The conformational rigidity of butane-1,2-diacetals as a powerful synthetic tool†‡§

Emilio Lence, Luis Castedo and Concepción González-Bello*

Received 20th March 2008
First published as an Advance Article on the web 17th June 2008
DOI: 10.1039/b717902b

Butane-1,2-diacetals are selective protecting groups for *trans*-diequatorial-1,2-diols and have been widely used in carbohydrate chemistry. The scope of diacetal protection has been extended more recently to include other important hydroxylated chiral templates containing *trans*-1,2-diols, such as quinic and shikimic acids, the protection of which as diacetals leads to a strong conformational rigidity that induces excellent diastereoselectivity control. In addition, the chiral information stored in the diacetal backbone has also been exploited in the synthesis of important building blocks, such as glycerate, glycolate and tartrate diacetal derivatives. In this *critical review*, the synthetic power of the conformational rigidity and the chirality stored in the diacetal backbone is described. This phenomenon will be illustrated with recent examples of applications in the synthesis of natural products or biologically interesting compounds (80 references).

Introduction

Carbohydrates are cheap and widely used starting materials that are suitable for the synthesis of very complex molecules.[1–3] The use of these materials in synthetic chemistry usually requires the selective protection of their hydroxyl groups and, in this respect, a wide range of protecting groups has been developed.[4,5] The selective protection of primary and anomeric hydroxyl groups is normally easy to achieve, although secondary hydroxyl groups, which are frequently present in similar environments, are more complicated systems. In this context, several protecting groups have been developed for the selective protection of *cis*-1,2-diols, with acetals probably being the most widely used. Until a few years ago, the selective protection of cyclic *trans*-1,2-diols could only be achieved using disiloxanyl protecting groups, which can easily accommodate a *trans*-fusion by forming a seven-membered cycle.[6] However, this type of protecting group is often incompatible with conventional transformations in carbohydrate chemistry. A solution to this problem was finally provided by Ley's group with the development of diacetals.[7,8]

More importantly, the synthetic applications of diacetals proved not to be limited to the selective protection of *trans*-diequatorial-1,2-diols alone. Especially remarkable is their use in oligosaccharide synthesis for the control of glycosidation diastereoselectivity and the donor/acceptor reactivity. Both of these findings have been extensively exploited and reviewed by Ley's group and others in the synthesis of a wide range of complex oligosaccharides.[8,9] More recently, the scope of diacetal protection has been extended to other important hydroxylated chiral templates containing *trans*-1,2-diols, such as

Laboratorio de Química Orgánica (CSIC) y Departamento de Química Orgánica, Facultad de Química, Universidad de Santiago de Compostela, Avenida de las Ciencias s/n, 15782 Santiago de Compostela, Spain. E-mail: cgb1@usc.es; Fax: +34 981 595012; Tel: +34 981 563100

† This work was supported by the Xunta de Galicia (PGIDIT05RAG20901PR, PGIDT07PXIB209080PR and GRC2006/132) and the Spanish Ministry of Education and Culture (SAF2007-63533).

‡ In memory of Rafael Barca.

§ Electronic supplementary information (ESI) available: ^{1}H NMR spectra of compounds **25** and **74** as well as ^{13}C NMR spectra of compound **25** are provided. See DOI: 10.1039/b717902b

Emilio Lence

Emilio Lence was born in Sarria, Galicia, Spain. He graduated in chemistry in 2000 from the University of Santiago de Compostela. Since 2001, he has been a PhD student under the supervision of Dr Concepción González-Bello and Professor Luis Castedo, working on solid-phase synthesis and diacetal chemistry.

