1,2-Diacetals: A New Opportunity for Organic Synthesis

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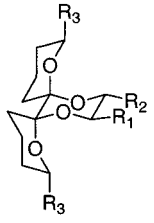
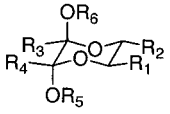
Contents

I. Introduction

While 1,2-diacetals have been known in the literature since 1938,[1] their specific application in organic synthesis has been recognized only recently. It seems remarkable to us that given the importance of acetals, carbonyl compound and diols that aspects of the chemistry described in this review have not been discovered previously; nevertheless, that is the case. Since we pioneered the use of dispiroketals **1**[2] in synthesis and have reviewed this topic in detail,[3] we have become interested in the use of other 1,2-diacetals **2** which provide alternative opportunities for selective diol protection and for reactivity control, hence this new review.



Dispiroketals **1**



1,2-Diacetals **2**

During the work with dispiroketals it was shown that due to the predictable operation of anomeric effects at the newly formed spiro centers and the favored placement of peripheral substituents in equatorial environments, these compounds were particularly useful for selective protection of diequatorial 1,2-diols.[3] Moreover, it was also possible to use chiral versions of these systems to desymmetrize enantiotopic diol pairs,[4−8] to thermodynamically resolve racemic 1,2-diols,[9−12] and to discriminate diequatorial diols in many carbohydrate derivatives.[13−15] In addition, these dispiroketals were found to be useful as chiral auxiliaries[16−19] and act as effective α−hydroxy acid protecting groups.[20−22] Their most impressive usage, however, was in carbohydrate chemistry where they were shown to be highly selective protecting agents for diols, often giving crystalline products.[23−25] The fusion of these rigid units to carbohydrate substrates also proved effective for tuning the reactivity during glycosidic coupling reactions allowing the assembly of complex oligosaccharides in a single reaction vessel.[26]

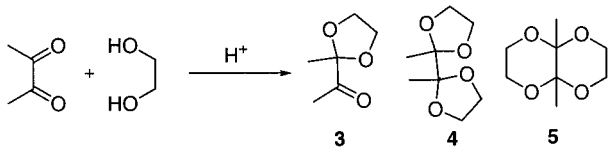
In this review we summarize the earlier literature concerning 1,2-diacetals and then describe the new applications and opportunities of these systems for organic synthesis.

II. The Early Years

The main interest in 1,2-diacetals prior to 1992, when we began our studies in the area, was from a structural and conformational point of view since these systems can undergo interesting isomerization and interconversion reactions owing to the complex sets of equilibria which are operating.

In an early report, Böeseken and Tellegen[1] characterized a number of 1,2-diacetals formed from the reaction of simple 1,2-diones with vicinal diols. In particular, they described the coupling of butane-2,3-dione with ethylene glycol in the presence of acid, which afforded a mixture of acetals **3**−**5** in low yield (Scheme 1).

Scheme 1



3 **4** **5**

Later, Orth et al.[27] also examined the reaction of glyoxal and butane-2,3-dione with 1-chloropropane-

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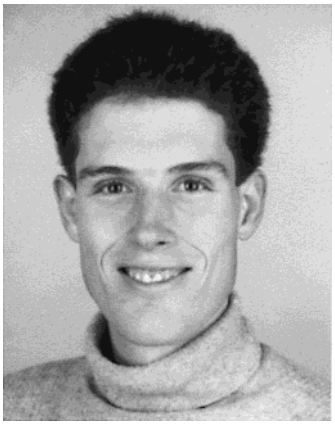
Steven V. Ley is currently the B.P. 1702 Professor of Organic Chemistry at the University of Cambridge. He studied for his Ph.D. degree at Loughborough University working with Harry Heaney and carried out postdoctoral work in the United States with Leo Paquette at the Ohio State University and then with Derek Barton at Imperial College. He remained at Imperial College until 1992, when he moved to Cambridge to take his present position. He has been the recipient of numerous awards including the Royal Society of Chemistry Organic Synthesis Award, the Natural Products Award, the Simonson, Pedler and Rhône Poulenc Lectureships, the Flintoff Medal, and the Adolf Windaus Medal. Recently he was awarded the prestigious Paul Janssen Prize for Creativity in Organic Synthesis and the Bakerian Lectureship of the Royal Society. He is engaged in research covering a diverse range of areas including the total synthesis of complex natural products, new synthetic methodology, organoiron chemistry, combinatorial chemistry with solid-supported reagents, and the assembly of large oligosaccharides.



Daniel K. Baeschlin was born and raised in Winterthur (Switzerland). In 1996 he graduated from the ETH Zürich (Switzerland) with his master's degree in Natural Sciences. For his Ph.D. degree he studied with Steven V. Ley at the University of Cambridge working on the application of butanediacetals to the total synthesis of a GPI anchor. He is currently carrying out postdoctoral studies in natural product synthesis with Samuel Danishefsky at the Sloan-Kettering Institute in New York.

2,3-diol, which gave 1,2-diacetal products that were then eliminated with base to give the corresponding enol ether derivatives for use in polymerization studies (Scheme 2).

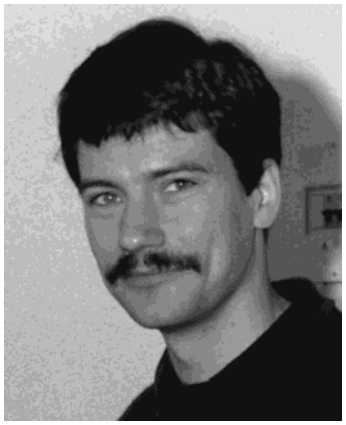
The next advance in the area came following the careful and detailed structure and conformational studies of a number of other 1,2-diacetals by Fuchs and co-workers.[28−33] Their method of synthesis of these systems similarly involved the acid-catalyzed condensation of 1,2-diones with vicinal diols (Scheme 3). From later dynamic conformational analysis studies,[34−36] using variable-temperature NMR techniques combined with crystallography of some of these derivatives, they showed that the tetraoxa-

Darren J. Dixon received his B.A. (Hons) degree in Chemistry from the University of Oxford in 1993. His studies for his D. Phil degree at the University of Oxford working with Stephen G. Davies were completed in 1996. This work focused on the total synthesis of β-amino acid-containing bioactive natural products. He is currently carrying out postdoctoral studies with Steven V. Ley at the University of Cambridge, and his work focuses on the development of new practical asymmetric methodologies and their application to efficient natural product synthesis.

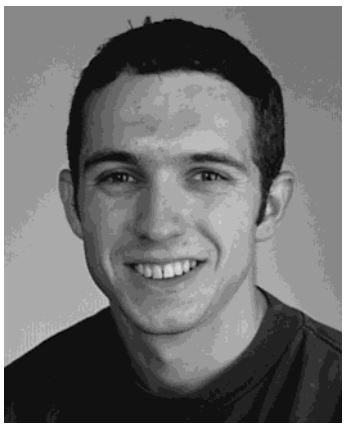
Alison C. Foster was an undergraduate at Jesus College of the University of Oxford and received her B.A. (Hons) degree in Chemistry in 1996. From 1996 to 1998 she worked as a Medicinal Chemist for Glaxo-Wellcome, Stevenage, U.K. She is currently working toward her Ph.D. degree with Steven V. Ley.

Stuart J. Ince received his B.A. (Hons) degree in Natural Sciences from the University of Cambridge in 1996. He has recently completed his Ph.D. studies on the application of butanediacetals to the reactivity tuning of glycosyl fluorides with Steven V. Ley. He is currently conducting postdoctoral studies with Dieter Enders at the Institute for Organic Chemisty of the RWTH in Aachen.

decalin structure **6** adopts a double-chair conformation and a cis ring junction.

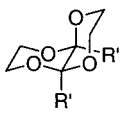


Henning Priepke received his diploma at the University of Marburg in 1989 and his Ph.D. degree at the University of Würzburg working in the field of asymmetric synthesis under the supervision of Professor Brückner. Following this he undertook postdoctoral studies in Cambridge with Steven V. Ley in carbohydrate chemistry. Currently, he is a Research Scientist in the area of thromboembolism and oncology at Boehringer Ingelheim in Biberach/Riss.



Dominic J. Reynolds received his B.A. (Hons) degree in Natural Sciences from the University of Cambridge in 1997 and is currently in the final year of his Ph.D. studies with Steven V. Ley working toward the total synthesis of Muricatetrocin C.

These systems have continued to fascinate spectroscopists,[37] who, using line-shape analysis, have demonstrated the equilibration of enantiomeric double-chair conformations and correlated these results with MM2 calculations to determine the minimum energy structures. For example, Jørgensen has shown,[38] by MM1 molecular orbital calculations, that the *cis*-arrangement is 12−15 kJ mol^{-1} more stable than the corresponding trans isomer. More recently, derivatives **7**−**9** have been prepared to study the stereo-



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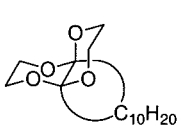

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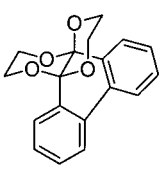

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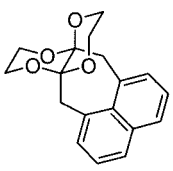

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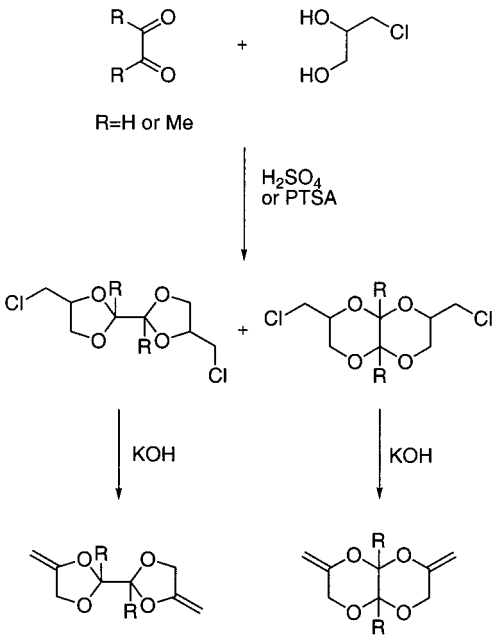
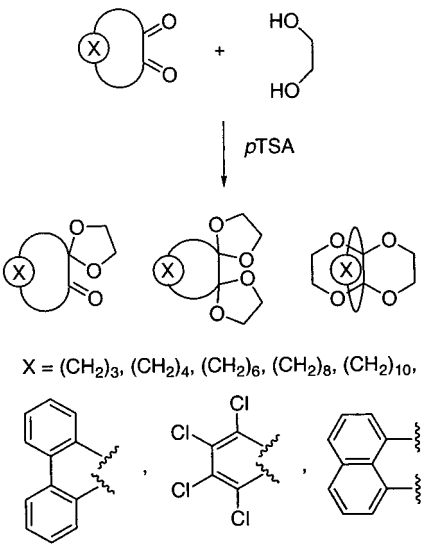
Scheme 2



Scheme 3



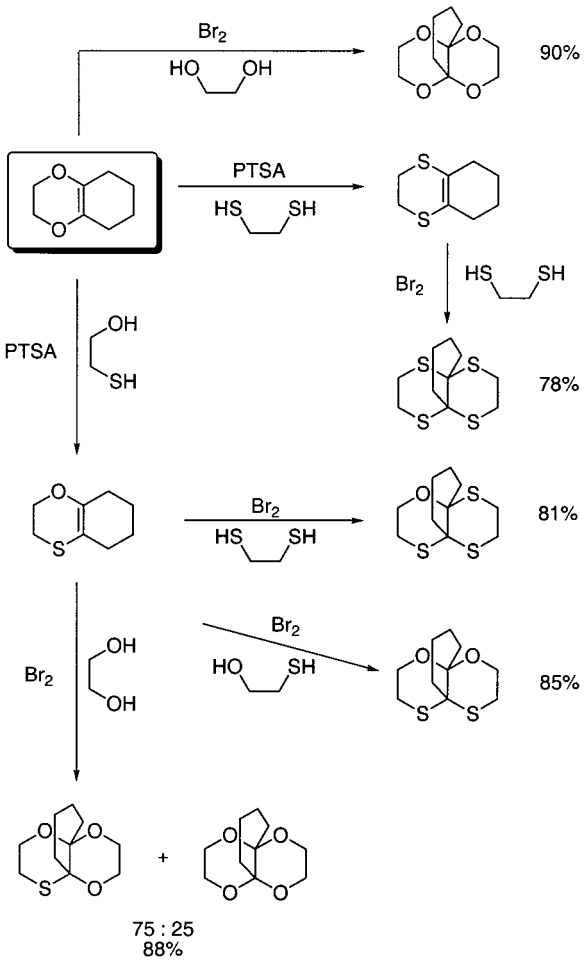
electronics of 9,10-annelated-1,4,5,8-tetraoxadecalins, thus providing some idea of the conformational and configurational preferences as a result of the operating anomeric effects.[39]

Thio derivatives have also been synthesized in order to compare their relative barriers toward conformational interconversion.[40] These compounds were obtained by reaction of 5,6-dihydro- 1,4-dioxins, 1,4-oxathiins, and 1,4-dithiins with bromine or acid in the presence of ethylene glycol, 2-mercaptoethanol, or 1,2-ethanedithiol (Scheme 4).[41]

Under different acetal-forming conditions,[42] namely, in the presence of chlorotrimethylsilane, bis-1,3-dioxolanes are formed as the only product upon reaction of butane-2,3-dione with ethylene glycol in excellent yield (Scheme 5).

In addition, Bryce-Smith et al. reported that the photoaddition reaction of diphenylacetylene and tetrachloro-1,2-benzoquinone in acetone gave the cor-

Scheme 4



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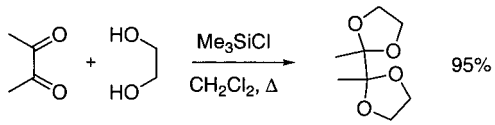

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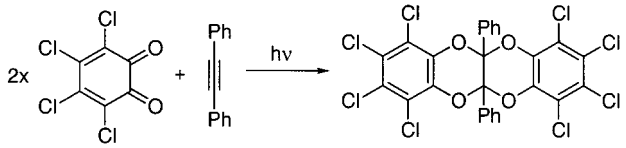
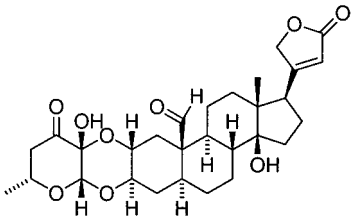


responding 2:1 diacetal adduct (Scheme 6), although no further use was made of the product of this reaction.[43]

Finally, in this introductory section it is worthy to note the existence of an interesting family of natural products which contain the 1,2-diacetal motif. Although first isolated by Hesse[44] in the 1930s from the milk of the *Calotropis procera*, full structure elucidation of these Cardenolide glycosides of the *Asclepiadaceae* was not possible until four decades later. [45] A representative member of these steroid glycosides, namely, uscharidin **10**, is shown below.

While all the above processes and structures are interesting, they provide very little evidence to suggest how they might be used more generally in organic synthesis programs.

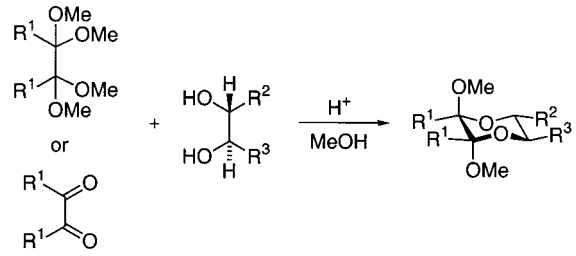


Uscharidin **10**

III. The Concept and Potential Application in Synthesis

Owing to the previous success of dispiroketals, which of course are also 1,2-diacetals, we decided to extend the concept to other derivatives which might find complementary applications in synthesis. We reasoned that vicinal diols should undergo acid-catalyzed acetal exchange with 1,2-diacetals or even react with 1,2-diones, in methanol, to give the corresponding 1,4-dioxane products with high stereoselective control owing to favorable anomeric effects and equatorial placement of functionality around the periphery of the 1,4-dioxane ring (Scheme 7).

Scheme 7

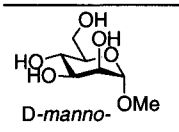
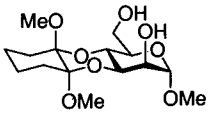
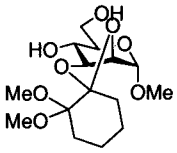
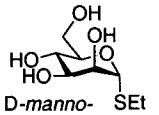
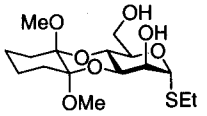
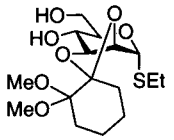
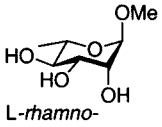
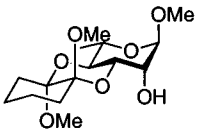
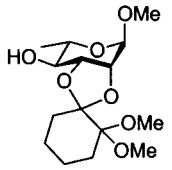
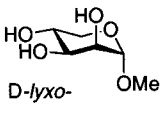
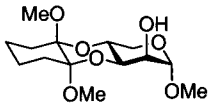
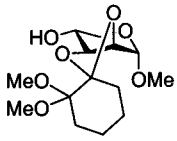
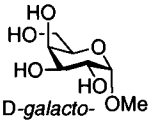
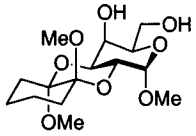
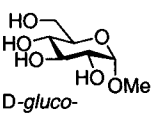
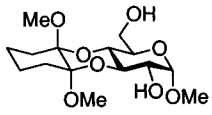
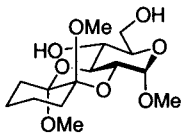


This new diol protection method should be selective for equatorial vicinal diols in cyclic polyols and might even be extended to include triol protection in acyclic systems. Similarly, based upon the knowledge from the dispiroketal work, one might anticipate that when these 1,2-diacetals are fused to carbohydrates, their reactivity in glycosidation reactions might be affected and that we may be able to take advantage of this property in the assembly of large oligosaccharides. Indeed, all of these ideas have worked out in practice.

