomes available for natural product synthesis programs.

The annonaceous acetogenins are an important class of natural products that have attracted worldwide attention from the synthesis community. Two members of this family that show interesting anti-tumor properties have been synthesized using modular BDA building blocks. The first of these, muricatetrocin

SCHEME 17. BDA-Protected Modular Fragments in the Synthesis of 10-Hydroxyasimicin



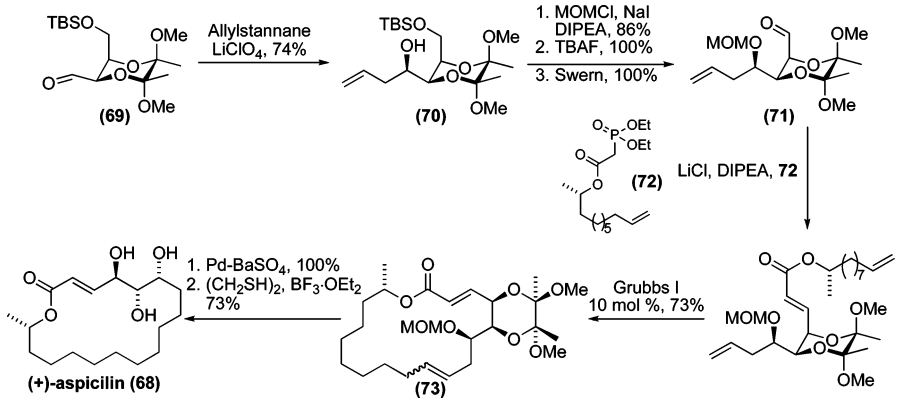
SCHEME 18. Synthesis of 10-Hydroxyasimicin



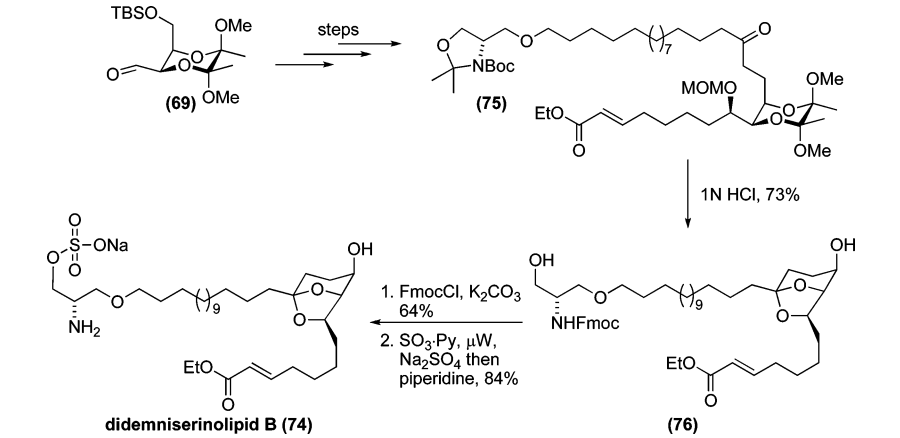
C **56**,[51] was constructed in a very efficient fashion from the axially monosilylated compound **53**.[52] Both side chains of **53** were differentiated and readily transformed to a lithium acetylide intermediate **57** that was then coupled to the furan aldehyde **58**. Further steps progressed the product to muricatetrocin C **56** (Scheme 16). Here, the modular BDA fragment **53** was used to install just two stereogenic centers in the 1,2-trans diol entity of the natural product.[53]

In the next synthesis, a different route was investigated that would allow for the encoding of many more stereogenic centers into the system potentially providing access to other members of the acetogenin family. The key to success in the synthesis of 10-hydroxyasimicin **59** was the use of *p*-bromomethylbenzoyl chloride **60** as a workbench to bring together BDA-protected modular diol fragments that were suitably decorated to undergo an intramolecular metathesis process.[54] Consequently, when **60** was reacted with an excess of the homologated BDA fragment **61** the product **62** was obtained. Clearly, had different stereochemistries been necessary for the other members of the annonaceous acetogenins family, then they could have been accessed by separately reacting the acyl chloride of **60** with one BDA building block and then separately reacting the bromomethyl substituent with a different BDA unit. Also, the length of the alkene chain determines whether furan rings or

SCHEME 19. Access to Enantiopure 1,2,3-Triols from BDA in the Synthesis of (+)-Aspicillin



SCHEME 20. Synthesis of (+)-Didemniserinolipid B



pyran rings are the ultimate target, since both occur commonly in the natural products. Following metathesis of **62** with the para-templating agent **60**, only a *trans*-alkene was produced, which underwent stereoselective glycolation and tosylation to give **63**. Had the ortho species been used, then the metathesis would have favored a cis product. In this way, all stereochemistries at these positions became potentially available. In this particular synthesis, however, **63** was progressed by orthogonal deprotection and introduction of the saturated side chain to give **64**. This is also the point at which other members containing different numbers of carbon atoms in the side chain could be accessed. Following hydrolysis of the BDA units in **64** and treatment with potassium carbonate, the required bisfuran unit of the natural product was revealed (Scheme 17).

Further transformations to the alcohol **65** gave a fragment, which was then taken through further steps to the natural product **59** (Scheme 18).