Concepción González-Bello

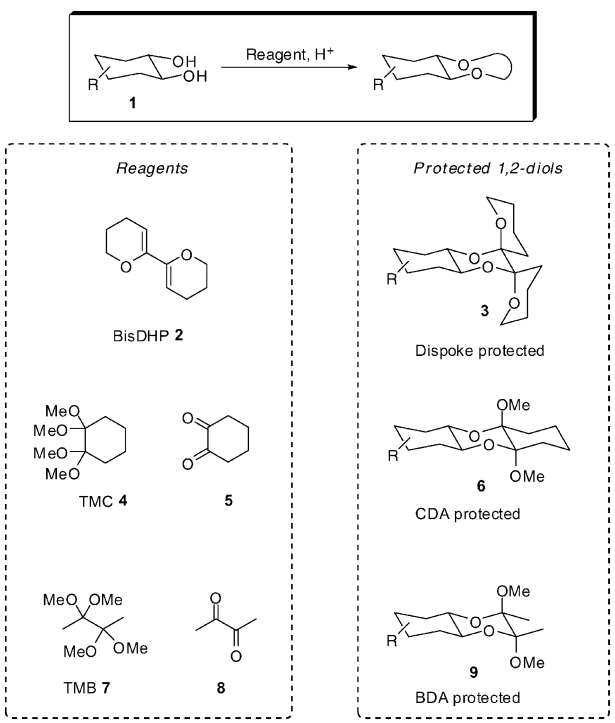
Concepción González-Bello obtained her PhD in organic chemistry in 1994 from the University of Santiago de Compostela, Spain. She undertook postdoctoral studies on catalytic antibodies and mechanistic studies on dehydroquinase enzymes at the University of Cambridge. She is now a lecturer in organic chemistry at USC. Her research interests include carbohydrate chemistry, solid-phase synthesis and enzyme inhibition.

quinic and shikimic acids, the protection of which as diacetals leads to a strong conformational rigidity that induces excellent diastereoselectivity control. This stereoselectivity has been successfully used in the synthesis of natural products and biologically interesting compounds and this will be the main topic of this review. In addition, the chiral information stored in the diacetal backbone has been exploited in the synthesis of important building blocks, such as glycerate and tartrate diacetal derivatives. This type of derivative has shown excellent facial stereoselectivity that has been exploited in the total synthesis of diverse natural products. The most relevant synthetic uses of diacetals of this type as building blocks will be highlighted.

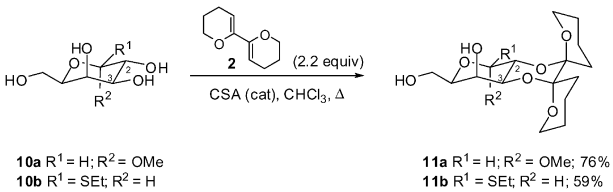
Diacetals as selective protecting groups for diequatorial-1,2-diols: an overview

In 1992, Ley and co-workers discovered that cyclic diequatorial-1,2-diols **1** can be selectively protected as dispiroacetals **3** by treatment with bis-3,4-dihydropyran (**2**, BisDHP) under acid-catalyzed conditions (Scheme 1).[10] For instance, treatment of α-D-galactopyranosides **10** with an excess of BisDHP (**2**) in refluxing chloroform and in the presence of a catalytic amount of camphorsulfonic acid affords dispoke derivatives **11** in moderate to good yields (Scheme 2).

However, the synthetic utility of the dispoke protection in carbohydrate chemistry[8] is partially limited by the high cost of BisDHP (**2**),[7] which is prepared by the oxidative dimerization of 6-lithio-3,4-dihydro-2*H*-pyran, by its limited shelf-life and also by the low solubility of some polyhydroxylated compounds, like sugars, in the required reaction solvents (*e.g.* chloroform or toluene). Two years later the same group



Scheme 1 Protecting groups for diequatorial-1,2-diols and the corresponding protected products.



10a R^1 = H; R^2 = OMe
10b R^1 = SEt; R^2 = H

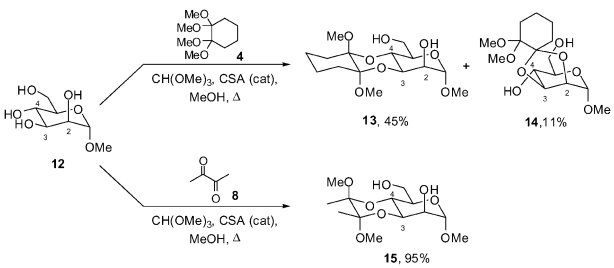
11a R^1 = H; R^2 = OMe; 76%
11b R^1 = SEt; R^2 = H; 59%

Scheme 2

reported the cheaper, more easily synthesized and now commercially available 1,1,2,2-tetramethoxycyclohexane (**4**, TMC) as a good alternative to BisDHP (**2**) (Scheme 1).[11] TMC (**4**), which is easily prepared from cyclohexane-1,2-dione (**5**), affords cyclohexane-1,2-diacetals **6** (CDA) in higher yields than dispoke and also allows the use of more polar solvents such as methanol or *N,N*-dimethylformamide, which usually led to decomposition of BisDHP (**2**).[11] For example, the reaction of methyl α-D-mannopyranoside (**12**) with TMC (**4**) in boiling methanol in the presence of trimethyl orthoformate and a catalytic amount of camphorsulfonic acid affords the corresponding cyclohexane diacetal **13** in 45% yield together with 11% of the corresponding *cis*-2,3-protected product **14** (Scheme 3).[12]