IV. Selective Protection of 1,2-Diols

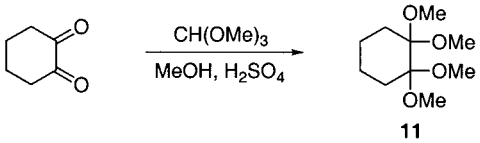
Initially cyclohexane-1,2-diacetals (CDA) were chosen for potential application in the carbohydrate area.[46] This was particularly important as the selective protection of 1,2-diequatorial diols in sugars, in the presence of other hydroxyl group combinations, had proved to be an especially difficult task.[47] Even though the dispiroketal chemistry developed earlier was one solution to the problem, it was not entirely satisfactory in all situations. We therefore sought alternative conditions, especially those which would solubilize more easily the highly polar carbohydrate substrates. For this reason, acetal formation in methanol was investigated since this solvent had been commonly used in carbohydrate chemistry. It was anticipated that 1,2-diones, such as cyclohexane-

Table 1

Sugar	CDA Protection: 3, 4-protected		CDA Protection: 2, 3-protected	
 D-*manno*-		48%		11%
 D-*manno*- SEt		53%		10%
 L-*rhamno*-		74%		8%
 D-*lyxo*-		45%		11%
 D-*galacto*-	—			46%
 D-*gluco*-		30%		50%

1,2-dione, would, under thermodynamic conditions, be converted to the corresponding 1,1,2,2-tetramethoxycyclohexane derivative **11**. Indeed, this was obtained in 75% yield from the inexpensive dione by reaction with trimethylorthoformate in methanol containing a few drops of sulfuric acid, after purification by silica gel chromatography (Scheme 8). Since this work, compound **11** has now become commercially available.[48]

Scheme 8



11

Next, the selective reaction of **11** with a variety of carbohydrate derivatives was investigated (Table 1).[46] In typical experiments the derivatives were reacted with **11** in boiling methanol containing some trimethylorthoformate and a catalytic amount of camphorsulfonic acid. In all cases the corresponding cyclohexane-1,2-diacetals were formed as the major product, which were often highly crystalline, together with some spiroketal as minor products. In these experiments similar results were obtained using cyclohexane-1,2-dione itself rather than the acetal exchange from compound **11**.[49]

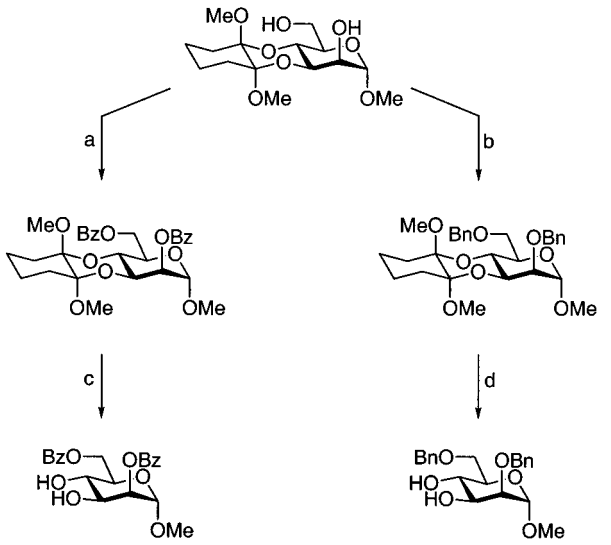
In this work it was also shown that the CDA protecting group could be removed readily by aqueous trifluoroacetic acid following benzylation or benzoylation (Scheme 9).

In later work, full details of the use of these cyclohexane-1,2-diacetals together with a more detailed discussion of the ^{1}H-nmr parameters of these unusual units were described.[50] The work also highlighted further chemistry indicating the tolerance of the CDA moiety toward iodination, reduction, oxidation, Wittig, silylation, and glycosidation reactions.

Other research groups soon became attracted to the opportunities presented by these initial 1,2-diacetals. For example, Berens reported that (*R*,*R*)-diethyl tartrate **12** reacted with the monoacetals **13** and **14**, obtained from butane-2,3-dione, to give the corresponding butane diacetals (BDA) **15** and **16** (Scheme 10).[51]

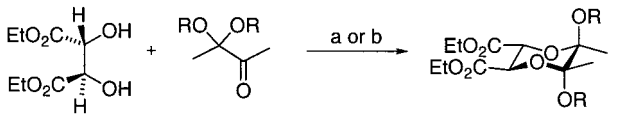
Likewise, Frost et al. prepared the butane-2,3-diacetal **17** in 53% yield from butane-2,3-dione using our previously reported protocol for cyclohexane-1,2-diacetals and then reacted this with a variety of polyols to give the corresponding butane diacetals. Although diacetal **17** is not yet commercially available and the yield of formation of pure material is

Scheme 9[a]



[a] Reagents and conditions: (a) BzCl, Py, 94%. (b) NaH, DMF, BnBr, *n*-Bu_4NI (cat.), 78%. (c) TFA/H_2O (19:1), 20 min, 96%. (d) TFA/H_2O (4:6), 16 h, 86%.

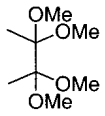
Scheme 10[a]



12 **13** R = Me, **14** R = Et **15** R = Me, **16** R = Et

[a] Reagents and conditions: (a) 1 equiv of **12** + 2.2 equiv of **13**, PTSA (cat.), 60 °C, 40 mmHg, 88%. (b) 1 equiv of **12** + 1.1 equiv of **14**, $BF_3{\cdot}OEt_2$ (cat.), EtOAc, 65%.

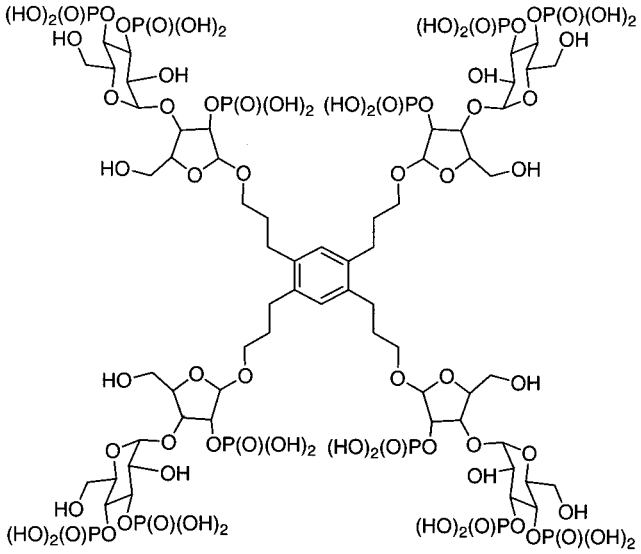
only moderate, it is noted that crude **17** can also be used for the protection reactions (Table 2). [52]



17

Our group continued to develop these reactions and, in particular, showed that it was not necessary to premake the initial tetramethoxydiacetal coupling component; rather one could proceed directly from the corresponding 1,2-diones.[49,53] Some of these protection reactions and their yields are shown in Tables 3−5. The work also described alternative reaction conditions whereby $BF_3{\cdot}Et_2O$ was used as the catalyst rather than camphorsulfonic acid. This variation of conditions, which was first reported by Berens et al.,[51] proved to be especially useful in cases where triol protection is also a possibility as in certain acyclic systems.

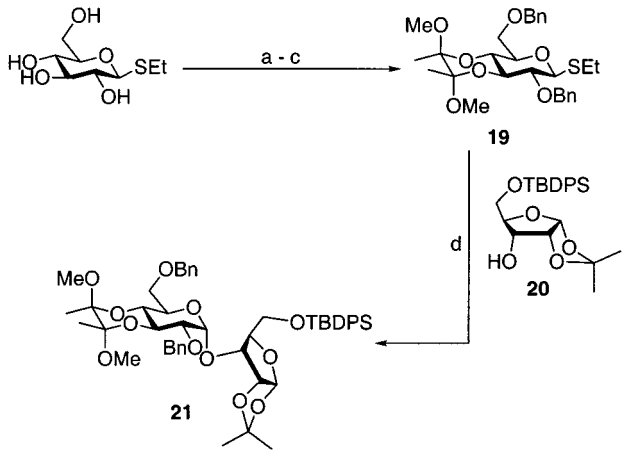
It is not surprising that the use of 1,2-diacetals, as protecting groups, has been most commonly exploited in carbohydrate chemistry since selectivity is such an important issue. For example, van Boom and co-workers,[54] during the preparation of a clustered disaccharide polyphosphate analogue **18**, synthesized the BDA 3,4-protected ethyl-1-thio-D-glucopyranoside, which after separation from some 2,3-isomer was dibenzylated to give **19**. This then became the



18

glycosyl donor for coupling with the ribose acceptor molecule **20** in the presence of *N*-iodosuccinimide and catalytic triflic acid to give the required α-linked disaccharide **21** (Scheme 11). This was eventually transformed to the clustered analogue **18** in a series of seven further steps.

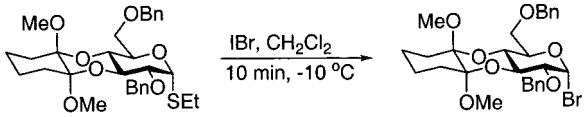
Scheme 11[a]



[a] Reagents and conditions: (a) butane-2,3-dione, CSA (cat.), $CH(OMe)_3$, MeOH, reflux, 78% (1:1 mixture of 3,4- and 2,3-isomers). (b) Chromatography. (c) BnBr, NaH, DMF, 98%. (d) **20**, NIS, TfOH (cat.), Et_2O, 83%.

Interconversion of thioglycosides to the corresponding bromide donors, using iodine monobromide, is also possible even in the presence of the torsionally deactivating CDA protecting group (Scheme 12).[55]

Scheme 12



The CDA protection method proved to be particularly attractive during synthesis of 2,2-difluoro oleandrose analogue **22**, which was required for coupling with an avermectin aglycone to afford a novel anti-

Table 2

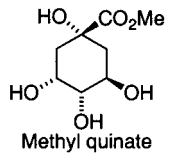
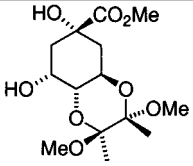
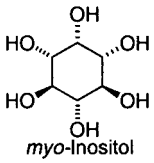
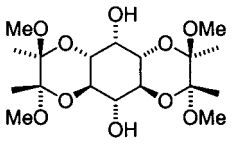
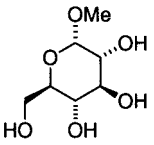
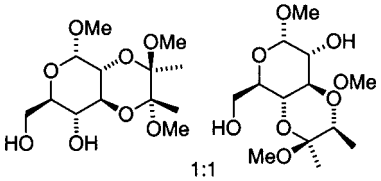
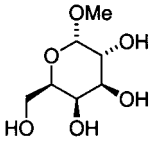
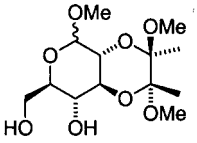
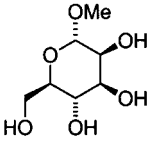
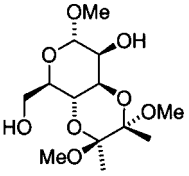
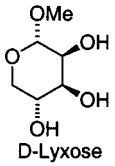
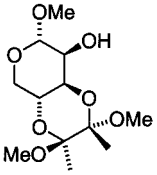
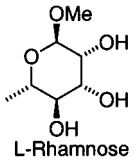
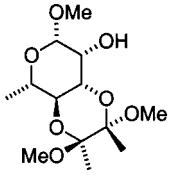
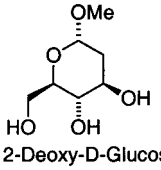
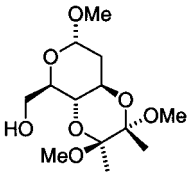
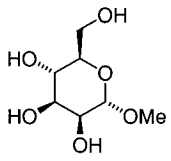
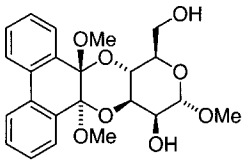
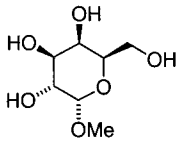
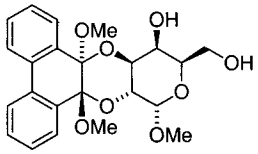
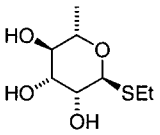
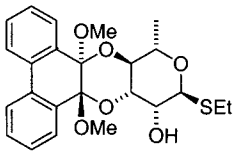
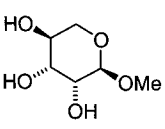
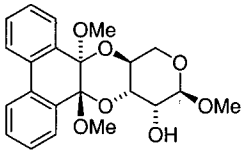
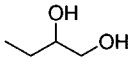
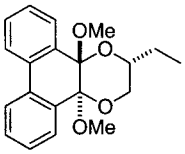
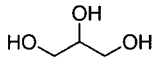
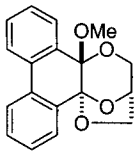
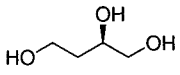
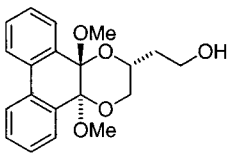
Starting Material	Product	Yield
 Methyl quinate		87%
 *myo*-Inositol		79%
 D-Glucose	 1:1	82%
 D-Galactose	 α/β = 10:1	54%
 D-Mannose		91%
 D-Lyxose		83%
 L-Rhamnose		81%
 2-Deoxy-D-Glucose		77%

Table 3

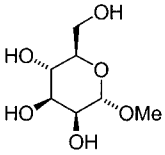
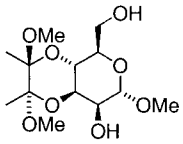
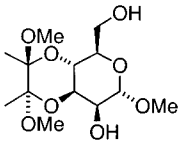
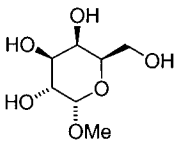
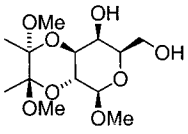
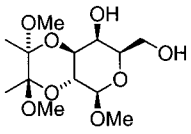
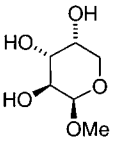
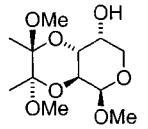
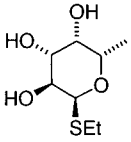
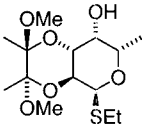
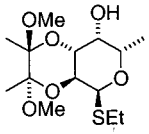
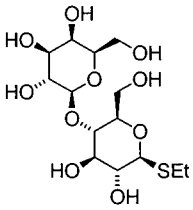
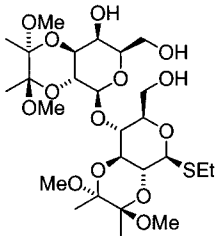
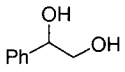
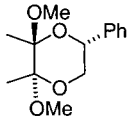
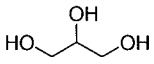
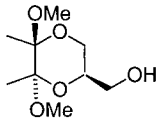
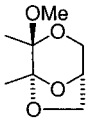
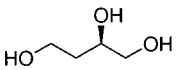
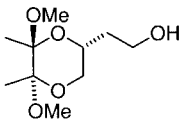
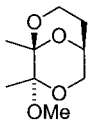
Substrate	1,2 -Diacetal product	Yield
 D-Mannose		67%
 D-Galactose		66%
 L-Rhamnose		68%
 D-Lyxose		48%
		57%
		69%
		65%

parasitic agent.[56] This synthesis similarly exploits the selective diequatorial diol protection of rhamnose described previously. Transformation to the difluoro derivative **22** follows a sequence of reactions which further demonstrates the robust qualities of the CDA unit. Nevertheless, easier removal of this group under standard acid hydrolysis conditions was possible at the appropriate stage in the synthesis (Scheme 13).

The preference for selective protection of diequatorial diol pairs with diacetal protecting groups has been demonstrated further in the protection of inositol derivatives. Potter and Riley reported the reaction of D,L-1,4-di-*O*-benzyl-myo-inositol **23** with 2,3-butanedione, trimethylorthoformate, and CSA in refluxing methanol. Under these conditions, diol **24** was obtained in good yield. After resolution, this product was transformed into bicyclic analogues of inositol 1,4,5-triphosphate **25** and **26** (Scheme 14).[57,58] Furthermore, **24** can be converted into poly(ethylene glycol)-linked dimers of D-myo-inositol 1,4,5-trisphosphate, which were synthesized as probes for multisubunit binding proteins.[59]

In certain examples where there is more than one diequatorial diol pair present in the molecule, as in the D-xylose derivative **27**, reaction with the butane-2,3-diacetal **17** affords a 1:1 mixture of BDA isomers.

Table 4

Substrate	Acid catalyst $BF_3.OEt_2$		CSA	
 manno-		99%		95%
 galacto-		85%		80%
 arabino-		42%	-	
 fuco-		14%		80%
 lacto-	-			31%
	-			94%
		62%		98%
		64%		65%

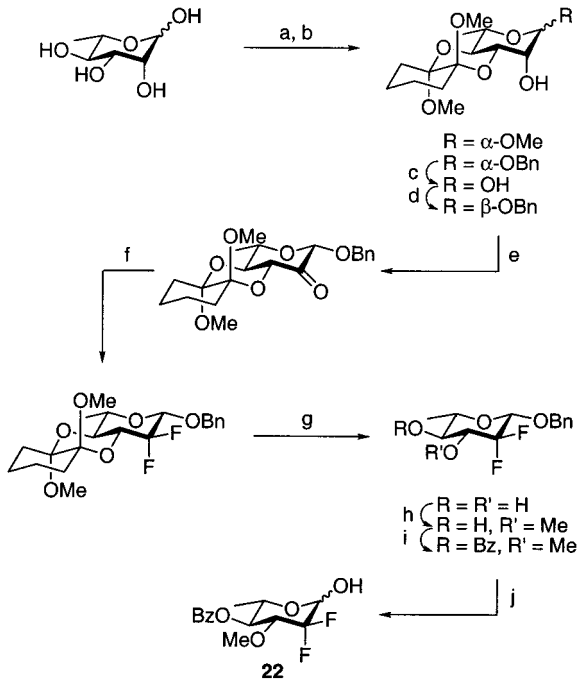
However, these were readily separated and processed further to give materials which were converted to novel cyclopentyl triphosphate derivatives such as **28** (Scheme 15).[60]

Similarly, Branchaud et al. employed BDA protection of methyl-α-D-glucopyranoside during synthetic studies toward the natural product (+)-pancratistatin. However, no differentiation of the two diequatorial diol pairs was achieved, resulting in a 1:1 mixture of the BDA isomers (Scheme 16).[61]

V. Use in the Synthesis of Rare Natural Pyranosides

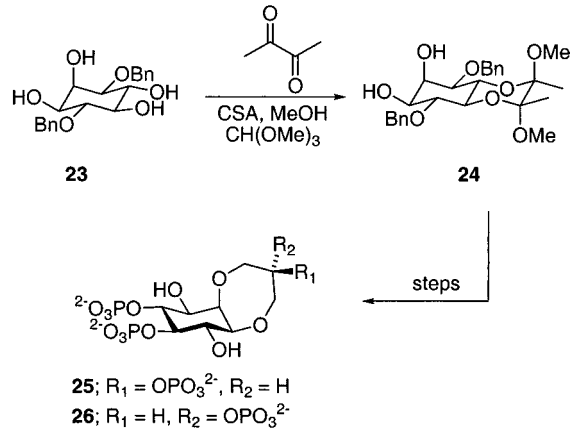
Since many biologically active natural products are often substituted by unusual carbohydrates or even consist solely of rare monosaccharide units, there is a need to develop efficient and rapid access to these important materials. Because BDA protection of mannose and galactose derivatives proceeds so well, it is not surprising that the products of these reactions should be excellent precursors to rare pyrano-

Scheme 13[a]

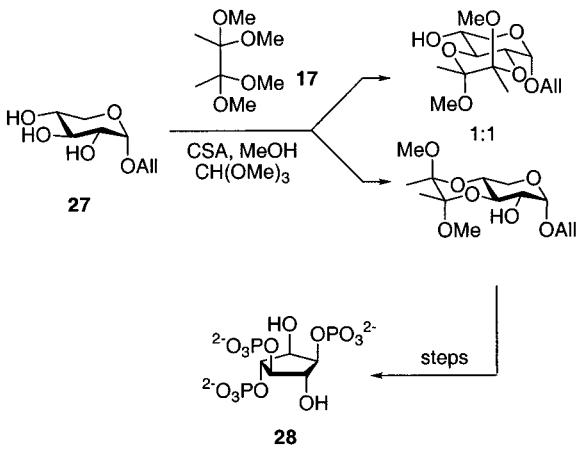


[a] Reagents and conditions: (a) BnOH, AcCl, 69%. (b) 1,1,2,2-Tetramethoxycyclohexane, CSA (cat.), MeOH, reflux, 61%. (c) H_2, Pd/C (cat.), MeOH/AcOEt. (d) Bu_2SnO, benzene, reflux, then BnBr, *n*-Bu_4NBr, reflux, 68% over two steps. (e) PCC, NaOAc, CH_2Cl_2, 97%. (f) DAST, CH_2Cl_2, 69%. (g) TFA/H_2O (95:5), 82%. (h) Bu_2SnO, benzene, reflux, then MeI, *n*-Bu_4NBr, toluene, reflux, 80%. (i) BzCl, DMAP (cat.), Py, 84%. (j) H_2, Pd/C (cat.), MeOH/AcOEt, 100%.