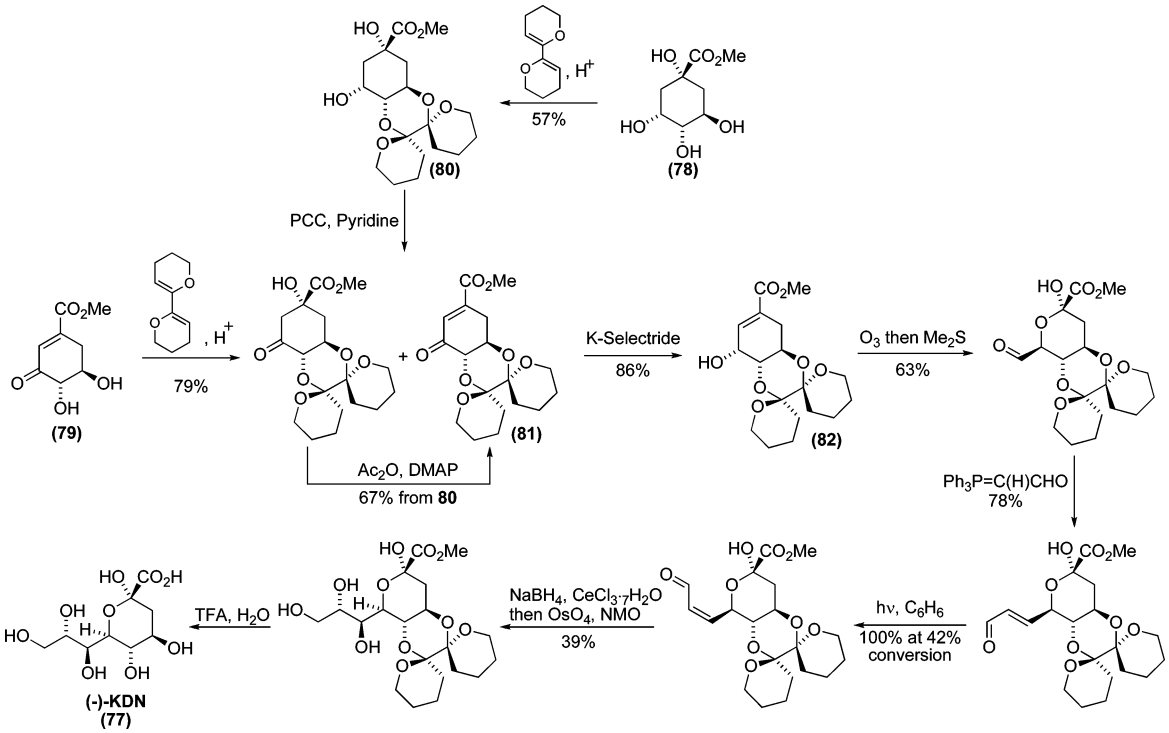
To this point, the 1,2-diacetal structures had not been used to stereoselectively introduce further oxygen substituents by side-chain manipulation reactions, yet this should be possible, given the special chiral features and the constraints imparted by the six-ring and its acetal groups. Two natural products that contain 1,2,3-triols, therefore, became attractive synthesis targets.

The first of these was the macrolide (+)-aspilicin **68**.[55] The route began with the BDA aldehyde **69**, itself derived in two steps from the *meso*-tartrate protected tetraol **51**. Facially selective addition of allyltributylstannane in the presence of 5 M lithium perchlorate in diethyl ether gave the desired addition product **70** with better than 9:1 stereoselectivity for the newly formed side-chain asymmetric center.[56] The stereoselectivity at this center can be reversed in a ratio 1:9 by running the reaction in the presence of $ZnCl_2$. Next, following MOM protection, silyl group removal, and oxidation under Swern conditions, the aldehyde **71** was realized. Homologation with an appropriate phosphonate ester **72** under Masamune−Roush conditions followed by metathesis afforded the macrolide **73**. Once the double bond had been removed, global deprotection to (+)-aspilicin **68** was effected in good yield by treatment with ethane dithiol and $BF_3{\cdot}OEt_2$ (Scheme 19).[57]

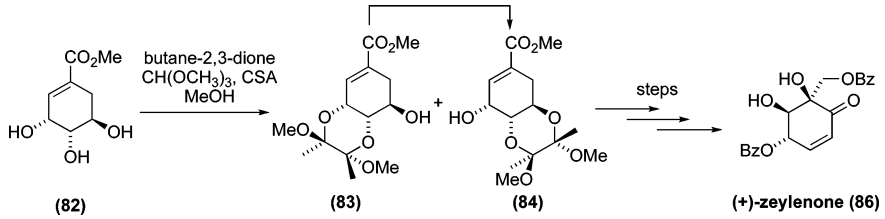
The second natural product containing a masked 1,2,3-triol feature was (+)-didemniserinolipid B **74**, isolated from the tunicate *Didemnum* sp.[58] This synthesis was important in that it defined the absolute configuration as (+)-**74** and revised the first isolated structure as a **31**-sulfated material.[59] The initial steps to this molecule now began to follow a common pattern, namely using the BDA aldehyde **69**, used in the previous synthesis, to undergo sequential side chain modification to the derivative **75**. This compound contained all of the requisite carbon atoms necessary to lead to the natural product.

The interesting step in this synthesis occurred during the planned removal of the BDA group from **75**, using HCl in ethanol. These conditions additionally removed the Boc protection and the acetonide from the terminal amino alcohol and also removed the MOM protecting group from the secondary alcohol to give an intermediate keto tetraol that was not isolated but spontaneously folded on itself to generate the acetal **76** in excellent 73% overall yield. This compound was then clearly set up for completion of the synthesis using temporary Fmoc-protection of the amine; formation of the sulfate under micro-

SCHEME 21. Synthesis of (-)-KDN



SCHEME 22. Synthesis of (+)-Zeylenone



SCHEME 23. Synthesis of (*S,S*)-BDA Glycolate

wave irradiation and final piperidine treatment to remove the protecting group gave didemniserinolipid B **74** (Scheme 20).