Scheme 14



Scheme 15



Scheme 16

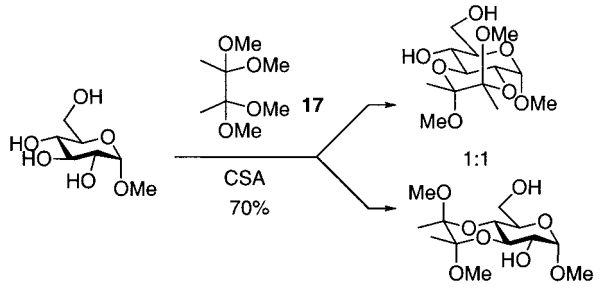
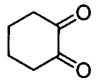
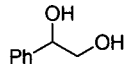
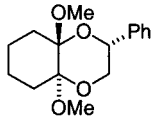
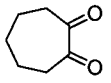
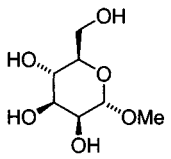
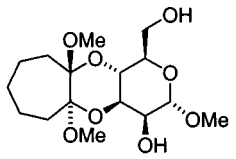
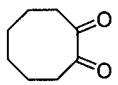
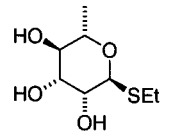
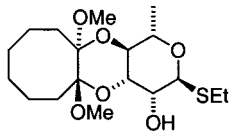
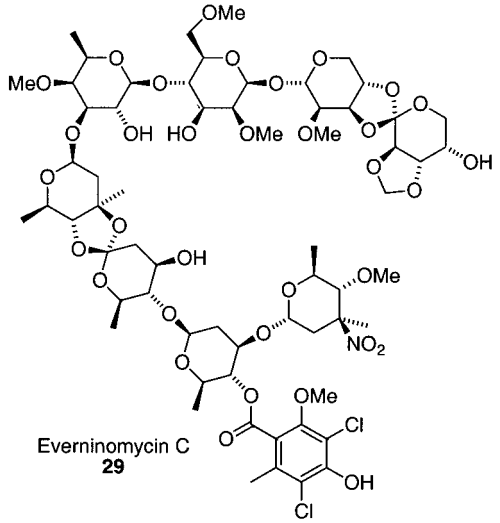


Table 5

Dione	1, 2-Diol	Diacetal	Yield (%)
			61
			49
			60

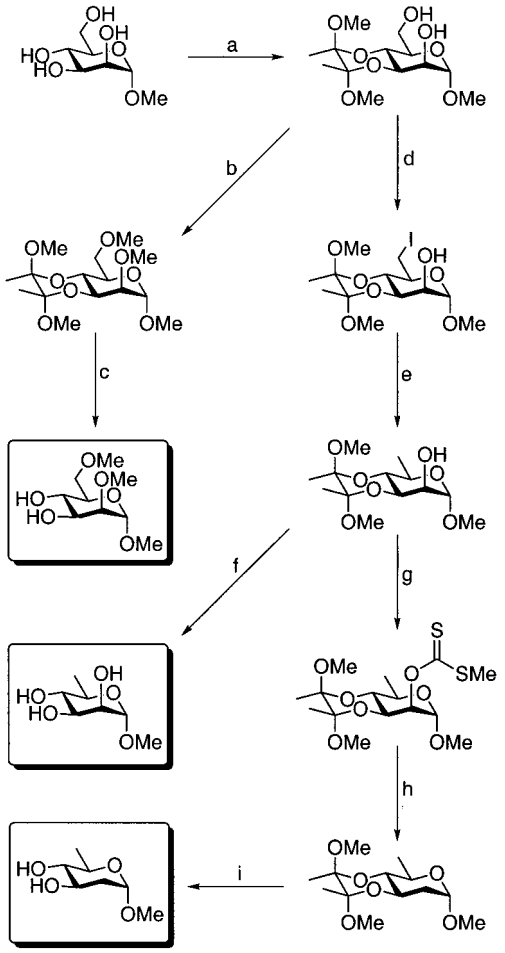
sides that would be difficult to obtain by conventional methods. For example, natural product everninomycin C **29** is an antibiotic which contains several unusual pyranoside ring systems.



Everninomycin C
29

Two examples which illustrate the rapid access to these types of molecule are shown in Schemes 17 and 18.[62] The BDA unit plays an essential role in providing suitably protected starting materials in a single step, which may then be diverted to various unusually methylated or deoxygenated derivatives (Schemes 17 and 18).

Scheme 17[a]



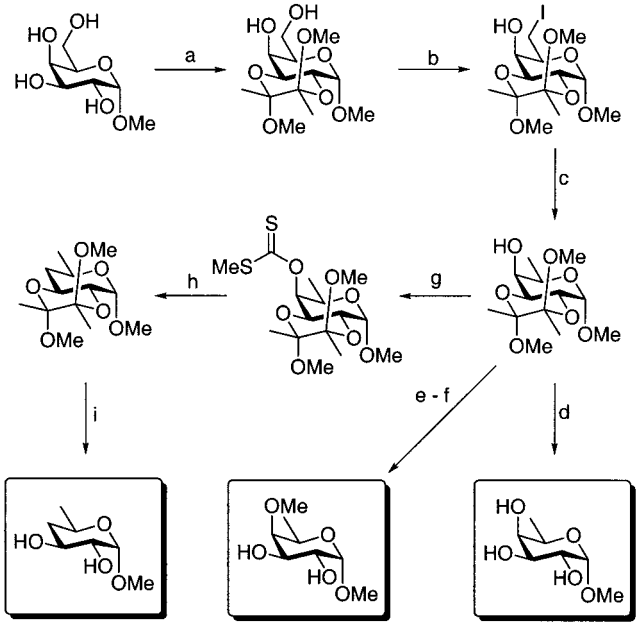
[a] Reagents and conditions: (a) Butane-2,3-dione, CSA (cat.), $CH(OMe)_3$, MeOH, reflux, 99%. (b) NaH, MeI, DMF, 86%. (c)TFA/H_2O (9:1), 99%. (d) I_2, PPh_3, imidazole, toluene, 75 °C, 85%. (e) H_2, Pd/C (cat.), Et_2NH, MeOH, 86%. (f) TFA/H_2O (9:1), 99%. (g) BuLi, CS_2, THF then MeI, 82%. (h) Bu_3SnH, AIBN, toluene, reflux, 71%. (i) TFA/H_2O (9:1), 99%.

VI. Conformationally Restricted Cyclohexane-1,2-Diones

In an effort to develop an asymmetric version of the cyclohexane-1,2-diacetal (CDA) protection procedure, the (*S*,*S*)-dimethyl-substituted derivative **30** was prepared.[63] It was hoped that incorporation of the methyl substituents and their known preference for equatorial positions in cyclohexane rings might control the absolute stereochemistry of acetal products. However, reaction of **30** with (±)-cyclohexane-1,2-diol **31** under the standard reaction conditions afforded *four* major diacetal products **32**−**35** together with a minor aromatic compound **36** (Scheme 19).

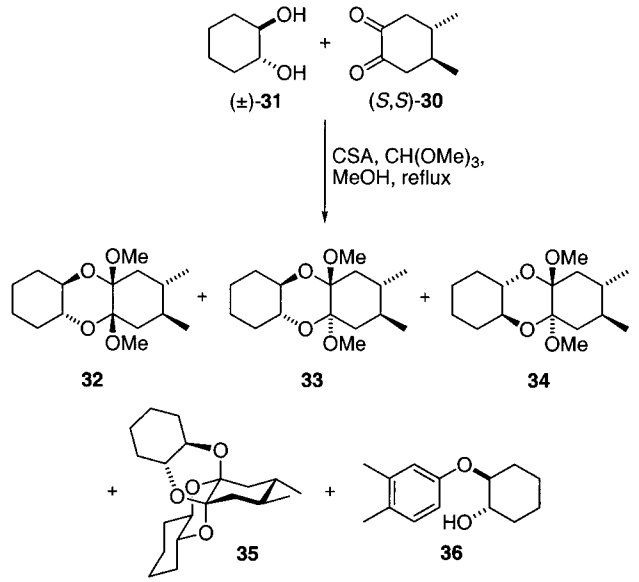
While this was a disappointing result, especially in terms of usefully obtaining enantiopure products, it did give considerable insight into the mechanism and the stereoelectronics operating during the formation of various 1,2-diacetal products. In any future development using chiral diones for asymmetric synthesis it would be wise to consult this work prior to embarking on the study, since many complex equilibria are operating in these reactions.

Scheme 18[a]



[a] Reagents and conditions: (a) Butane-2,3-dione, CSA (cat.), $CH(OMe)_3$, MeOH, reflux, 80%. (b) I_2, PPh_3, imidazole, toluene, 75 °C, 55%. (c) H_2, Pd/C (cat.), Et_2NH, MeOH, 90%. (d) TFA/H_2O (9:1), 99%. (e) NaH, MeI, DMF, 69%. (f) TFA/H_2O (9:1), 97%. (g) BuLi, CS_2, THF then MeI, 90%. (h) Bu_3SnH, AIBN, toluene, reflux, 71%. (i) TFA/H_2O (9:1), 96%.

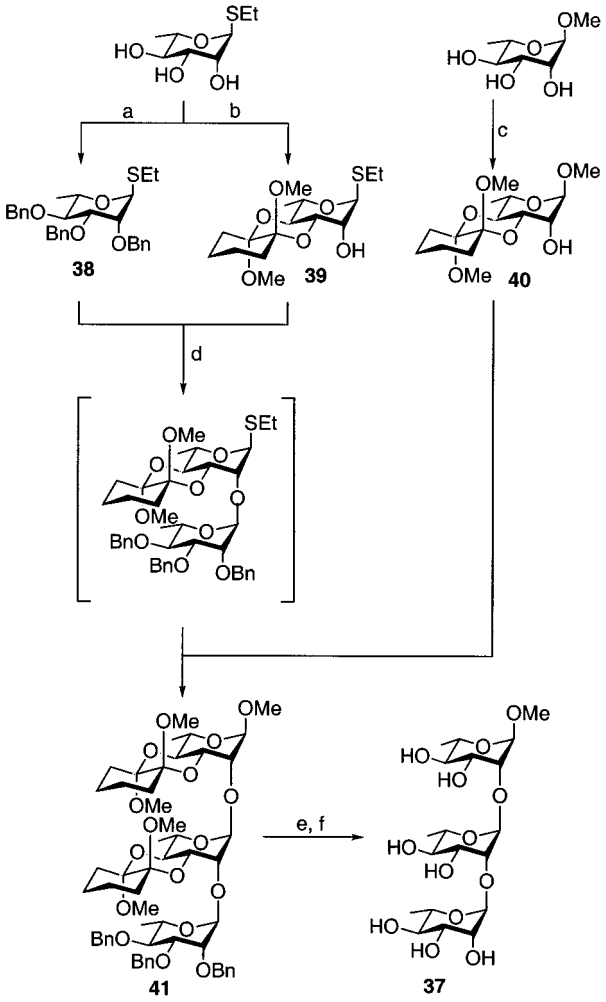
Scheme 19



VII. Reactivity Tuning during Glycosidation Reactions Using 1,2-Diacetal-Protected Substrates

The primary driving force behind the development of 1,2-diacetals for organic synthesis was undoubtedly their potential application in carbohydrate chemistry. We have already demonstrated, in earlier sections in this review, the power of these new methods to selectively protect 1,2-diequatorial diols, especially in monosaccharide building blocks. These methods considerably shorten the number of conventional steps needed to unmask particular protecting group patterns required for large molecule assembly. In-

Scheme 20[a]

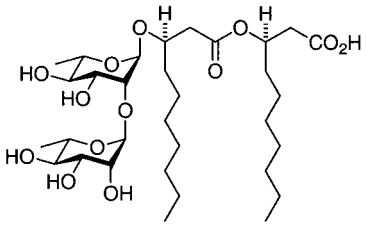


[a] Reagents and conditions: (a) BnBr, NaH, *n*-Bu_4NI (cat.), DMF, 94%. (b) 1,1,2,2-Tetramethoxycyclohexane, CSA (cat.), $CH(OMe)_3$, MeOH, reflux, 55%. (c) 1,1,2,2-Tetramethoxycyclohexane, CSA (cat.), $CH(OMe)_3$, MeOH, reflux, 74%. (d) NIS, TfOH (cat.), DCE/Et_2O (1:1), then **40**, NIS, TfOH (cat.), 62%. (e) HOAc/H_2O (2:1), 100 °C. (f) H_2, Pd/C (cat.), EtOH/HOAc (20:1), 53% over two steps.

deed, protecting groups are crucial in this type of synthesis, performing the uninteresting task of masking functionality that would otherwise interfere with a carefully planned strategy. The work on dispiroketals showed that these rigid structural architectures play a crucial role, mediating glycosidic coupling reactions via operating torsional effects.[26] It seems reasonable therefore that 1,2-diacetals, when similarly fused to carbohydrate coupling donors, should also be able to effect reactivity tuning.[64] This property should be exploitable in oligosaccharide synthesis and cut down on the number of steps normally associated with conventional coupling reactions. In 1994 we reported the first example of this reactivity tuning concept during the one-pot synthesis of a trisaccharide unit **37** found in the common polysaccharide antigen Group B *Streptococci* using CDA-protected rhamnosides as precursors.[65] The preparation of the necessary building blocks for this synthesis, compounds **38**−**40**, follows from α-L-rhamnose or methyl α-L-rhamnose using standard chemistry to prepare **38** or by using 1,1,2,2-tetramethoxycyclohexane **11** to generate the required cyclohexane diacetals **39** and **40**. Torsional deactivation operates by resisting the flattening of the pyranose ring during the formation of the putative oxonium ion intermediate. In this way, perbenzylated thioethyl donor **38** was selectively activated with *N*-iodosuccinimide (NIS) and catalytic triflic acid in the presence of the CDA detuned acceptor **39**. The in situ derived disaccharide was then coupled, without isolation, with the final acceptor **40**, thus assembling trisaccharide **41** in one reaction vessel and in 62% isolated yield. No homocoupling of thioethyl acceptor **39** was observed. Simple deprotection furnished the trirhamnoside in excellent overall yield (Scheme 20).

This one-pot coupling sequence complements other methods in the literature,[66−70] for example, those using orthogonal leaving groups, but provides the added bonus of being able to be amalgamated with these alternative methods to prepare much larger oligosaccharide arrays in a single reaction pot (vide infra).

Van Boom et al. recently applied these reactivity tuning concepts using 1,2-diacetals in a very concise preparation of a bis-rhamnoside oxadecanoic acid derivative **42**, thought to be the rhamnolipid component from *Pseudomonas aeruginosa*.[71] During this one-pot synthesis, the third component was a protected lipid side chain rather than another sugar acceptor unit.

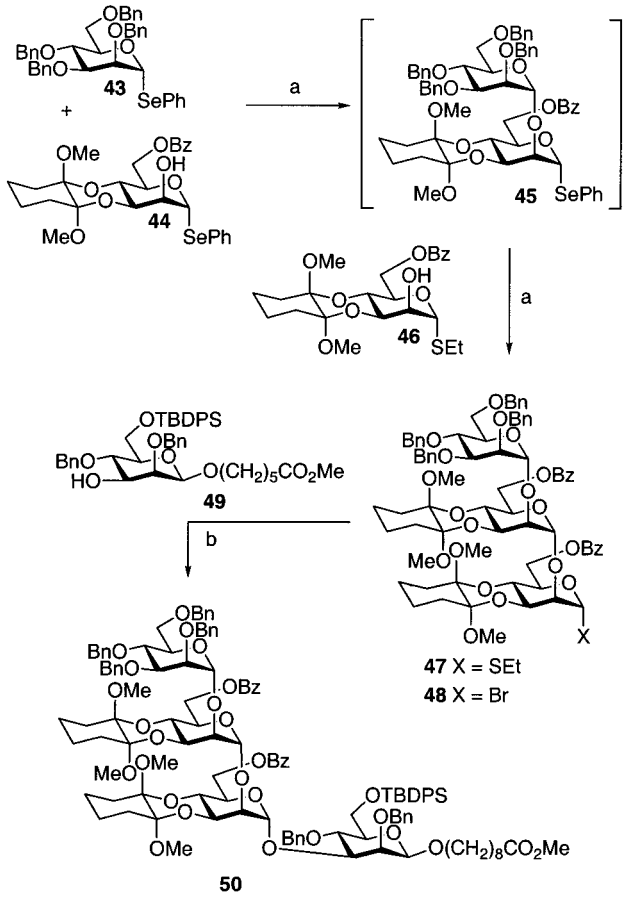


42

Having established principles for one-pot coupling reactions, using torsional effects, the ideas were extended by combining more reactive phenylseleno donors with slower reacting thioethyl derivatives making up to four levels of reactivity possible.[72] As an example of these alternative coupling protocols, the highly reactive donor **43** can be reacted with the CDA detuned phenylseleno acceptor **44** to give the disaccharide **45** after only 10 min with NIS and triflic acid. This disaccharide can then itself be activated and coupled with the third component **46**, which contains a poorer thioethyl leaving group, to afford the trisaccharide **47** after the addition of a second portion of promoters. Although the thioethyl trisaccharide **47** is now very deactivated by both the CDA and the C-6 benzoyl substituent, it can be persuaded to react with Br_2 in the presence of silver triflate. The presumed intermediate bromide **48** can then be coupled with a fourth monomeric building block **49** to give the tetrasaccharide **50** (Scheme 21).

The next advance came by combining these ideas of reactivity tuning with the principles of orthogonality,[73] whereby different leaving groups at the anomeric position could be differentially activated in the presence of one another.[74] Scheme 22 illustrates this concept for the preparation of a linear tetrasaccharide

Scheme 21[a]



[a] Reagents and conditions: (a) NIS, TfOH (cat.), DCE/Et_2O (1:1), then **46**, NIS, TfOH (cat.), 67%. (b) Br_2, AgOTf, **49**, CH_2Cl_2, 60%.

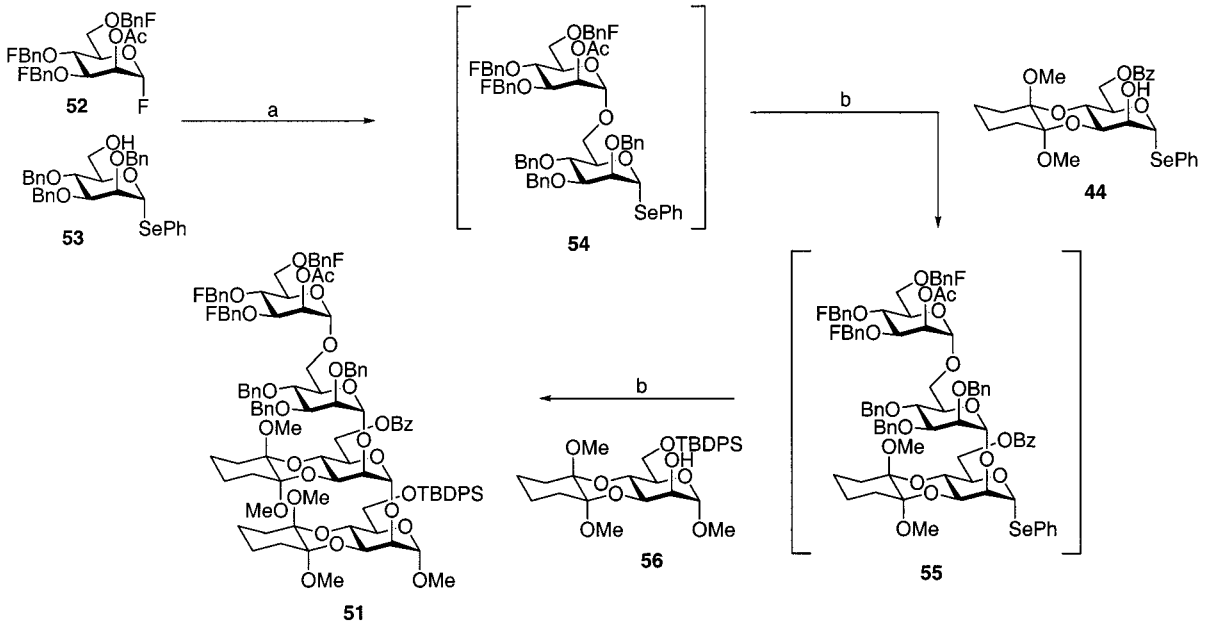
51, which is obtained in a single reaction vessel. Here the fluoro donor **52** may be selectively activated in the presence of other potential leaving groups, such as the phenylseleno substituent, and consequently coupling with **53** can take place to give the disaccharide **54**. This then reacts with a CDA-detuned phenylseleno derivative **44** to afford the trisaccharide **55**, which in turn reacts with a fourth component **56** to give the tetrasaccharide **51** (Scheme 22).

These one-pot processes can be extended even further to give linear pentamers[75] (Scheme 23). Here fluoro donor **57** reacts with BDA-detuned fluoro acceptor **58,** which in turn reacts with phenyseleno monomers **59** and CDA-detuned phenyseleno derivative **44**. Last, coupling with a thioethyl sugar containing **60** gives the final pentasaccharide **61**. While the overall yield is not high in this particular case, it does demonstrate the potential of the method.

Not only are linear sequences possible by the above one-pot methods but branched isomers can be obtained, very simply, by adapting these methods to include diols as acceptors in the coupling process.[75] A number of branched pentamers have been prepared using these procedures, although even larger compounds may be obtained by judicious choice of coupling components. For example, in Scheme 24, two heptamers **62** and **63** have been prepared by splitting the reaction stream at the linear trimer stage and coupling with two different diol acceptors, **64** and **65**, respectively. For all these products, selective deprotection is possible to generate a wide range of compounds. These products can be further reacted in a block coupling process to give large libraries of oligosaccharides. One-pot synthesis of glycoclusters has also been reported.[76]

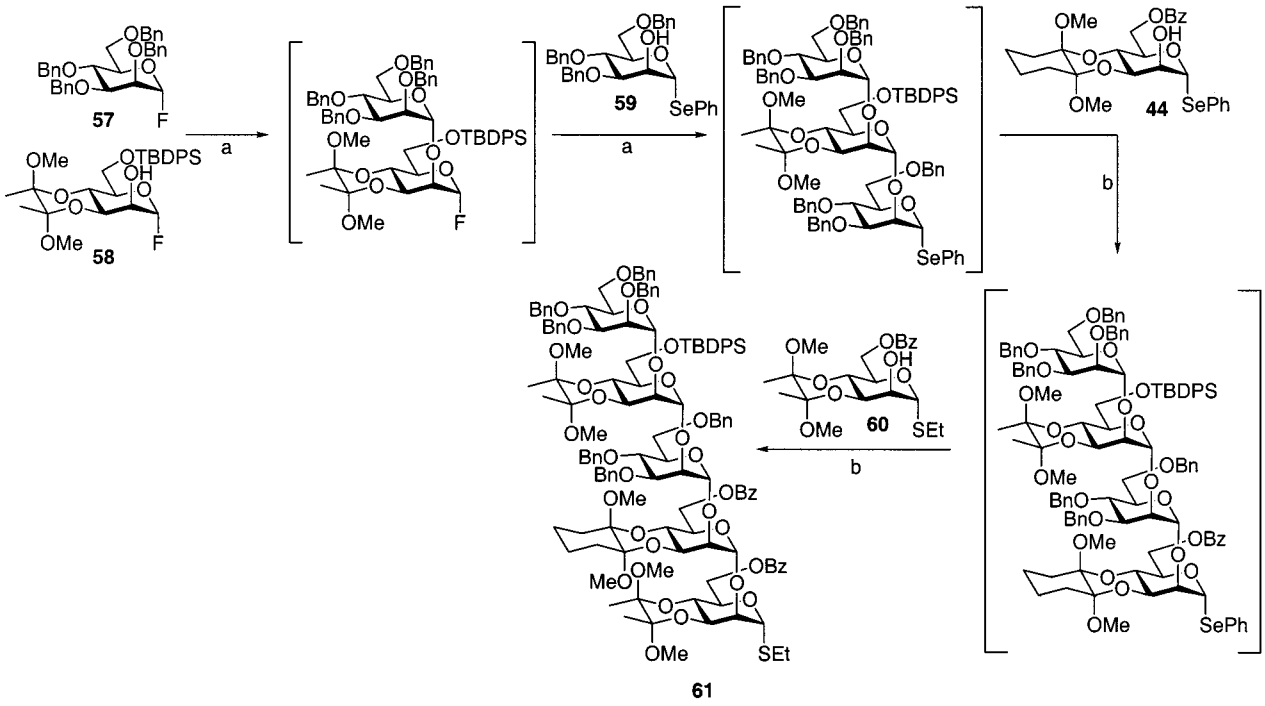
To give some idea of the quantitative effects of fusing cyclohexane or butane diacetals to glycosyl donors during glycosidation reactions, a detailed study has been undertaken such that one can now use these data as a crude predictive tool in designing oligosaccharide syntheses.[77] Moreover, these studies have paved the way to develop even more extensive predictive tools using a combination of experimental and computational methods.[78] In the future, one

Scheme 22[a]



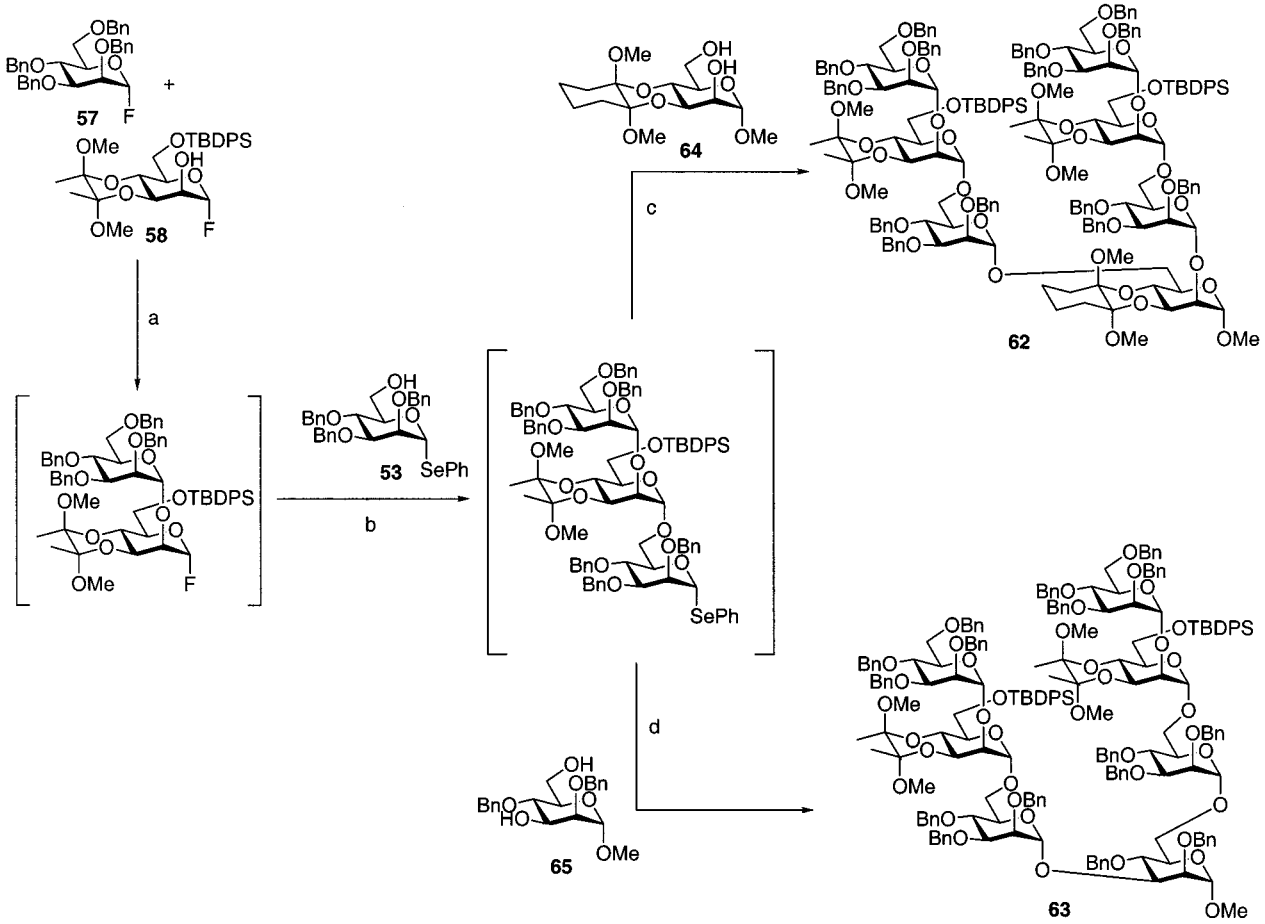
[a] Reagents and conditions: (a) Cp_2HfCl_2, AgOTf, CH_2Cl_2. (b) **44**, NIS, TfOH (cat.), CH_2Cl_2/Et_2O (1:1), then **56**, NIS, TfOH (cat.), 21% overall.

Scheme 23[a]



[a] Reagents and conditions: (a) Cp_2HfCl_2, AgOTf, CH_2Cl_2, then **59**, Cp_2HfCl_2, AgOTf. (b) **44**, NIS, TfOH (cat.), CH_2Cl_2/Et_2O (1:1), then **60**, NIS, TfOH (cat.), 8% overall.

Scheme 24[a]

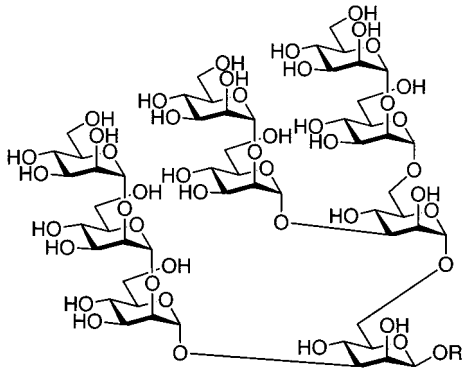


[a] Reagents and conditions: (a) Cp_2HfCl_2, AgOTf, CH_2Cl_2. (b) **53**, Cp_2HfCl_2, AgOTf, CH_2Cl_2. (c) **64**, NIS, TfOH (cat.), CH_2Cl_2/Et_2O (1:1) 21%. (d) **65**, NIS, TfOH (cat.), CH_2Cl_2/Et_2O (1:1), 9%.

could imagine a reactivity matrix being available such that one is better able to design synthetic pathways to more complex oligosaccharides in a more efficient fashion.

VIII. Synthesis of High-Mannose Carbohydrates

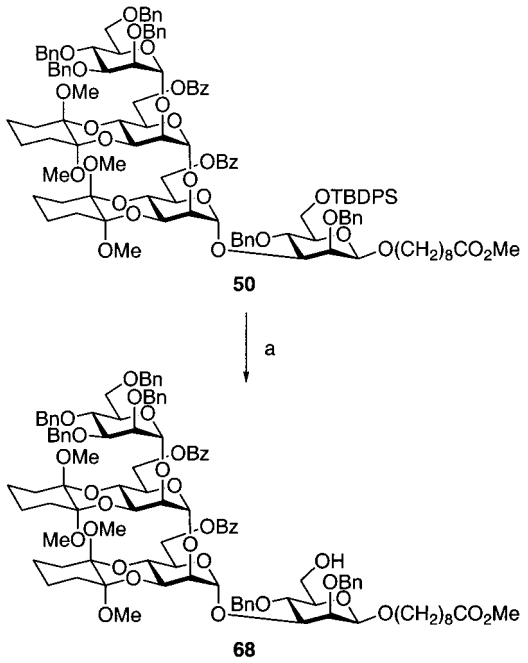
With these new methods for oligosaccharide synthesis available, it is essential to test these procedures in much more challenging situations. For example, high-mannose-type oligosaccharides are ubiquitous in nature and have attracted particular attention[79] owing to their involvement with the envelope glycoprotein gp120 of the human immunodeficiency virus (HIV), which is known to bind to human T4 lymphocytes causing AIDS. The glycans on the viral envelope of this protein are possible targets for immunotherapy and for vaccine development.[80−85] Consequently, routes to these high-mannose residues are particularly important. In preliminary studies a strategy was developed which led to an efficient assembly of a model nonamannose residue **66**.[86] This work confirmed the importance of using cyclohexane diacetals to prepare suitable monomer building blocks and that these could then be used to control the reactivity in the later glycosidation steps. Following these preliminary studies, the synthesis of a nine-mannose residue fragment **67**, containing a linker suitable for eventual coupling to the protein, was reported.[87] Using the one-pot procedures, the assembly of the whole carbohydrate fragment was achieved in just five steps from component building blocks.



66 R = Me
67 R = $(CH_2)_8CO_2Me$

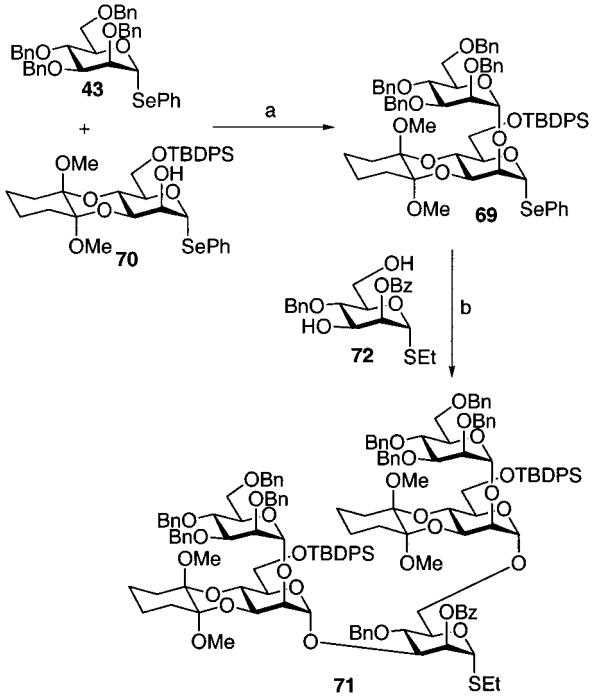
The required starting materials for this synthesis were prepared using standard carbohydrate chemistry or the diacetal methodology introduced earlier. The CDA functionalities in **50** played a pivotal role in expediting its synthesis. Subsequently, deprotection of the TBDPS group under carefully buffered conditions unmasked the hydroxyl in acceptor **68** (Scheme 25). Similarly the diacetal method provided disaccharide **69** via the reactivity tuned coupling of selenides **43** and **70** (Scheme 26). The branching at the 3- and 6-positions in pentasaccharide **71** was achieved by reacting 2 equiv of the phenylseleno disaccharide **69** with the thioethyl-deactivated diol **72** (Scheme 26). Finally, coupling of the tetra- and pentasaccharide fragments affords the whole carbohydrate core of the target molecule **73** without the need to introduce any extra steps common to other approaches. Last, the protecting groups were removed over four steps to unmask the fully deprotected nonamannose derivative **67** (Scheme 27).

Scheme 25[a]



[a] Reagents and conditions: (a) TBAF, HOAc (cat.), THF, 87%.

Scheme 26[a]

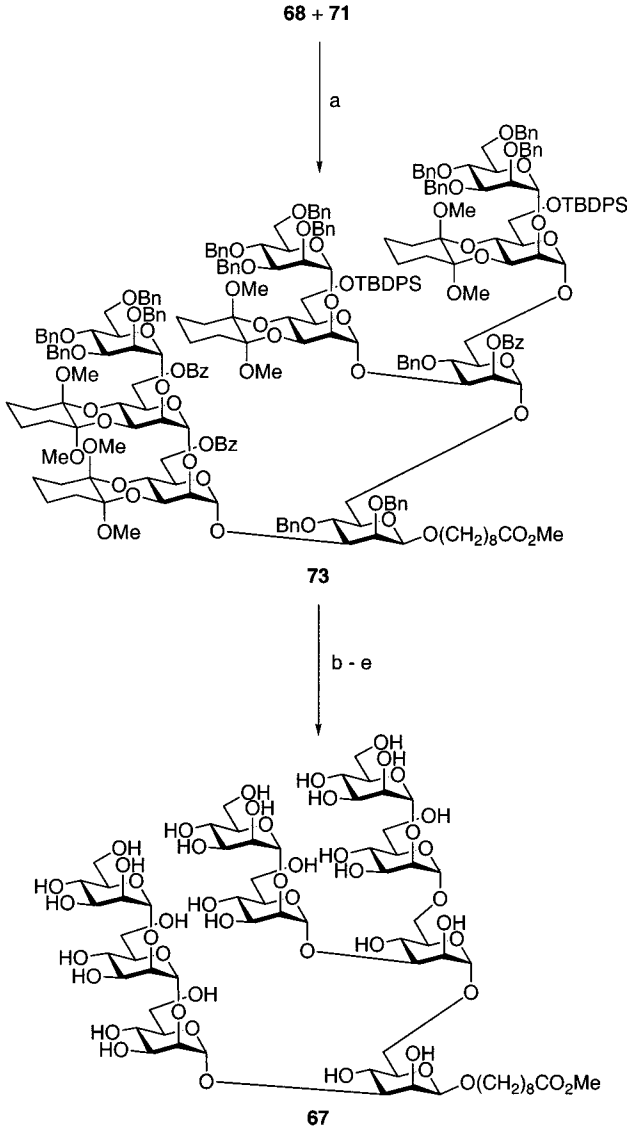


[a] Reagents and conditions: (a) NIS, TfOH (cat.), DCE/Et_2O (1:1), 46%. (b) **72**, NIS, TfOH (cat.), DCE/Et_2O (1:1), 63%.