The unnatural (−)-form of the sialic acid derivative, (−)-KDN **77**, has been prepared for biological studies by the Banwell group,[60] starting from either (−)-quinic acid methyl ester **78** or, more efficiently, from (−)-3-dehydroshikimic acid methyl ester **79**, using dispiroketal protection. Consequently, using **78** with bis-dihydropyran, a 78% yield of the dispiroketal product **80** was obtained, once again demonstrating a clear preference for selective 1,2-diequatorial diol protection in the presence of other alcohol functionality. Compound **80** was then oxidized and eliminated to give the shikimate derivative **81**. Alternatively, **81** was accessed directly from **79** as the precursor in 79% yield using the bis-dihydropyran. Stereoselective reduction of **81** to **82** gave material that was readily processed to (−)-KDN **77** (Scheme 21).

Interestingly among these steps was the stereoselective photoisomerisation of an intermediate enal and the use of TFA/H_2O to remove the dispiroketal group in the last step.

During work by Liu et al. which aimed to determine the absolute stereochemistry of the antitumor material product zeylenone **86**, (−)-shikimic acid methyl ester **82** was chosen as the starting material.[61] In this case, the methyl ester was reacted using typical butane-2,3-diacetal-forming conditions that we developed, but this, surprisingly, led to two BDA products, **83** and **84**. Although the required isomer **84** was formed in 87% yield, the minor isomer **83** which formed in 10% yield was separated and subsequently re-exposed to butan-2,3-dione, methyl orthoformate, and camphor sulfonic acid for a further 18 h to give **84** as the most thermodynamically stable BDA product **84**.

A further 10 steps connected **84** to the (+)-isomer of zeylenone **86** (Scheme 22). By comparison of CD spectra, they

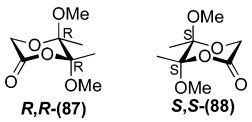


FIGURE 3. New generation BDA building blocks as chiral auxiliaries.

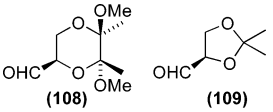
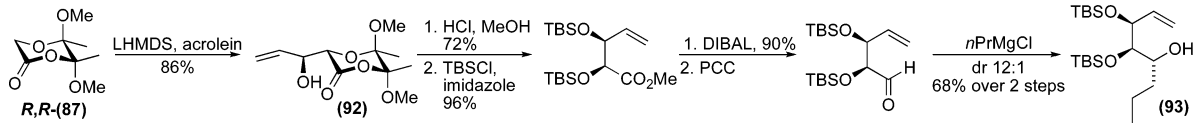
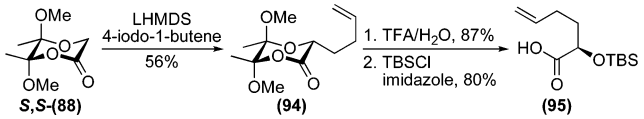


FIGURE 4. BDA-protected equivalent of glyceraldehyde acetonide.

SCHEME 24. Highly Stereoselective Aldol Reaction of the (*R*,*R*)-BDA Glycolate



SCHEME 25. Higly Stereoselective Alkylation of the (*S*,*S*)-BDA Glycolate



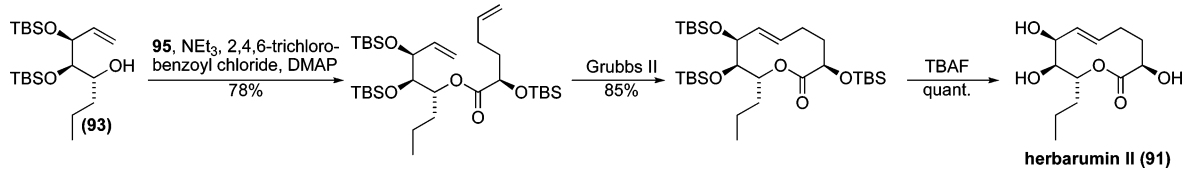
were subsequently able to assign the absolute stereochemistry of the natural product as the antipode of the synthesized material.

Quinic acid also serves as a useful precursor for the synthesis of substituted cyclohexanone derivatives using 1,2-diacetal protection methods and has been used in the synthesis of epibatidines.[62]

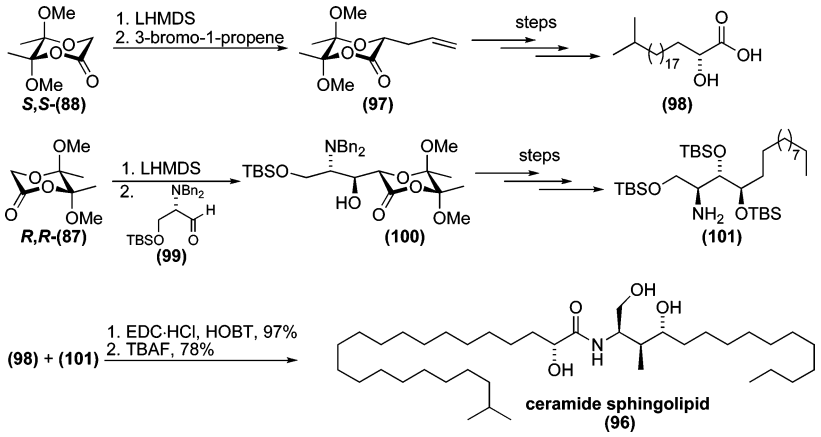
Another development of the butane diacetal building blocks was now necessary to expand the repertoire of reaction opportunities still further. An obvious area was the application of glycolate[63−65] and glycinate[66] derivatives, as auxiliaries for asymmetric synthesis. Although it is easy to prepare BDA derivatives of glycolic acids, thioglycolic acids, and lactamides,[67] a route to chiral versions of the parent glycolate systems *R*,*R*′-**87** or *S*,*S*-**88**, would be particularly useful (Figure 3).