IX. Synthesis of a Glycosylphosphatidylinositol Anchor

A particularly impressive example of the use of 1,2-diacetals in the synthesis of complex carbohy-

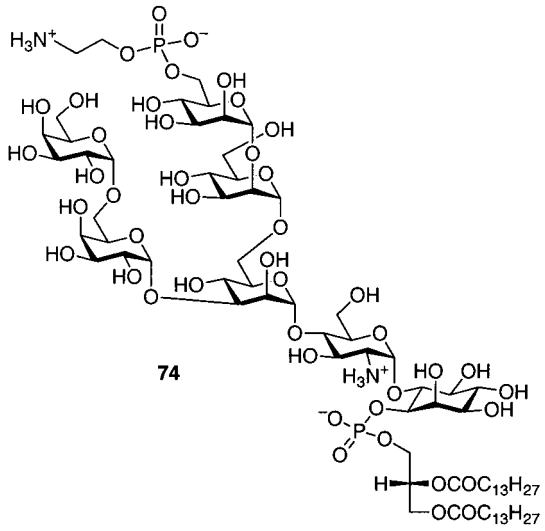
Scheme 27[a]



[a] Reagents and conditions: (a) NIS, TfOH (cat.), DCE/Et_2O (1:1), 89%. (b) MeONa, MeOH, 55 °C, 80%. (c) HF−Py, THF, 80%. (d) TFA/H_2O (20:1), 62%. (e) H_2, $Pd(OAc)_2$ (cat.), MeOH, 35%.

drates[88,89] was the total synthesis of the glycosylphosphatidylinositol (GPI) anchor **74** from *Trypanosoma brucei*.[90] GPI anchors attach proteins to membranes via a phosphoethanolamine unit linked to a trimannose−glucosamine−inositol backbone and a hydrophobic lipid that anchors the system to the membrane.[91,92] The discovery of these compounds is becoming increasingly common in eukaryotic species.[93] Protozoan parasites express high levels of GPI anchors on their cell surfaces.[94] Therefore, in an effort to find methods of prevention of these diseases, greater access to the linking carbohydrate species is urgently needed to unravel the biosynthetic pathways to these molecules. A route was therefore devised to one member of the series to display the power of the new methods. It is not possible in this review to do full justice to this synthesis; however, key elements of the route are emphasized.

It was anticipated that the use of the BDA groups and appropriate anomeric leaving groups should allow the assembly of the carbohydrate core **75** in just



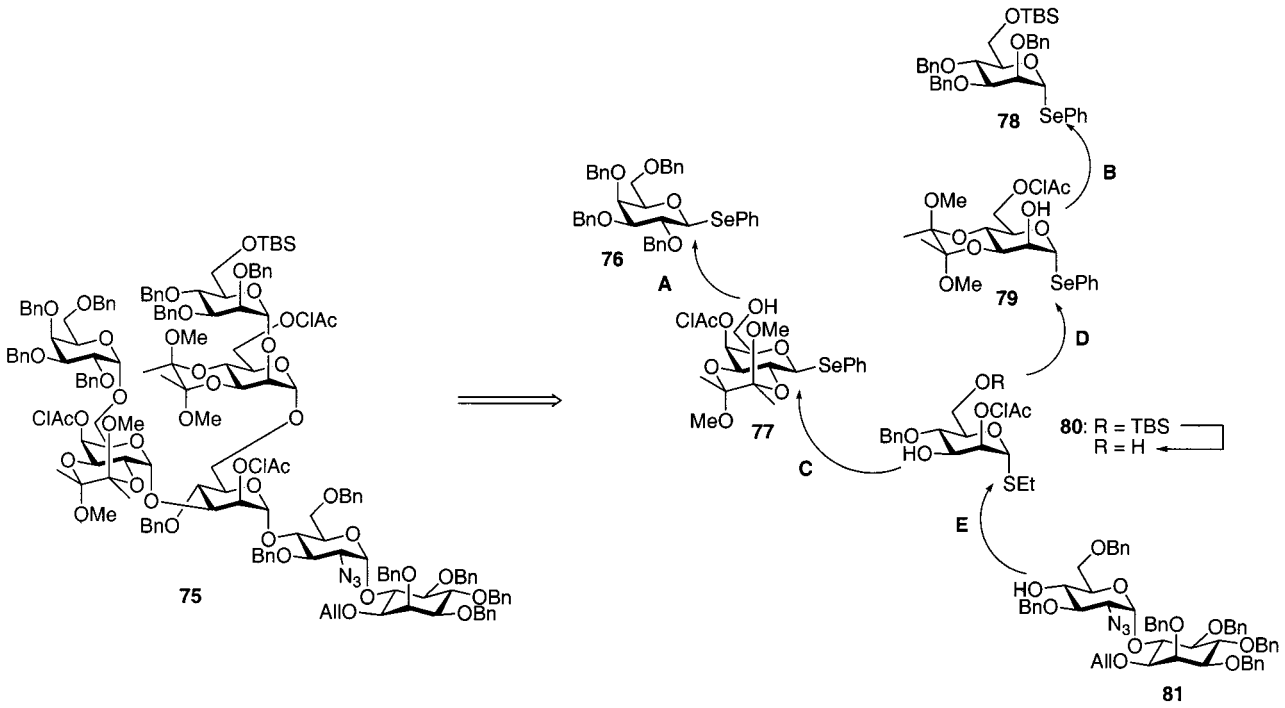
six steps from six building blocks **76**−**81** including only one protecting group manipulation (Scheme 28)

In couplings A and B, selective activation of the donor's selenium leaving group should be possible because of the deactivating effect of the BDA and chloroacetate groups in the acceptor, while in couplings C and D, the higher reactivity of the anomeric selenium groups in comparison to their sulfur equivalents should allow for selective activation. The strategy is also flexible: first, couplings C, D, and E can be envisaged to proceed in any sequence in the event of a steric mismatch; second, the selenium and sulfur leaving groups could be transformed into a more reactive halide should this prove necessary. For details of the synthesis of the building blocks, one is referred to the full paper. Some of the key compounds were prepared using dispiroketal methodology, while the BDA protection method was particularly effective in providing compounds **77**, **79**, and the inositol unit in **81**. As anticipated, the controlling effects of the BDA units worked well, permitting the expected coupling of **76** with **77** and **78** with **79** to give the corresponding disaccharides **82** and **83**. The whole of the carbohydrate core **75** was then assembled following the details presented in Scheme 29.

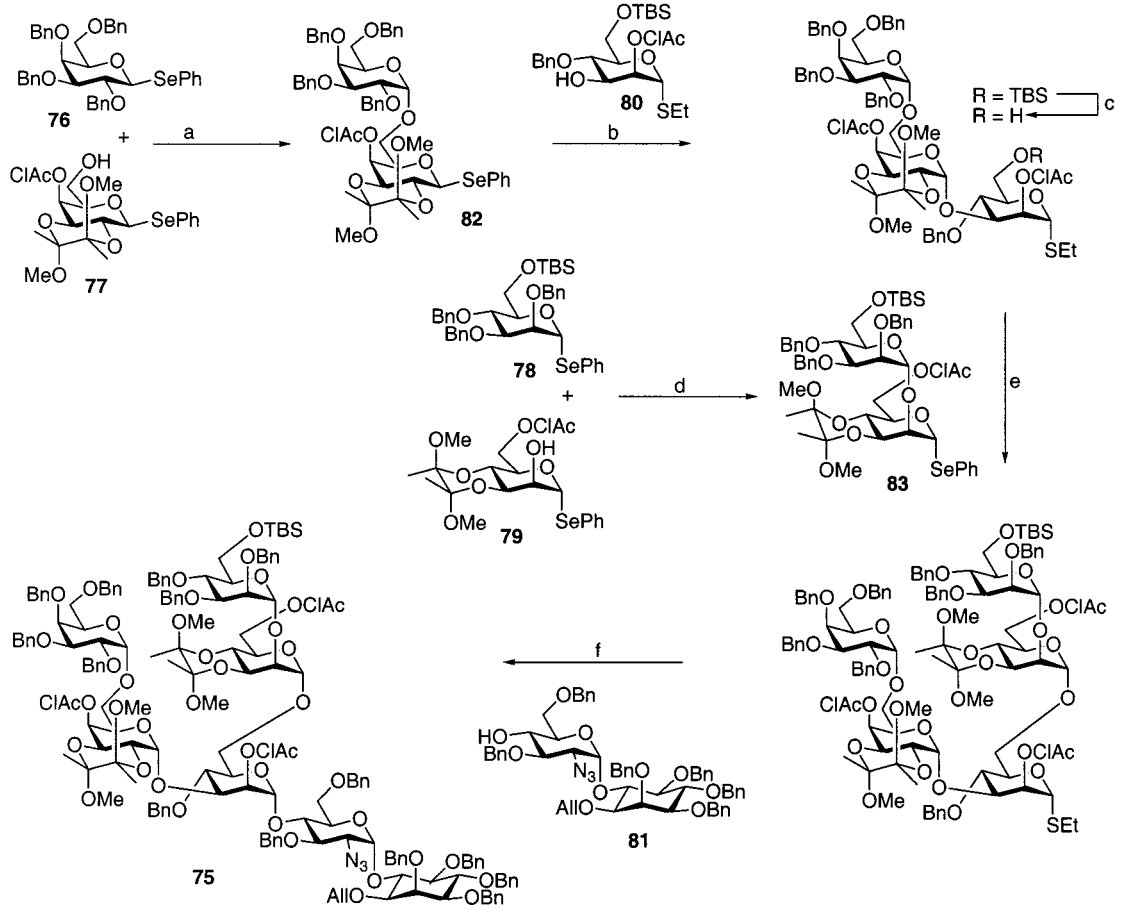
What is important in these reactions is that the BDA protecting groups survived all the reagent steps. The next steps in the synthesis required selective deprotection and coupling, first of the ethanolamine phosphate side chain and last the acylglyceride phosphate fragment. These steps proceeded uneventfully via **86**−**88** to give the fully protected GPI anchor **89**. Finally, all the protecting groups in **89** had to be removed. This was undoubtedly a challenging phase of synthesis; however, on model compounds, the compatibility of many of these transformations and especially the deprotection of the BDA groups had been previously established. In the event, all these reactions proceeded well to afford the GPI anchor **74** (Scheme 30).

We believe this synthesis is a testimony to the power of using 1,2-diacetals in carbohydrate assembly and obviously could be adapted to the preparation of many other analogues of GPI anchors which

Scheme 28



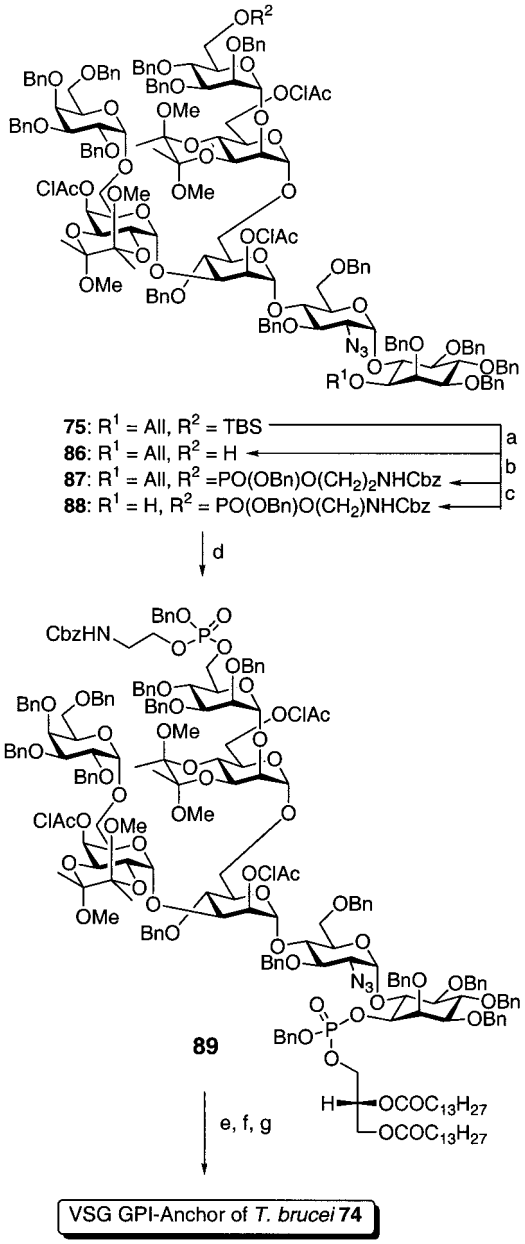
Scheme 29[a]



[a] Reagents and conditions: (a) NIS, TMSOTf (cat), CH_2Cl_2/Et_2O (6:1), 75%. (b) **80** MeOTf, Et_2O, 75%. (c) 48% HF (aq), CH_3CN, 89%. (d) NIS, TMSOTf (cat), CH_2Cl_2/Et_2O (1:1), 87%. (e) **83**, MeOTf, CH_2Cl_2, 75%. (f) NIS, TfOH (cat), CH_2Cl_2/Et_2O (3:1), 51%.

would help in our understanding of these compounds in controlling biological events. In line with this rationale, studies toward a yeast GPI anchor have recently been reported.[95]

Scheme 30[a]



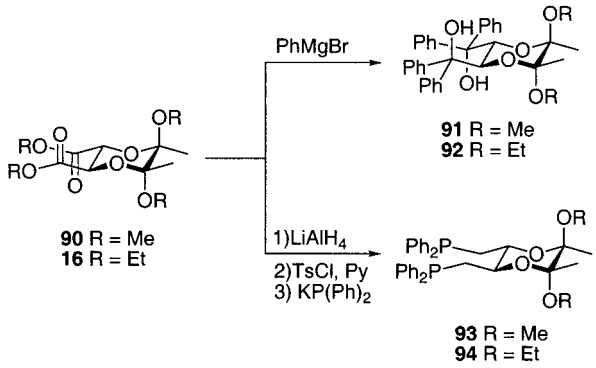
[a] Reagents and conditions: (a) 48% HF (aq.), CH_3CN, 75%. (b) (i-Pr_2N)P(OBn)O(CH_2)$_2$NHCbz, tetrazole, CH_3CN/CH_2Cl_2 (1:1), then mCPBA, 85%. (c) $PdCl_2$ (cat.), NaOAc, HOAc/H_2O (19:1), 66%. (d) (i-Pr_2N)P(OBn)OCH$_2$CH(OCO$C_{13}H_{27}$)CH$_2$OCO$C_{13}H_{27}$, tetrazole, CH_3CN/CH_2Cl_2 (1:1), then mCPBA, 81%. (e) H_2, Pd/C (cat.), $CHCl_3$/MeOH/H_2O 3:3:1. (f) H_2NNHC(S)SH, 2,6-lutidine/HOAc (3:1). (g) TFA/H_2O (9:1), 90% over three steps.

X. 1,2-Diacetals as Rigidifying Templates in Synthesis

Berens et al. were first to recognize the importance of the 1,2-diacetal motif in rigidifying structures for the design of novel diols and phosphine ligands for potential application in asymmetric synthesis.[51]

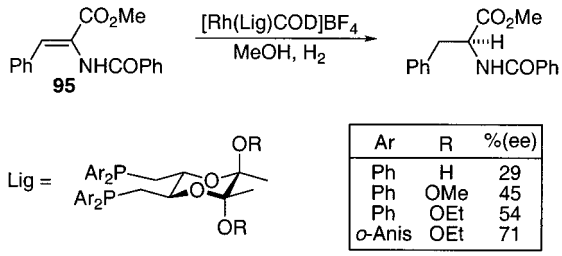
In these first experiments it was shown that BDA-protected tartrates **90** and **16** could be treated with an excess of phenylmagnesium bromide to give the corresponding hindered diols **91** and **92**. These materials were designed to compare with the well-known Seebach TADDOL ligands (Scheme 31).[96]

Scheme 31



Also, if **90** and **16** were reduced, tosylated, then converted to the bisphosphines **93** and **94**, these could be exploited in asymmetric hydrogenation reactions when chelated to form cationic Rh(I) complexes for example (Scheme 32). Some of these ligands were

Scheme 32

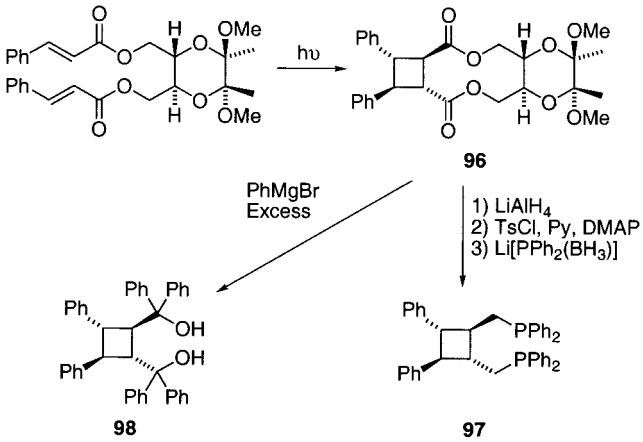


Ar	R	%(ee)
Ph	H	29
Ph	OMe	45
Ph	OEt	54
o-Anis	OEt	71

then used in the reduction of methyl benzamidocinnamate **95** (Scheme 32).[97] While the enantiomeric excesses in these reactions are only moderate, further optimization could lead to useful results.

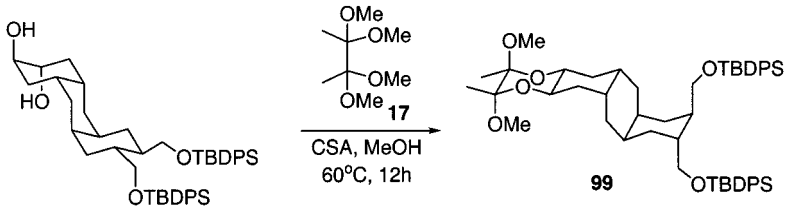
Other workers have prepared chiral cyclobutane bisphosphines as potential ligands employing the BDA functionality to act as a templating unit to append reacting cinnamates.[98] After photocyclization to give **96** followed by detachment, it was converted to the corresponding bisphosphine **97** (Scheme 33).

Scheme 33



The photoadduct **96** was also treated with excess Grignard reagent to afford novel cyclobutane TADDOL analogue **98**. This was then studied as a ligand for asymmetric hydrosilylation of ketones. A number of related ligands were also prepared and compared in Rh(I)-catalyzed hydrosilylation reactions of various

Scheme 34

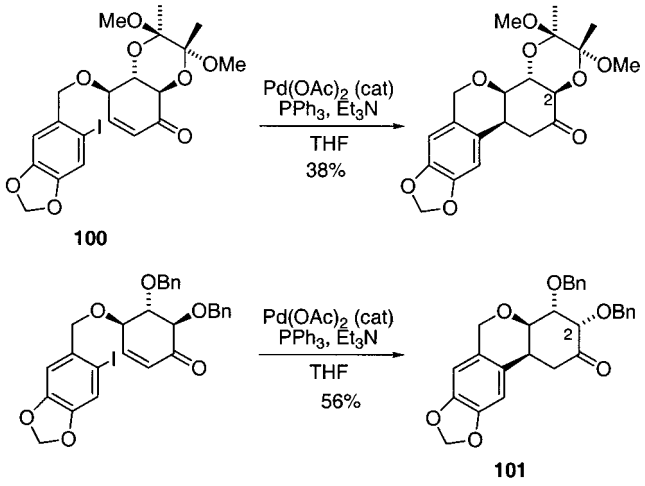


ketones, but only a modest level of enantioselectivity was observed in all cases.[99]

Butane diacetals have also been used to protect 1,2-diols in polysubstituted perdroanthracenes whereby a conformational flip was observed owing to the preferred diequatorial arrangement of the 1,2-diol pair in the BDA derivative **99** (Scheme 34). Without the diacetal being present, the rings are oriented in such a way as to place the diol in a diaxial environment with the OTBDPS groups equatorial.[100]

A particularly elegant application of BDA acting as a rigidifying template has been reported by Branchaud and co-workers in their studies toward (+)-pancratistatin. In this work the BDA functions as both a diequatorial diol protecting group and a conformational lock; the reductive cyclization of **100** afforded the product without epimerization at the C2 position. When nonrigidifying protecting groups, such as benzyl ethers, were used on this diequatorial diol pair, extensive epimerization was observed at C2 in the product **101** (Scheme 35).[61]

Scheme 35

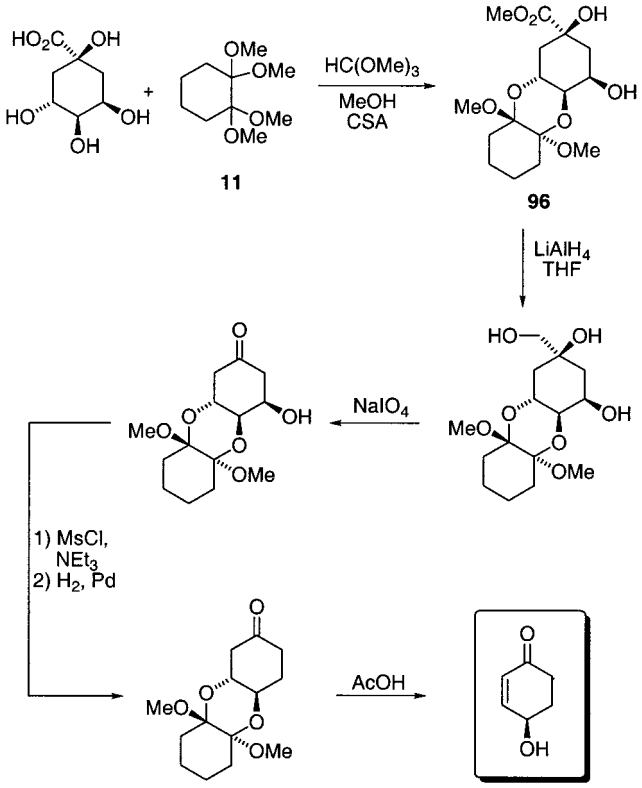


XI. Protection of Quinic Acid with 1,2-Diacetals

In 1996 two groups simultaneously studied the use of diacetals to selectively protect the 1,2-diequatorial diol pair in quinic acid and its derivatives. Brückner found that quinic acid reacted with the commercially available 1,1,2,2-tetramethoxycyclohexane **11**, under our previously established conditions, to give the CDA derivative **96** in 57% yield.[101] This was then converted to (*R*)-4-hydroxy-2-cyclohexane-1-one, an important chiral starting material, in a short number of steps and in a very efficient fashion (Scheme 36).

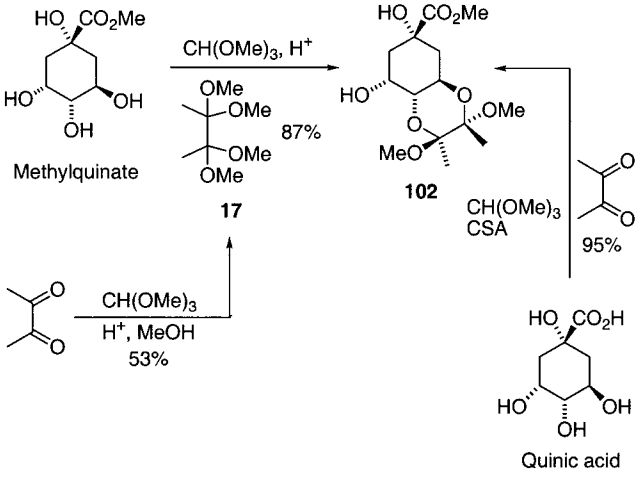
Similarly, Frost and co-workers reacted diacetal **17** with methyl quinate to give the corresponding BDA derivative **102** in an excellent 87% yield. However,

Scheme 36



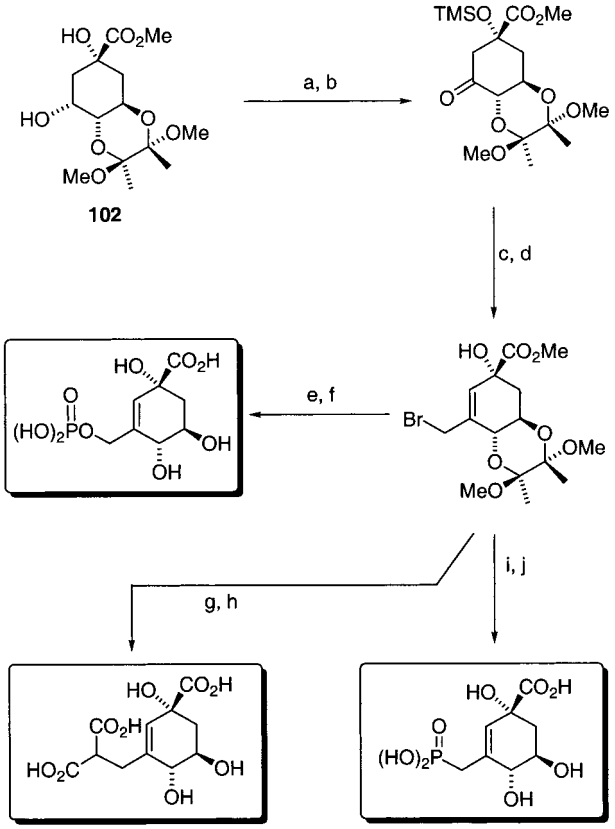
since the diacetal **17** is not yet commercially available nor is methyl quinate, the best way to prepare this usefully protected compound **102** is to use our direct method from butane-2,3-dione itself and free quinic acid, which gives **102** in 95% yield (Scheme 37). In

Scheme 37



an effort to prepare 3-dehydroquinate synthase inhibitors, Frost used BDA-protected methyl quinate

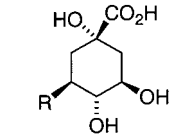
Scheme 38[a]



[a] Reagents and conditions: (a) KIO_4, K_2CO_3, $RuCl_3$, H_2O, $CHCl_3$, 77%. (b) TMSCl, HMDS, Py, 99%. (c) CH_2I_2, Zn, $TiCl_4$, THF, 92%. (d) i. PhSeBr, Na_2CO_3, CH_2Cl_2; ii. MCPBA, Py, CH_2Cl_2, 83%. (e) (^{t}BuO)P(O)OH, Ag_2O, CH_3CN, 63%. (f) i. TFA/H_2O (20:1), CH_2Cl_2; ii. 0.2 N aq NaOH; iii. Dowex 50 (H^+), 25%. (g) $CH_2(CO_2Et)_2$, NaH, THF, 68%. (h) i. TFA/H_2O (20:1); ii. 0.2 N aq NaOH; iii. Dowex 50 (H^+), 100%. (i) (^{i}PrO)$_3$P, toluene, reflux. (j) i. TFA/H_2O (20:1), CH_2Cl_2; ii. TMSBr, Et_3N, CH_2Cl_2; iii. 0.2 N aq NaOH; iii. Dowex 50 (H^+), 58%.

102 as a precursor to a number of potent novel analogues (Scheme 38).[102]

This work complemented earlier studies where they also used **102** as a key starting material. In this previous work several saturated derivatives were prepared with variations of the appending R group in **103**,[103] many of which also showed competitive inhibition of 3-dehydroquinate (DHQ) synthase.

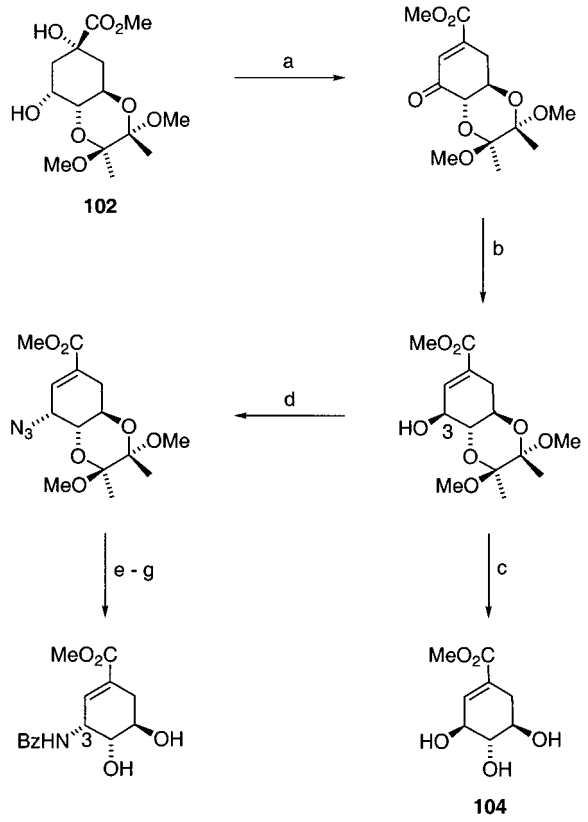


103

R = $CH_2PH(O)OH$
= $CH_2P(O)(OH)_2$
= $CH(CO_2H)_2$
= $C(OH)(CO_2H)_2$
= —O—CH(CO2H)—CH2CO2H

In related studies, Maycock and colleagues recently reported the use of the BDA-protected methyl quinate derivative **102** for the preparation of several (−)-shikimic acid species.[104] These compounds are key intermediates in the biosynthesis of aromatic amino

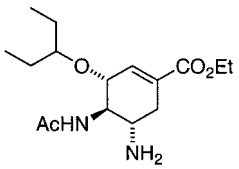
Scheme 39[a]



[a] Reagents and conditions: (a) i. $(COCl)_2$, DMSO, *i*-Pr_2NEt, CH_2Cl_2; ii. Ac_2O, *i*-Pr_2NEt, CH_2Cl_2, 95%. (b) DIBAL-H, THF, 73%. (c) TFA/H_2O (5:1), CH_2Cl_2, 98%. (d) DIAD, HN_3, PPh_3, THF, 98%. (e) PPh_3, THF, H_2O, reflux, 73%. (f) BzCl, DMAP (cat.), Py, 80%. (g) TFA/H_2O (10:1), CH_2Cl_2, reflux, 92%.

acids, precursors to the folate coenzymes, and various isoprenoid quinones.[105] For example, **102** was transformed to the C-3 *epi*-methyl shikimate **104** and to its 3-amino derivative (Scheme 39). In these reactions the BDA survives several steps but is readily removed by treatment with aqueous trifluoroacetic acid at the end of the synthetic sequence. Abell et al. also recently reported the first inhibitors of type II dehydroquinase (3-dehydroquinate dehydratase),[106] employing BDA-protected methyl quinate derivative **102** as starting material.

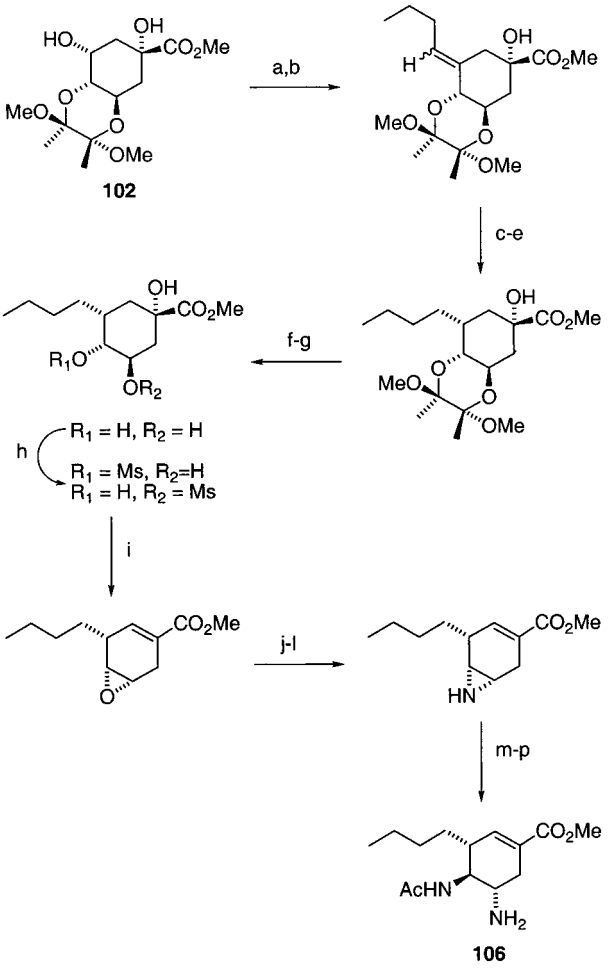
Owing to the success of a new class of carbocyclic influenza neuraminidase inhibitors,[107] **105** has recently been selected as a clinical candidate for the oral prophylaxis and treatment of influenza. Novel analogues of this material are therefore in considerable demand.



105

Hence, carba derivative **106** and other analogues have been synthesized.[108,109] The starting material for this work was, once again, BDA-protected methyl-quinate derivative **102**. This was converted in a series of straightforward steps to the compound **106** (Scheme

Scheme 40[a]



[a] Reagents and conditions: (a) PCC, Py, 74%. (b) *n*-BuPPh$_3$Br, BuLi, THF, 81%. (c) Et$_3$SiOTf, 2,6-lutidine, 93%. (d) H_2, Pd/C (cat.), 97%. (e) TBAF, THF, 77%. (f) i. SO_2Cl_2; ii. MeOH, 90%. (g) TFA/H_2O (2:3), CH_2Cl_2, 75%. (h) MsCl, Et$_3$N, 87%. (i) DBU, THF, 71%. (j) NaN_3, NH_4Cl, MeOH/H_2O, 95%. (k) MsCl, Et$_3$N, 97%. (l) i. PPh$_3$, THF; ii. Et$_3$N/H_2O, 71%. (m) NaN_3, NH_4Cl, DMF, 86%. (n) AcCl, Py, 68%. (o) PPh$_3$, THF/H_2O, 95%. (p) KOH (aq.), 85%.

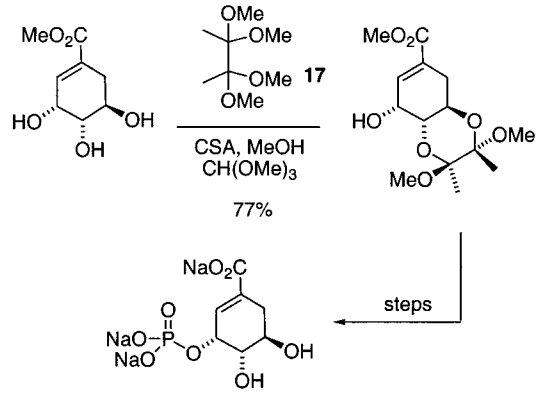
40). What should be noticed in this scheme is that the BDA group selectively protected the equatorial diol pair in quinic acid and then remained stable through several transformations such as oxidation, Wittig olefination, silylation, hydrogenation, and elimination. Finally, it was readily removed by treatment with 40% trifluoroacetic acid in the normal way.

More recently, Shih and Wu directly protected the diequatorial diol pair of methyl shikimate using acetal **17**, trimethyl orthoformate, and CSA in refluxing methanol in a good 77% yield. This product was subsequently transformed into (−)-shikimate 3-phosphate (Scheme 41).[110]

XII. 1,2-Diacetals of Tartaric Acid Derivatives

For many years tartaric acid and its derivatives have provided a rich source of chiral materials for asymmetric and natural product synthesis, whether as catalysts or as four-carbon building blocks.[111] While extensive reviews have appeared on the topic, there is still considerable scope for further developments. For example, it was reported earlier in this

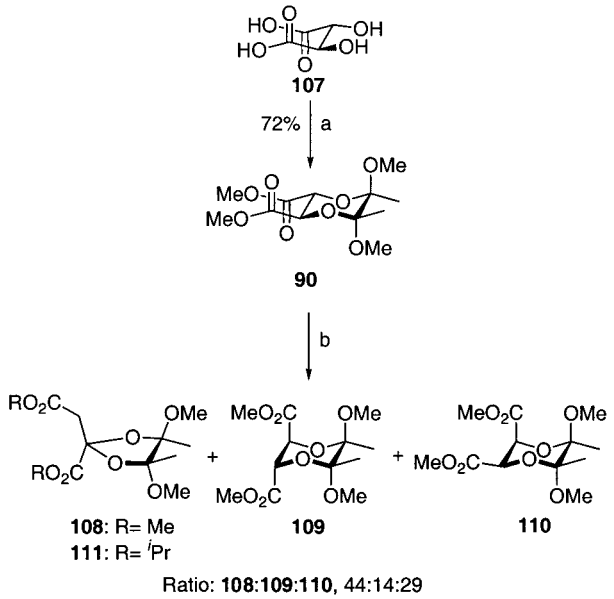
Scheme 41



review that Berens et al. reacted diethyl tartrate with 2,2-dimethoxybutane-3-one to form the corresponding BDA-protected ethyl tartrate derivative **15**.[51] This compound was then used in the preparation of potential ligands for asymmetric synthesis.

More recently, Maycock and co-workers reported that (*R*,*R*)-tartaric acid **107** itself when reacted with 2,2,3,3-tetramethoxybutane **17** gave the corresponding BDA derivative **90** (Scheme 42).[112] This was

Scheme 42[a]

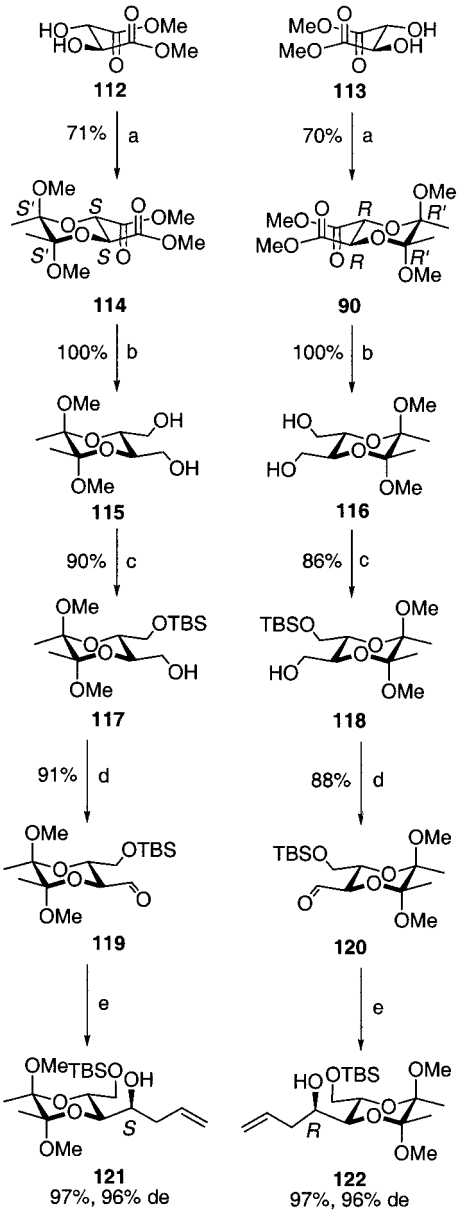


[a] Reagents and conditions: (a) 2,2,3,3-Tetramethoxybutane, CH(OMe)$_3$, PTSA (cat.), MeOH, reflux. (b) LDA, THF, −100 to −70 °C then MeOH, −100 to −70 °C then 10% aq NH_4Cl −70 °C to room temperature.

subsequently reacted with lithium diisopropylamide, under a variety of conditions, to give rearranged products **108**−**110** whose ratios depended upon the reaction times and equivalents of base used (Scheme 42). By varying the ester substituent to an *iso*-propyl ester, these authors found that the rearrangement favored the formation of the 1,3-dioxolane product **111**.