These were made on scale via BDA protection of commercially available 3-halopropane-1,2-diols. In *S*,*S*-**88**, for example, (*S*)-3-bromopropane-1,2-diol reacted with butane-2,3-dione under normal conditions to give **89** as a single product in 85% yield. The bromomethyl side chain adopts an equatorial disposition, owing to the thermodynamic conditions, while the methoxyl groups adopt their usual axial configuration due to anomeric effects. This process then embeds chirality into the two acetal centers with *S*,*S*-configuration to install a chiral

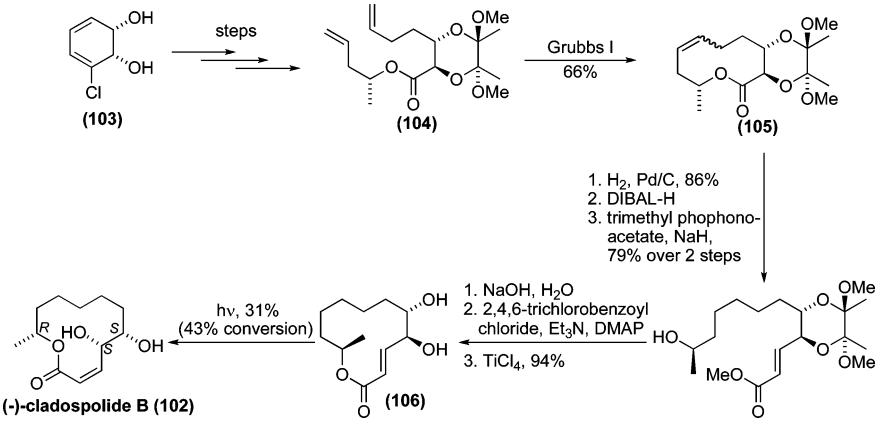
SCHEME 26. Synthesis of Herbarumin II



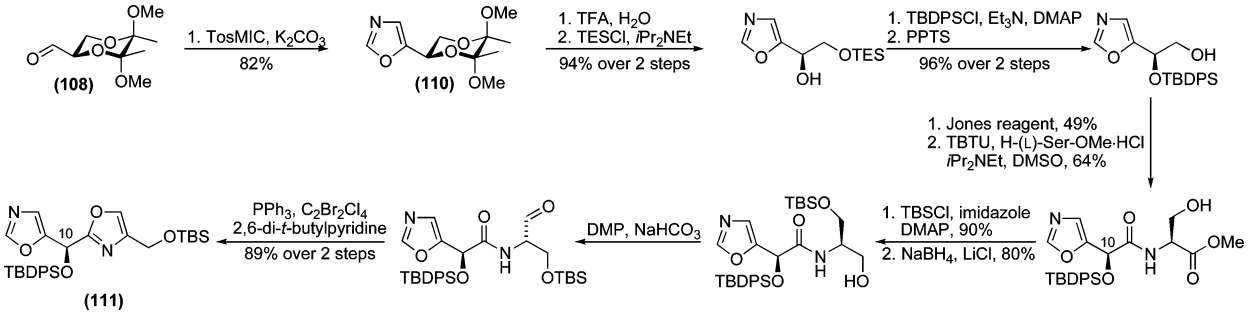
SCHEME 27. Synthesis of the Ceramide Sphingolipid



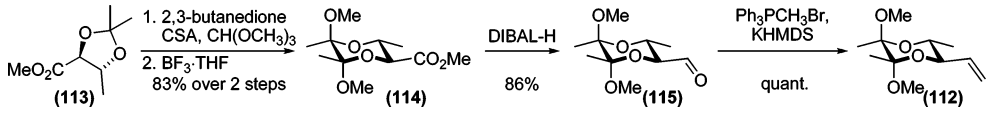
SCHEME 28. Synthesis of (−)-Cladospolide B



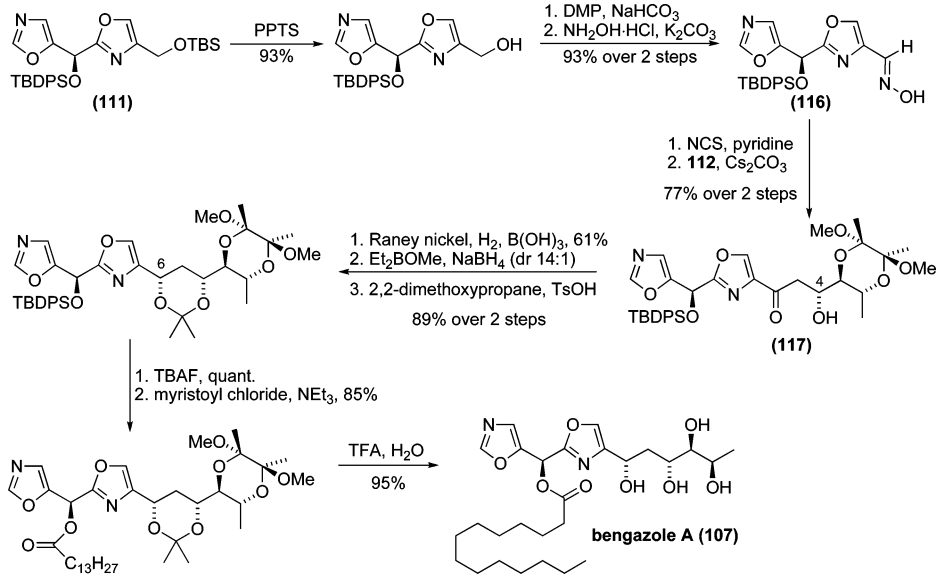
SCHEME 29. Synthesis of Fragment 111



SCHEME 30. Synthesis of Fragment 112



SCHEME 31. Synthesis of Bengazole A



memory into the molecule. Next, elimination gave the *exo*-methylene derivative **90** which was immediately ozonolyzed to the required crystalline lactone *S*,*S*-**88** in 59% overall yield (Scheme 23).

Other routes to these key chiral materials from cheaper starting materials, mannitol or ascorbic acid, are also available.[68] As anticipated, *R*,*R*-**87** and *S*,*S*-**88** undergo a wide range of asymmetric alkylation,[67] acylation,[69] aldol,[69] and Michael[70] addition reactions that are beyond the scope of this Perspective. However, with these auxiliaries in hand, we can now consider their application in natural product synthesis programs.

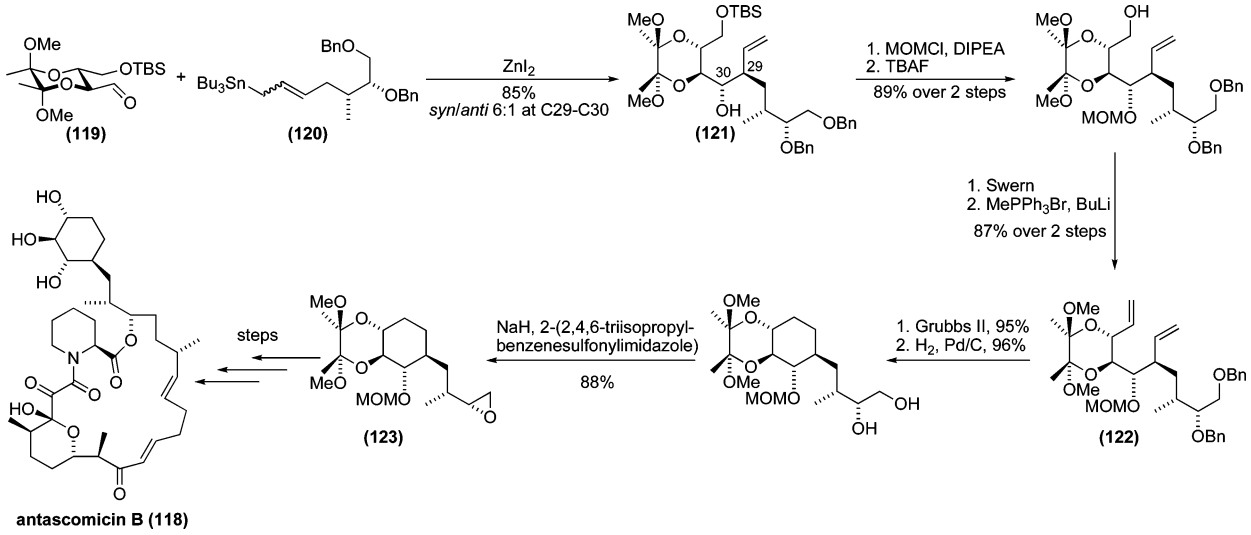
The herbarumins[71] are ideal targets in that they are 1,2-diols, as in the case of herbarumin II **91** but also contain additional α-hydroxy ester functionality that should be available from the new building blocks. These potential herbicidal agents have attracted considerable synthetic interest. A concise synthesis has been devised[72] which uses both the *R*,*R*-**87** and the *S*,*S*-**88** auxiliaries to install three of the four stereocentres. In the first part, the *R*,*R*′-**87** derivative was subjected to a highly stereoselective aldol reaction with acrolein to afford the coupled product **92**, whereby the 1,2-diol stereochemistry was created. This was then elaborated to give the protected triol unit **93** in a stereoselective manner (Scheme 24).

Next, the *S*,*S*-**88** enantiomeric building block was alkylated stereoselectively via an intermediate enolate with 4-iodo-1-butene to produce **94** and on to the second coupling fragment **95** (Scheme 25).

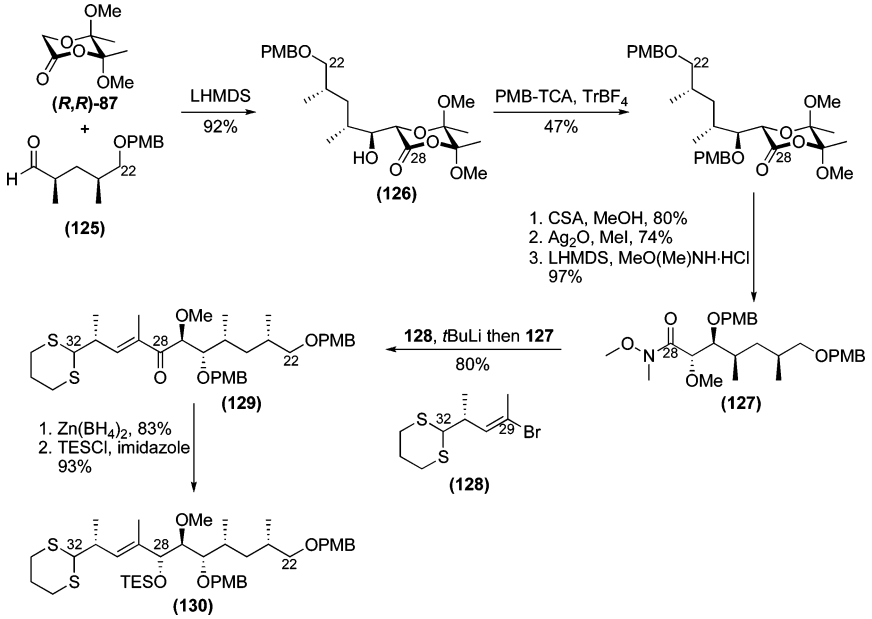
Finally, union of the coupling partners followed by ring-closing Grubbs second-generation metathesis and global deprotection afforded the natural product **91** (Scheme 26).[73]