We too have investigated BDA tartrate derivatives but with different goals in mind. Our primary aim was to exploit the chirality embedded in these units and to use the carbon atoms in a profitable way in synthesis of polyhydroxylated natural products. So

Scheme 43[a]



[a] Reagents and conditions: (a) Butane-2,3-dione (1.2 equiv), CSA (0.1 equiv), $CH(OCH_3)_3$ (3.0 equiv), CH_3OH, reflux, 14 h. (b) $LiAlH_4$ (1.1 equiv), THF, 0 °C to room temperature, 0.5 h. (c) NaH (1 equiv), THF, room temperature then TBSCl (1 equiv), 2 h. (d) $(COCl)_2$ (1.3 equiv), DMSO (2.6 equiv), CH_2Cl_2, −78 °C then Et_3N (3.5 equiv), −78 °C to room temperature over 30 min. (e) $Bu_3SnCH_2CHCH_2$ (3 equiv), $LiClO_4$ (3 equiv), Et_2O, 0 °C to room temperature overnight.

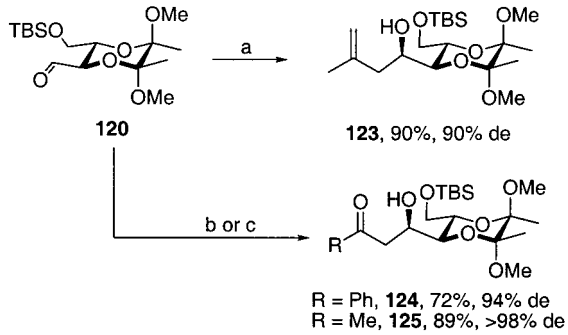
far we have published only five papers on this subject, but we can see enormous potential for these systems.

In the first experiments,[113] both (*S*,*S*)- and (*R*,*R*)-dimethyl tartrate **112** and **113** were reacted with butane-2,3-dione, in boiling methanol containing catalytic camphorsulfonic acid, to give the corresponding BDA-protected derivatives **114** and **90**. These materials could be readily prepared, by this method, in 100 g quantities. Next, they were converted by treatment with lithium aluminum hydride to give the known diols[51,98] **115** and **116** in quantitative yield. To differentiate the two terminal hydroxyl groups for further synthetic applications, selective monoprotection was achieved, first by treating with 1 equiv of sodium hydride followed by the addition of *tert*-butyldimethylsilyl chloride to give the corresponding products **117** and **118** (Scheme 43).

Upon oxidation, using standard Swern conditions, these afforded the aldehydes **119** and **120** which were then suitable as precursors for a variety of carbon nucleophilic addition reactions. For example, reaction with allyl tri-*n*-butylstannane (3 equiv) and lithium perchlorate (3 equiv) in diethyl ether at 0 °C gave a readily separable 98:2 mixture of diasteroisomers favoring products **121** and **122**, respectively. The newly formed stereogenic center of the major product arose as a result of chelation control.

In a further reaction, when **120** was treated with methallyl tri-*n*-butylstannane, a 95:5 ratio of separable isomers was produced furnishing **123** in 90% isolated yield (Scheme 44). Mukaiyama aldol reac-

Scheme 44[a]

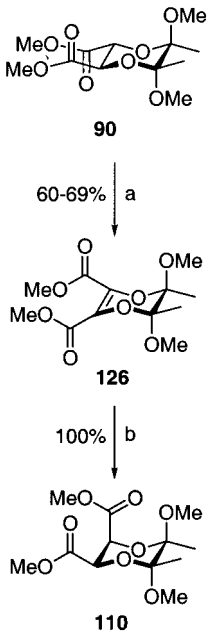


[a] Reagents and conditions: (a) $Bu_3SnCH_2C(CH_3)CH_2$ (3 equiv), $LiClO_4$ (3 equiv), Et_2O, 0 °C to room temperature overnight. (b) $MgBr_2$ (3 equiv), Et_2O, room temperature to 0 °C then 1-phenyl-1-trimethylsilyloxyethene (4 equiv), 0 °C, 30 min. (c) $MgBr_2$ (3 equiv), Et_2O, room temperature to 0 °C then 2-trimethylsilyloxypropene (4 equiv), 0 °C, 30 min.

tions with aldehyde **120** have also been investigated. Thus, precomplexation of **120** with magnesium bromide (3 equiv) at room temperature in ether, followed by cooling to 0 °C then reaction with an excess of 1-phenyl-1-trimethylsilyloxyethene, led to the formation of the aldol product **124** in good yield with high stereoselectivity (97:3). Similarly, when **120** was treated with trimethylsilyloxypropene, the aldol product **125** was formed with excellent diastereoselectivity (>99:1) (Scheme 44).

Following these encouraging reactions of C_2-symmetric BDA tartrate derivatives, a synthetic plan was devised to exploit further the chirality embedded within the BDA backbone. It was apparent that if one of the stereogenic centers of the C_2-symmetric (*R*,*R*)-tartrate functionality could be cleanly inverted, then the residual chirality of the conformationally rigid BDA backbone would necessarily place the two carboxylate functions in different steric environments. Selective differentiation of these termini would allow the preparation of various desymmetrized *meso*-tartrate derivatives.[114] Furthermore, this chiral memory protocol would allow the preparation of a building block with considerable potential in organic synthesis as a precursor to enantiopure *anti*-1,2-diols, especially as these units occur in a vast range of natural products.

Scheme 45[a]



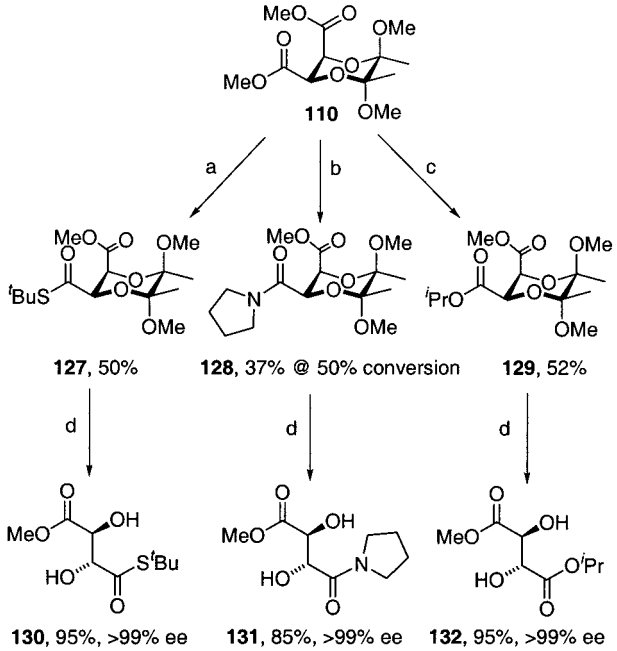
[a] Reagents and conditions: (a) LDA (2.0 equiv), THF, −78 °C, 30 min then I_2 (1.0 equiv). (b) H_2 (80 bar), Rh/Al_2O_3 (20%), MeOH, 5 days.

Consequently, oxidation of (*R′*,*R′*,*R*,*R*)-butane-2,3-diacetal-protected dimethyltartrate **90**, via double deprotonation with LDA in THF at −78 °C and treatment with 1 equiv of iodine, afforded **126** in excellent yield on a multigram scale (Scheme 45). Stereospecific hydrogenation of this material in methanol using hydrogen (80 bar) over rhodium on alumina afforded the crystalline product **110** in essentially quantitative yield (Scheme 45). Clearly, this efficient synthetic procedure relies on a chiral memory protocol where the natural chirality of the tartaric acid derivative fixes the chirality of the BDA backbone which, after the two- step inversion process, renders the resulting *meso*-dimethyl tartrate desymmetrized.

The differing reactivity of the axial and the equatorial carboxylate functions was clearly illustrated by the selective conversion of **110** to the corresponding equatorial *S*-, *N*- or *O*-carboxylate derivatives **127**−**129** (Scheme 46). These compounds could then be used in synthesis, where the dissymmetric *meso*-tartrates would provide an embedded *anti*-1,2-diol, four-carbon, chiral motif. To show that these units could also be readily deprotected, treatment of **127**−**129** with 90% TFA/H_2O gave the resulting diols **130**−**132** in excellent yield (Scheme 46).

The BDA-protected *meso*-tartrate derivative **110** has also proved useful in other chemistry.[115] As expected, lithium aluminum hydride reduction of **110** affords the diol **133** whereby the terminal primary hydroxyl groups are sufficiently different that one could expect them to react chemoselectively. Remarkably, when **133** was treated with *tert*-butyldimethylsilyl chloride and imidazole, in THF at room temperature, a 17:1 ratio of **134** to **135** was observed. Similarly, reaction with *tert*-butyldiphenylsilyl chloride gave a 5:1 ratio of **136** to **137**. Interestingly, when silylation was performed following prior deprotonation with sodium hydride then addition of the

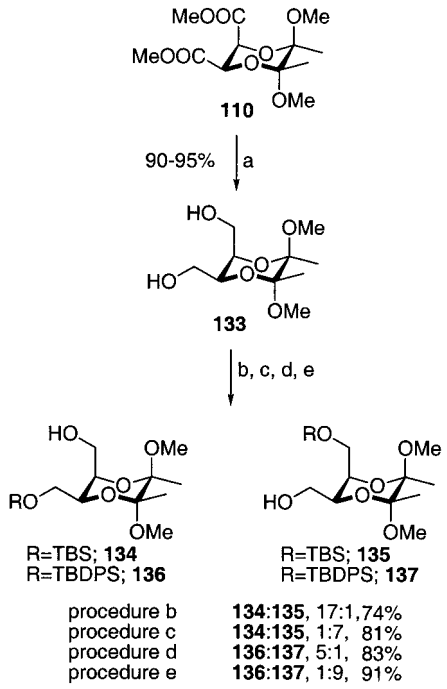
Scheme 46[a]



[a] Reagents and conditions: (a) Me_2AlS^tBu (4 equiv), toluene, room temperature, 24 h. (b) $Me_2AlN(CH_2CH_2)_2$ (4 equiv), toluene, room temperature, 72 h. (c) $Ti(O^iPr)_4$ (0.2 equiv), ^{i}PrOH, 70 °C, 72 h. (d) TFA (90%), room temperature, 5 min.

silyl chloride, the chemoselectivity in the reaction was reversed preferring instead to silylate the axial hydroxyl substituent. So, for example, using a *tert*-butyldimethylsilyl chloride quench, a 1:7 ratio of **134** to **135** was realized, while with *tert*-butyldiphenylsilyl chloride a 1:9 ratio of **136** to **137** was obtained (Scheme 47). Poorer selectivity in these reactions,

Scheme 47[a]

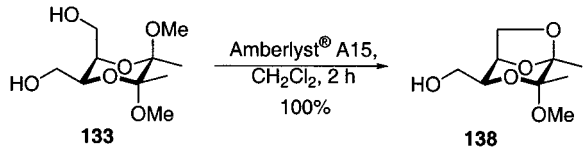


[a] Reagents and conditions: (a) $LiAlH_4$ (1.1 equiv), Et_20, 0 °C, 1 h. (b) imidazole (1.5 equiv), TBSCl (1.0 equiv), DMF, room temperature, 2 h. (c) NaH (1.0 equiv), THF, room temperature then TBSCl (1.0 equiv), 2 h. (d) imidazole (1.5 equiv), TBDPSCl (1.0 equiv), THF, room temperature, 2 h. (e) NaH (1 equiv), THF, room temperature then TBDPSCl (1.0 equiv), 2 h.

however, was observed when other electrophiles such as methyl iodide or benzyl bromide were used in the quenching experiment.

A unique mode of selective protection of the axial substituent was achieved by simply treating **133** with Amberlyst A15 in dichloromethane at room temperature for 2 h, the triol bicyclicacetal **138** being produced in quantitative yield (Scheme 48).

Scheme 48



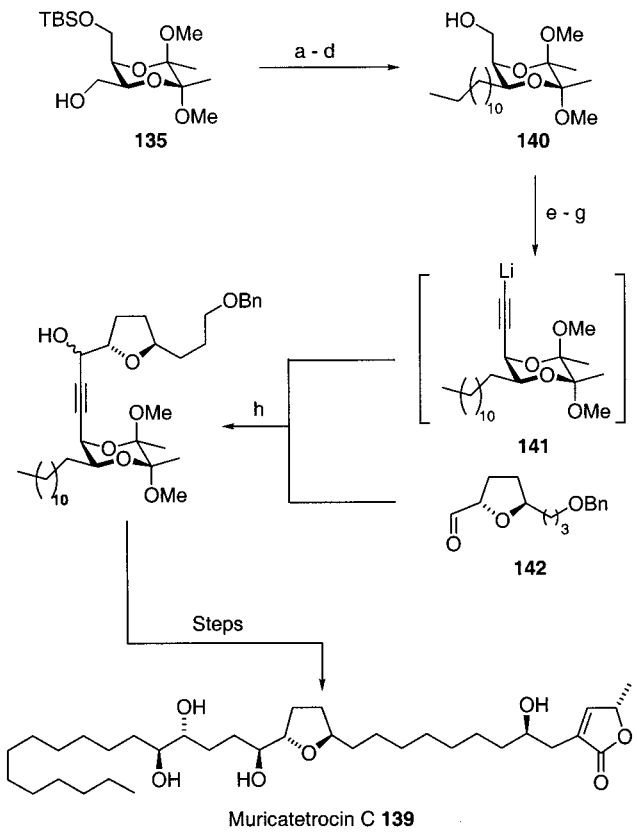
These preliminary studies encouraged us to use (*R*′,*R*′,*S*,*R*)-butane-2,3-diacetal-protected diester **110** and the (*R*′,*R*′,*R*,*S*)-butane-1,2-diacetal-protected diol **133** as building blocks for *anti*-1,2-diol motifs in natural products. Thus, we decided to embark upon the synthesis of the potential antitumor agent muricatetrocin C **139**.[116] This natural product displays an impressive biological profile and shows diverse structural makeup including an *anti*-1,2-diol functionality. The route took advantage of axially silylated alcohol **135** described above. Oxidation of the equatorial alcohol and homologation with ylide followed by hydrogenation and deprotection of the axial TBS group gave alcohol **140**. Oxidation and Corey−Fuchs homologation of the axial aldehyde gave lithium acetylide **141**, which was used directly in an efficient coupling with furanyl aldehyde **142**. Further manipulations and coupling reactions combined with a final trifluoroacetic acid-mediated deprotection afforded the target muricatetrocin C in good overall yield (Scheme 49).

Further work, however, showed that the tartrate-derived building blocks were perfectly suited for the production of polyols containing the *anti*-1,2-diol motif through stereoselective addition of carbon-centered nucleophiles to aldehyde functionality disposed at either axial or equatorial positions on the dioxane ring system.[117] The initial work focused on the use of **143** with the axially disposed aldehyde, which was readily synthesized through the aforementioned selective protection of the equatorial alcohol as the *tert*-butyldimethylsilyl ether followed by Swern oxidation of the residual axial hydroxyl group.

With Grignard reagents, reaction yields ranged from good to excellent with the exception of the hindered isopropyl nucleophile. Diastereoselectivities were generally very good with sp^3-derived reagents, but the control was observed to drop with sp^2 and sp^1 nucleophiles. In all cases the sense of the asymmetric induction is the same and was consistent with addition occurring at the *re*-face to produce alcohols **144**−**147** (Scheme 50).

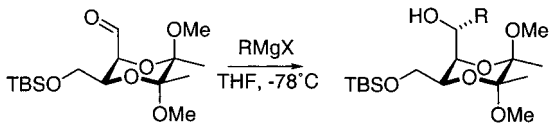
Lewis-acid-mediated nucleophilic additions also proceeded in good yield and with the same stereochemical induction. For example, the reaction with allyl tri-*n*-butylstannane in the presence of zinc(II) chloride afforded the homoallylic alcohol **148** in 88% yield and in >95% de (Scheme 51).

Scheme 49[a]



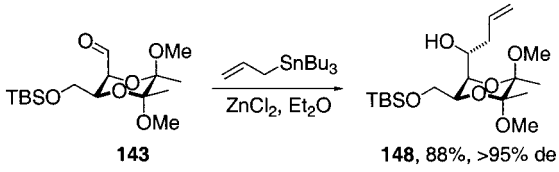
[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then Et_3N, −78 to 0 °C over 30 min. (b) *n*-BuLi, $C_{11}H_{23}PPh_3I$, THF −78 °C, 75% over two steps. (c) RaNi, H_2, EtOH, 20 °C. (d) TBAF, THF, 20 °C, 93% over two steps. (e) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then Et_3N, −78 to 0 °C over 30 min. (f) PPh_3, CBr_4, DCM, 0 °C, 91%. (g) *n*-BuLi (2.0 equiv), THF, 30 min, −78 to 0 °C. (h) −78 °C then **142**, 72%.

Scheme 50



R= Me **144** 94%, 96% de
R= ^{i}Pr **145** 22%, 97% de
R= $CHCH_2$ **146** 71%, 92% de
R= $CCCO_2{}^t$Bu **147** 69%, 85% de

Scheme 51



148, 88%, >95% de

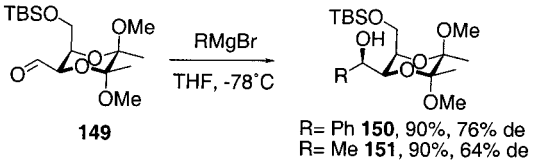
This reliable stereocontrol makes this approach to polyol production attractive in synthesis. More specifically, these reactions yield products, after removal of the BDA group, consisting of a 1,2,3-triol motif with an anti−anti relationship. This type of arrangement is common to many naturally occurring and biologically important substances.

As a direct comparison, studies into stereoselective carbon−carbon bond formation at the equatorially disposed aldehyde in **149** were performed. This

material was readily prepared on multigram scales via selective protection of the axial alcohol as the *tert*-butyldimethylsilyl ether using the method described above, followed by Swern oxidation of the residual equatorial hydroxy group.

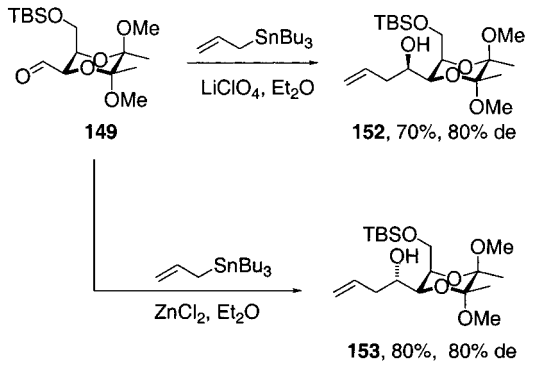
The addition of Grignard reagents, in general, occurred efficiently, and moderate to good diastereomeric excesses were observed where the stereochemistry of the major product was consistent with addition occurring under chelation control. For example, phenylmagnesium bromide at −78 °C in THF gave the benzylic alcohol **150** in 76% de and 90% yield, whereas under analogous conditions, methylmagnesium bromide afforded alcohol **151** in 64% de and also in 90% yield (Scheme 52).[118]

Scheme 52



Similar stereocontrol was observed when allyl tri-*n*-butylstannane was used as the nucleophile and the reaction mediated by lithium perchlorate in diethyl ether. In this example the addition occurred selectively to give homoallylic alcohol **152** in 70% yield and 80% de, mirroring the analogous reactions performed on the isomeric aldehydes derived from the C_2-symmetric building blocks. Surprisingly, when this reaction was repeated using zinc(II) chloride as the Lewis acid, the opposite sense of stereoinduction was observed with the diastereomeric homoallylic alcohol **153** being produced in 80% yield and 80% de (Scheme 53).