In a similar fashion, both the *R*,*R*-**87** and the *S*,*S*-**87** glycolate lactones performed their duties extremely well during the synthesis of a ceramide sphingolipid **96**, which has been shown to be a pheromone of the hair crab *Erimacrus isenbeckii*.[74] Without detailing all the steps of the synthesis, the *R*,*R*′-**87** isomer was alkylated via its corresponding enolate to **97** and onto the hydroxy acid **98** in a series of straightforward steps. The *S*,*S*-**88** building block was used in a highly stereoselective chirality matched aldol coupling with the aldehyde **99** to generate compound **100**, which contains the remaining three stereogenic centers. After further homologation, the free amine **101** was obtained and could be acylated in high yield with the

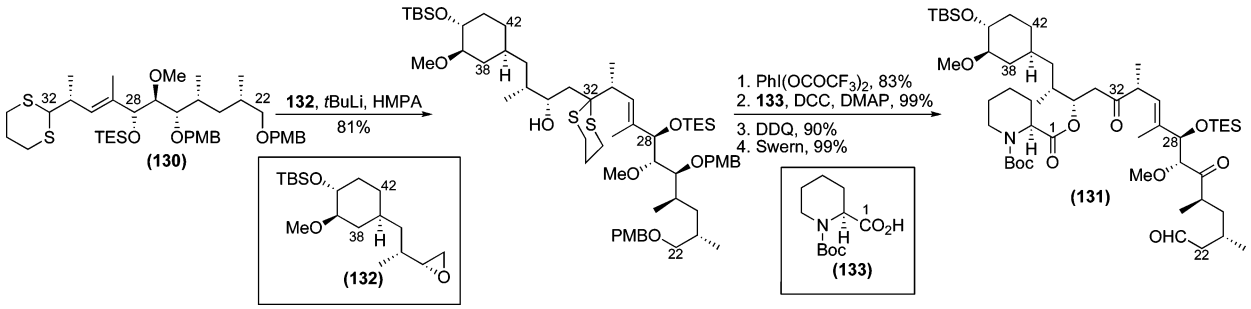
SCHEME 32. Synthesis of Antascomicin B



SCHEME 33. 1,2-Diacetals in the Synthesis of Rapamycin



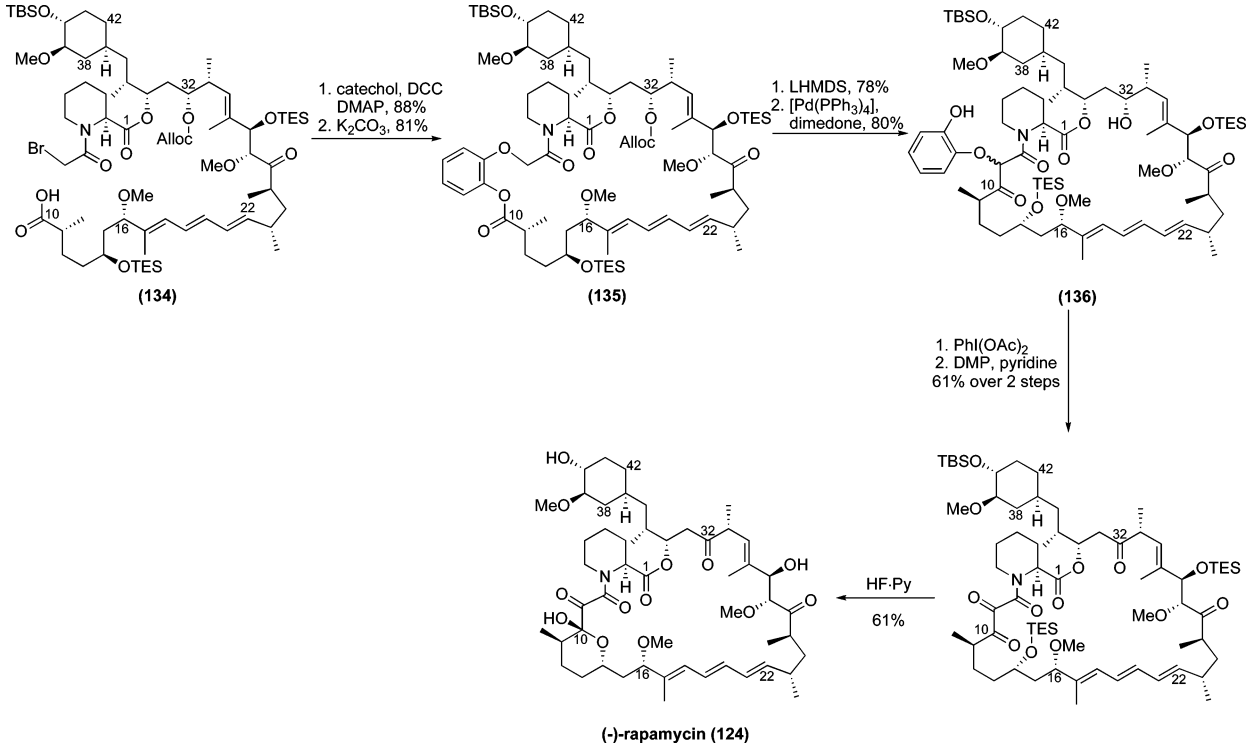
SCHEME 34. Total Synthesis of Rapamycin



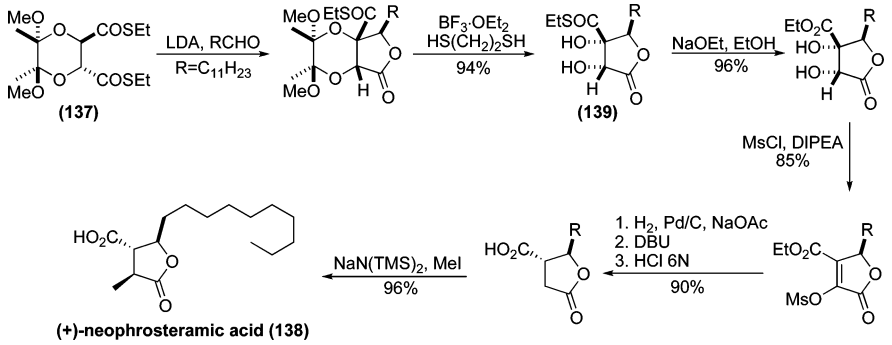
acid **98**. A final tetra-*N*-butyl ammonium fluoride deprotection then delivered the natural product **96** (Scheme 27).

In a recent synthesis by Banwell[75] of the undecenolide−cladospolide B **102**, the butane-2,3-diacetal fusion to a diol generated a useful templating architecture to bring together alkene units for ring-closing metathesis. A similar strategy was employed in our antascomycin synthesis, which will be discussed later in this paper. A very interesting aspect of the (−)-cladospolide work was their choice of the chiral chlorocyclohexadiene diol **103** as starting material available directly from chlorobenzene using microbial oxidation with *Pseudomonas putida*. In a series of eight steps, **103** was readily modified to

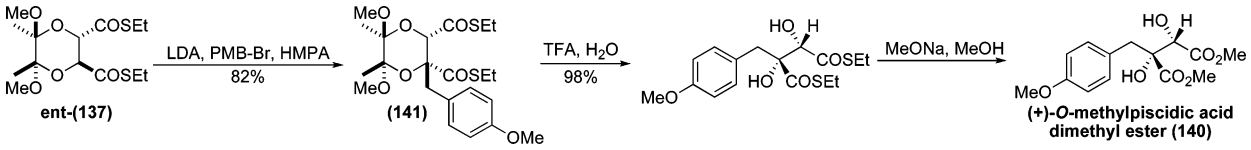
SCHEME 35. Synthesis of Rapamycin



SCHEME 36. Synthesis of (+)-Neophrosteramic Acid



SCHEME 37. Synthesis of (+)-*O*-Methylpiscidic Acid Dimethyl Ester



the BDA protected templating material **104**. Ring-closing metathesis then afforded the alkene **105**. Once the appropriate carbon−carbon bond had been formed, reduction, ring opening, homologation, and conversion to the *trans*-macrolide **106** were achieved in an efficient manner. Last, to access the natural product, a photo trans to cis isomerization gave (−)-cladospolide B **102**. Also of interest in this synthesis was the final removal of the BDA protection using titanium tetrachloride in CH_2Cl_2, which proceeded in an excellent 94% yield (Scheme 28).