Scheme 53



Barring the anomally of the zinc chloride-mediated allyl tri-*n*-butylstannane addition, these results compliment well those of the axially disposed aldehyde and translate into an ability to selectively construct a 1,2,3-triol motif having an anti−syn relationship.

To utilize some of these reactions in synthesis, we have devised a short route to the natural product (+)-aspicilin **154** which contains an anti−syn triol arrangement.[119] The route is similar in concept to that described by Nishioka et al.[120] but makes use of the new chiral building block and stereoselective reactions. First, the equatorial aldehyde **149**, readily-prepared from diester **110,** was reacted with allyl tri-*n*-butylstannane in the presence of lithium perchlorate to give **152** in excellent yield and in a highly stereoselective manner. Following protection of the hydroxyl group with methoxymethyl chloride (MOMCl), removal of the *tert*-butyldimethylsilyl group and subsequent oxidation gave aldehyde **155**. This was immediately reacted with phosphonate **156** under Masamune−Roush conditions to give the product **157**. This compound was subjected to metathesis using the Grubbs catalyst to give the macrolide **158** in 73% yield. Finally, selective hydrogenation and simultaneous deprotection of the MOM and BDA group gave the natural product (+)-aspicilin[121] **154** in excellent yield (Scheme 54).

XIII. Stereoselective Additions to 1,2-Diacetals

As well as functioning as protecting groups for vicinal diols, 1,2-diacetals have been employed as precursors to oxocarbenium ions. Unsurprisingly, the acetal centers of the diacetal protecting group are susceptible to Lewis-acid-mediated cleavage resulting in reactive carbocation intermediates that can be subsequently trapped by suitably nucleophilic reagents.

For example, Pellissier and Santelli reported that treatment of diacetal **5** with allyltrimethylsilane in the presence of titanium tetrachloride leads to the selective formation of *meso*-2,3-diallyl-2,3-dimethyl-1,4-dioxane. Clearly, double addition of the allyl moiety is occurring, and the authors suggest a stepwise process (Scheme 55).[122]

In an extension of the work, Pellissier and coworkers have also shown it possible to use bisallytrimethylsilane in the stereoselective addition reactions. Thus, treatment of **5** with **159** in the presence of titanium tetrachloride at low temperature afforded the diastereomeric bicyclic products **160** and **161** in 1.22:1 ratio and in reasonable yield (Scheme 56).[123]

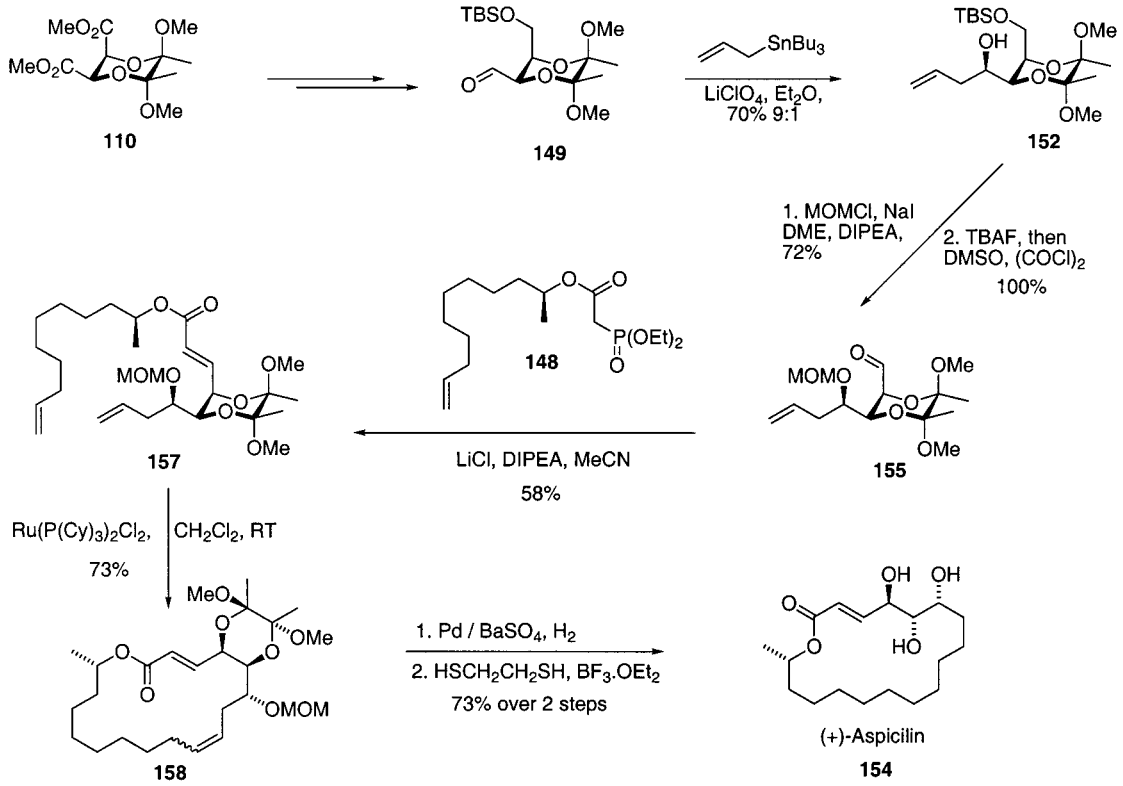
Recently Hanna and Michaut reported a rapid route to oxabicyclo[4.2.1]nonene systems using the stereoselective allylation of carbocation intermediates derived from 1,2-diacetals as a key step. Thus, treatment of enol ether derivative **162** with *m*-CPBA afforded acetal **163**, which when treated with excess allyltrimethylsilane in the presence of titanium tetrachloride afforded bis-allyl species **164** as a single diastereoisomer. Subsequent ring-closing metathesis afforded the desired products in good yield (Scheme 57).[124]

XIV. Total Synthesis of Okadaic Acid

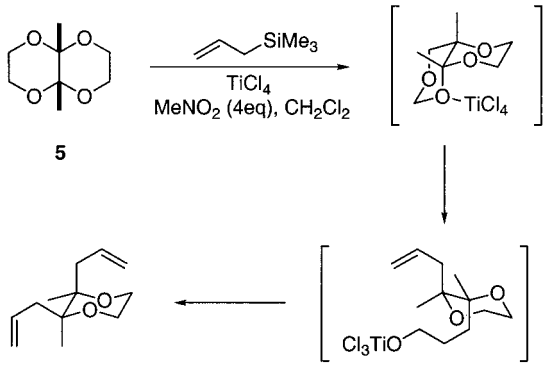
During the total synthesis of the potent protein phosphatase inhibitor okadaic acid **165**, a synthetic plan was conceived that required the preparation of a C15−C26 central fragment **166** (Scheme 58).[125] This was then coupled with two other units **167** and **168** to assemble the full carbon backbone of the natural product. Final functional group manipulation and deprotection gave okadaic acid.

In practice, the synthesis of the central fragment was readily achieved from penta-*O*-acetyl α-D-mannopyranose **169** as a readily available starting mate-

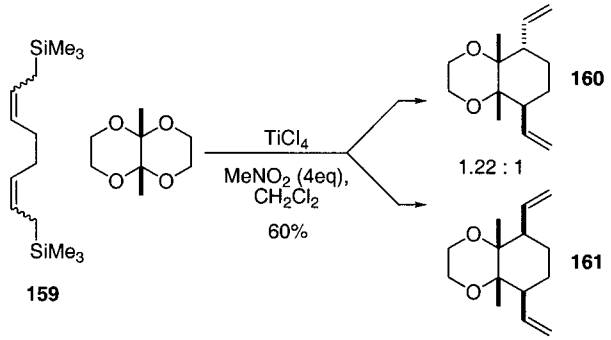
Scheme 54



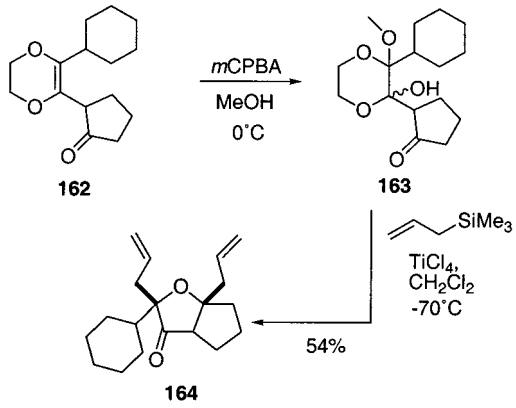
Scheme 55



Scheme 56



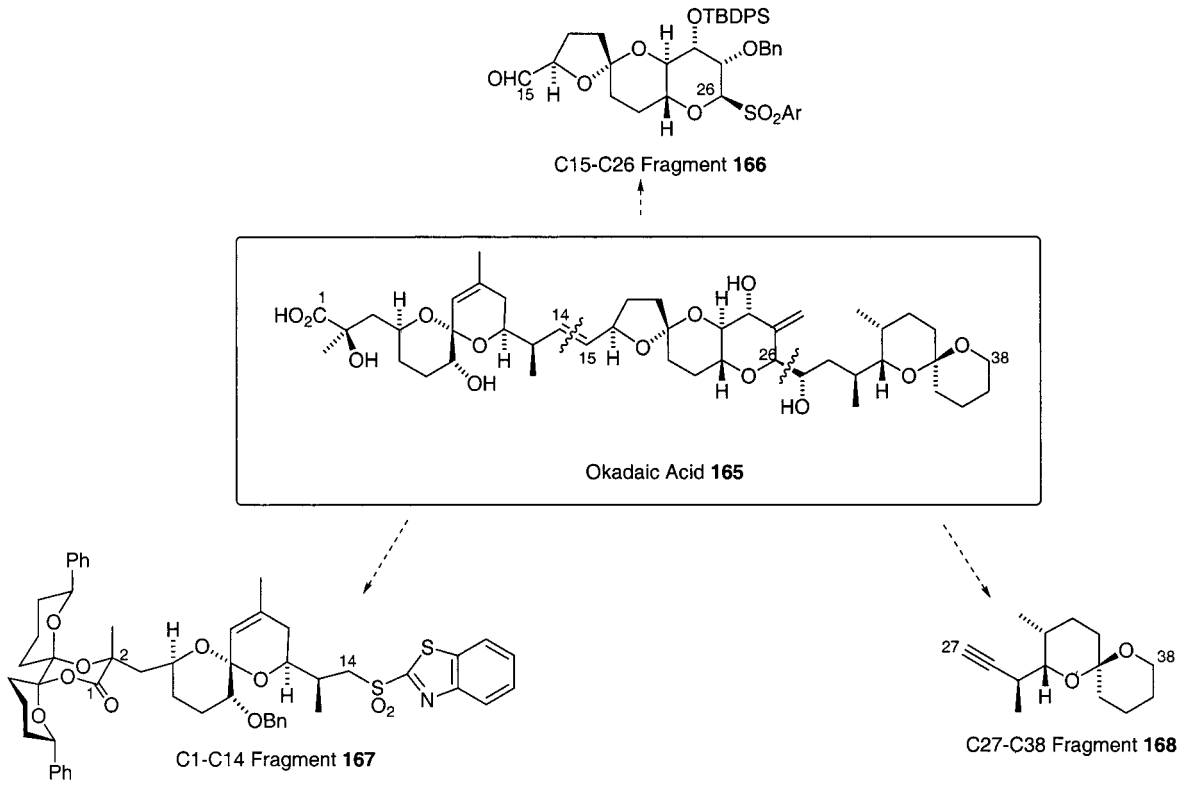
Scheme 57



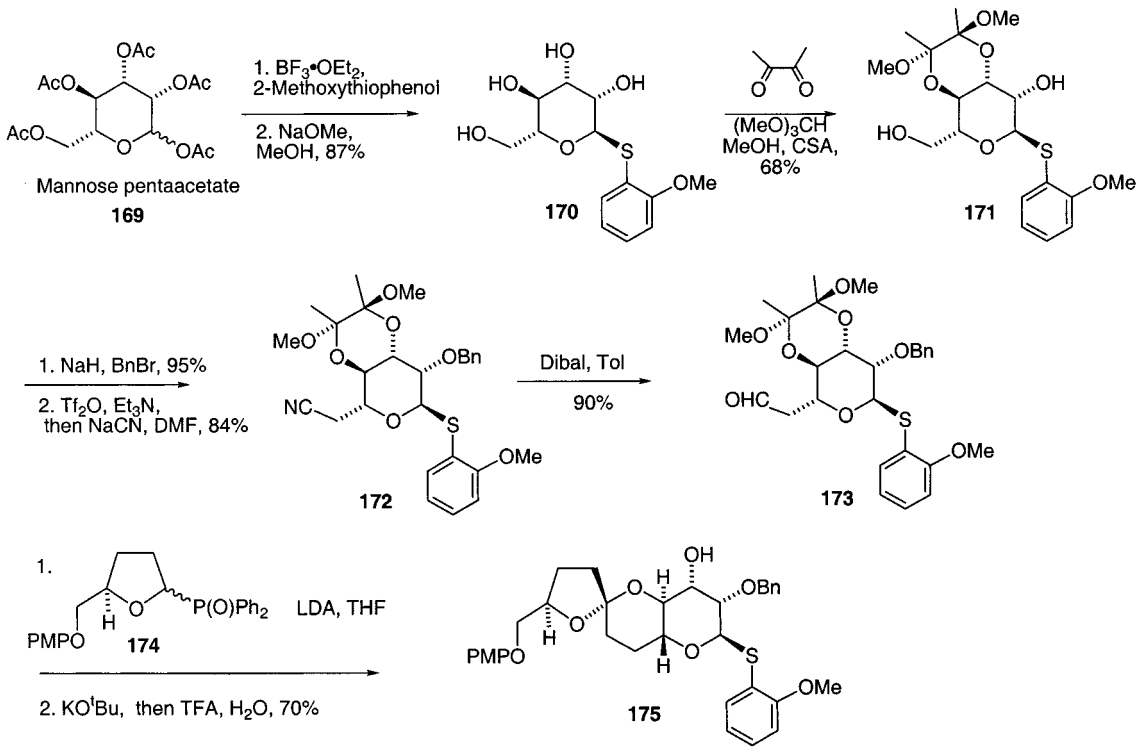
rial. Following anomeric exchange and removal of the acetate groups, a tetraol **170** was produced which then required the selective protection of the diequatorial 3,4-diol. This was readily achieved in 68% yield using the standard protocol to give corresponding to the BDA derivative **171** (Scheme 59). Following selective benzylation of the axial hydroxyl and homologation to nitrile **172**, a diisobutylaluminum hydride reduction afforded aldehyde **173**. Horner–Wittig coupling of this material to the anomeric position of furan derivative **174** followed by workup with trifluoroacetic acid spontaneously removed the BDA group and spirocyclized to give **175**. This was then readily transformed to the required central coupling fragment **166** in only a few steps (Scheme 59).

This synthesis impressively demonstrates the power of using this diacetal methodology to cut down on the number of protection steps that would be normally necessary in the selective conversion of the tetraol derivative **170** but also shows that the deprotection sequence of the BDA group with trifluoroacetic acid can be usefully combined with other key chemical steps such as spirocyclization. This synthesis also showcased the use of the dispiroketals (themselves 1,2-diacetals) to assemble the C1–C14 fragment of okadaic acid. Here, the spiroketal was used to install the necessary α-hydroxy acid stereogenic center at

Scheme 58



Scheme 59



C-2 but also acted as a protecting group which was removed at the last step of the synthesis using calcium in liquid ammonia.[125]

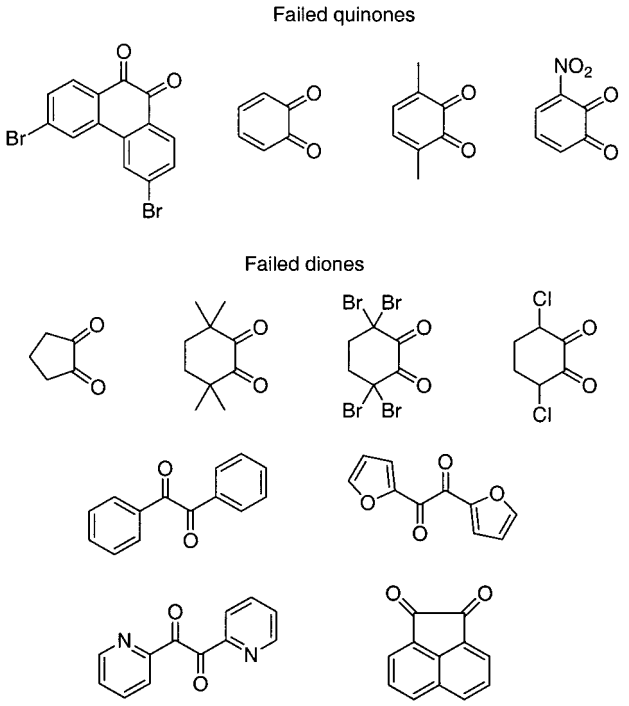
XV. Conclusions and Limitations

In this review we have tried to indicate how 1,2-diacetals have been used in a number of synthetic applications ranging from selective 1,2-diequatorial diol protection and reactivity control in oligosaccharide coupling reactions to rigidifying templates and their use in chiral memory protocols. Several applications of these systems to natural product synthesis were reported, but we can envisage many more applications in the future, particularly as the necessary starting materials and building blocks become commercially available.

It is pertinent however to comment on some generalities of the use of 1,2-diacetals and to point out the failures as well as the successes. First, although we have commented earlier on the use of phenanthrene-9,10-quinone as a 1,2-diol protecting agent through its corresponding diacetal, the difficulty in removing this at the end of a synthesis sequence is a serious problem. We therefore advise the best compromise is to use either the cyclohexanone-1,2-diacetal (CDA) or the butane-1,2-diacetal (BDA) protocols since these usually give the best set of desirable features. The CDA derivatives are often highly crystalline and usually do not require chromatography. They are stable but can be deprotected readily. They are also able to withstand a wide variety of reaction types such as oxidation, Wittig olefination, silylation, hydrogenation, and elimination.

By contrast, the BDA derivatives are usually isolated as solids rather than highly crystalline materials but have very desirable NMR features that help analysis of the products since the methyl groups act as useful diagnostic markers. As with CDA, BDA groups are readily removed at the end of the synthesis sequence.

It should also be appreciated that a large number of quinones and 1,2-diones as precursors for 1,2-diacetals have been investigated that have failed to react or lead to only monoacetals. These failures are listed below



Despite these failures, which reflect either steric or electronic limitations, cyclohepta-1,2-dione and cyclobutane-1,2-dione do react well to form the corresponding1,2-diacetal products (see Table 5). However, these 1,2-diacetal adducts offer no advantages in either reactivity tuning or selectivity. While the CDA and BDA groups have generally performed well under a wide variety of conditions as noted in this review, in an isolated example Falck reports that with bis-BDA-protected inositol derivatives that additionally contain phosphates, some migration/loss was detected upon attempted acetal hydrolysis.[126] This was not a problem however in the GPI work discussed earlier in this review. Rapid hydrolysis is therefore recommended in cases where functional group migration is a potential problem.

In the vast majority of this review the 1,2-diacetals have been prepared in alcohol (usually methanol) solution. This is usually acceptable for most substrates; however, if particular problems of insolubility occur, then we would suggest that the use of bis-dihydropyrans to form dispiroketals could be an alternative since these can be formed in other solvents (e.g., $CHCl_3$, CH_2Cl_2, toluene).

Overall, however, we feel that 1,2-diacetals offer an attractive new approach to diol protection.[127] Current work underway will extend these concepts into many new areas in the future.

XVI. References

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