The remaining syntheses in this Perspective describe additional fascinating and useful aspects of 1,2-diacetal chemistry. For example the synthesis of the potent antifungal agent bengazole A **107** was an ideal testing ground for the methods (Scheme 31).[76] This molecule contains a very sensitive stereogenic center between the two oxazole rings. Furthermore, the stereochemically dense tetraol side chain was ideally disposed for the application of the BDA methodology. In order to begin the synthesis we required a scalable and reliable route to the aldehyde **108**. This aldehyde should be recognized as the BDA protected equivalent of glyceraldehyde acetonide **109**, a commonly used chiral building block in organic synthesis (Figure 4).

However, the five-ring acetonide **109** is not without problems; it is prone to racemization, it forms hydrates, and in its pure state it undergoes very rapid polymerization. Compound **108**, on the other hand, is much more stable. It is a solid compound and can be stored for very long periods (4 years in the refrigerator) without serious decomposition. These compounds

can be prepared in both enantiomeric forms, on scale, from mannitol or ascorbic acid.[77,78] Along with their ester or alcohol derivatives, they form an attractive set of solid, stable, and easy to handle building blocks that, in our view, considerably outperform their acetonide equivalent counterparts.

For the bengazole A **107** synthesis, the aldehyde was reacted with TosMIC to give the 5-oxazole product **110**. Other methods used to set in place the stereogenic center in this compound had largely been unsuccessful. Compound **110** was then reacted through several steps in good yield to the bisoxazole **111** (Scheme 29). Careful checking was required at all stages to ensure that the integrity of the sensitive C-10 position had not undergone any racemization. Indeed, the modified Robinson−Gabriel reaction that directly leads to **111** is particularly noteworthy in that the use of triethylamine in this reaction was crucial for success to avoid epimerization at C-10. The next phase of the synthesis required the preparation of a BDA protected alkene **112** (Scheme 30).

This unit was intended to be the partner in a nitrile oxide cycloaddition process that would bring together the components of the bengazole synthesis. Although the ester **113** is commercially available, its conversion to the corresponding aldehyde and hence alkene was problematic due to polymerization of intermediates or volatility of the final material. However, transformation first to the BDA-protected material **114** and hence the aldehyde **115** gave a compound that was much easier to handle and that was a solid that could be stored at 0 °C for long periods of time without decomposition. In order to make way for the crucial cycloaddition process, the bisoxazole **111** was first taken on to the precursor oxime **116** (Scheme 31).

Cycloaddition with the alkene **112** took place in a facially selective manner to give the adduct **117**. Presumably this selectivity was in part due to the steric effects of the BDA appendage. Compound **117** was taken forward to the natural product bengazole A **107** with the crucial C-10 stereogenic center remaining intact (Scheme 31).

The natural product antascomycin B[79] **118** presents a further challenge to the BDA chemistry. Here, the tartrate-derived BDA protected aldehyde **119** features as the starting material for the trihydroxylated cyclohexane ring found in the natural product. First, the BDA assisted the facially selective addition of a substituted allylstannane **120** to give the product **121** with good control at the newly formed asymmetric centers (Scheme 32). Following a further sequence of steps, the metathesis precursor **122** was obtained readily. The BDA unit **122** now orientates the two alkene side chains into equatorial arrangements, which then favor the ring-closing metathesis by a BDA templating effect. Next, compound **122** was converted to the epoxide fragment **123**, which was ultimately one of the major fragments en route, via a number of steps, to yield antascomycin B **118** (Scheme 32).[80]

Although these additional steps are not reported here, the final macrocyclizing step is particularly interesting, and a variant of this process was then used in the next synthesis of the immunosuppressant rapamycin **124**.[81]

The molecule rapamycin represents a significant challenge for synthesis; indeed, this program took us 17 years to complete! Owing to space limitations, not all aspects of the synthesis can be presented; however, the use of 1,2-diacetals was an important contributor, especially for the stereoselective construction of the polyoxygenated fragment between C-28 and C-22. Earlier, we discussed the power of the chiral lactone building block *R*,*R*-**87** and now we show how it participated in a chirality-matched aldol coupling with the aldehyde **125** to give **126** as a single isomer, thereby installing a number of important stereogenic centers (Scheme 33).

This reaction compliments the previous stereoselective aldol reaction using the BDA templates. After further chemistry, the Weinreb amide **127** was coupled with the dianionic precursor **128** to give the C32−C22 fragment of rapamycin, compound **129**. Further transformations, which included a highly stereoselective reduction with zinc borohydride, established the stereochemistry at C28 to provide the dithiane **130**, which then engaged in fragment coupling, first with the epoxide **132** and subsequently with pipecolic acid **133**, to lead to a significant portion of the natural product **131** (Scheme 34).

Several steps transformed this fragment **131** to a precursor for cyclization **134**. It is at this point that we introduced a new approach to solve the difficult problem of forming carbon−carbon bonds during large-ring synthesis. A similar approach was used in the previous synthesis of antascomycin B where we chose to form more easily made carbon−oxygen bonds first, by stitching a molecule of catechol between the reactive centers in **134** to give the macrocyclic structure **136**. The effect of this process was to create a templated structure, which would then favor the required carbon−carbon bond formation through a Dieckmann-like cyclization to give **136**. This worked and was a very pleasing outcome since the product **136** now retained components that allowed for further oxidation and eventual completion of the synthesis of rapamycin **124** (Scheme 35).[81]

In a final topic, although our group has reported on alkylation reactions of BDA protected glycerates, we have not yet used these as building blocks in any published natural synthesis programs.[82] On the other hand, Maycock et al. have published attractive and short syntheses of two natural products, involving both stereoselective alkylation[83] and aldol[84] reactions, derived from a tartrate BDA substrate. In the first example, it was found that the dithioester **137** out-performed the normal methyl esters, especially during enolate trapping with aldehydes. This observation was neatly employed in the preparation of (+)-nephrosteranic acid **138** (Scheme 36).

In this work, the dithioester **137** was deprotonated with 22 equiv of LDA and quenched with $C_{11}H_{23}CHO$ at −78 °C to give the lactone **139** in good yield. This was then converted to (+) neophrosteramic acid **138** via a series of intermediate structures.

More recently, this same group reported a stereoselective alkylation protocol that led to (+)-*O*-methylpiscidic acid dimethyl ester **140**, a natural product isolated from *Narcissus poeticus* L.[84]

Here, the enantiomeric building block **137** was monoalkylated with 4-methoxybenzyl bromide to give **141** in a highly stereoselective fashion in 82% yield. This was then simply progressed to the natural product **140** using routine steps in an excellent overall yield (Scheme 37).

II. Conclusions

This Perspective hopefully displays both our fascination and enthusiasm for the use of 1,2-diacetals as special structural motifs for applications in natural product synthesis. These deceptively simple units feature in an impressive array of reactions: they can act as chemoselective or enantioselective protecting groups, they can give reactivity control through

torsional effects, as diol templating groups, or act as chiral auxiliaries during alkylation and aldol reactions, and they feature as desymmetrization agents in a variety of processes. We believe these readily available and often crystalline building blocks should be considered as first-choice components in complex polyol and natural product synthesis.

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