Later, it was shown that the simpler and cheaper 2,2,3,3-tetramethoxybutane (**7**, TMB) is also an efficient selective protecting group for diequatorial-1,2-diols, providing butane-2,3-diacetals **9** (BDA) in good to excellent yields.[13] Soon after, TMC (**4**) and TMB (**7**) were replaced by their corresponding synthetic precursors, cyclohexane-1,2-dione (**5**) and 2,3-butanedione (**8**), and methanol.[14,15] For instance, the reaction of commercially available butane-2,3-dione (**8**) with methyl-α-D-mannopyranoside (**12**) in boiling methanol, with a catalytic amount of camphorsulfonic acid, gave the corresponding butane diacetal **15** in 95% yield (Scheme 3).[15]

The high selectivity demonstrated in the protection of diequatorial-1,2-diols as diacetals is attributed to a combination of two factors. Firstly, the formation of the sterically less demanding *trans*-ring junction and, secondly, the stabilization by anomeric effects affording the most stable 1,4-dioxane derivative which has two oxygen atoms located in the axial positions of the 1,4-dioxane ring (Fig. 1). Similar protection for *cis*-1,2-diols would lead to derivatives that would suffer steric hindrance, forcing the 1,4-dioxane ring to flatten and therefore leading to the partial loss of the anomeric stabilization. Some examples of this high selectivity are summarized in Table 1. In most cases *trans*-protection occurs, with exceptions including *arabino* and *rhamno* derivatives (entries 4 and 6), in which *cis*-protection is also obtained.



Scheme 3

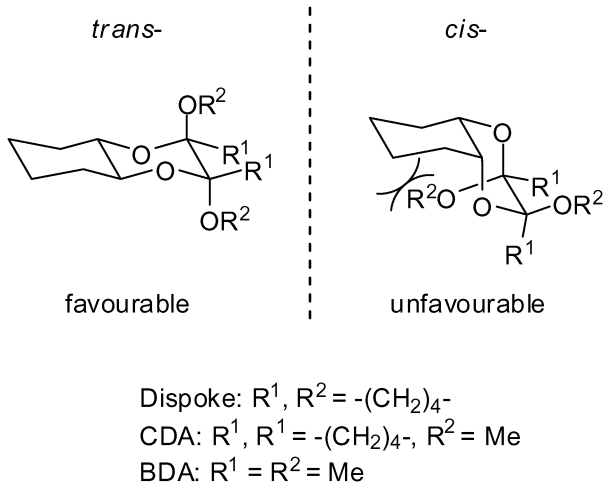


Fig. 1 Major conformers of a *trans*- and a possible *cis*-1,2-diol protection.

Typical diacetal formation reaction conditions involve heating a methanol solution of the 1,2-diol and the 1,2-diketone or its corresponding tetramethoxyketal under reflux in the presence of a catalytic amount of a protic acid, such as sulfuric or camphorsulfonic acids. Milder reaction conditions using Lewis acids have also been investigated. For example, the use of boron trifluoride diethyl etherate as a catalyst at room temperature provides better yields for the protection of *manno* **12** and *galacto* **16** derivatives (Table 2, entries 1 and 2) than the standard protic conditions.[15] However, relatively poor yields were obtained for the protection of similar *arabino* **17** and *fuco* **18** substrates (entries 3 and 4).

On the other hand, trimethylsilyl methyl ether (TMSOMe) in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as a catalyst smoothly protects *trans*-cyclohexane-1,2-diol (**19**) at 0 °C to give diacetals **21** in high yields (Table 3).[20] The use of the conventional protic method leads to monoacetalization of the more external ketone in ketones **20a**, **20d** and **20e** (Table 3, entries 2, 5–6); ketones **20b** and **20c** (entries 3 and 4) undergo monoacetalization with concomitant β-elimination and intramolecular cyclization, respectively; ketones **20f** and **20g** do not react under these conditions (entries 7 and 8). Use of the TMSOMe–TMSOTf method gives high yields of the corresponding diacetals **21** in all cases.

BDA-protected chiral templates: quinic and shikimic acids

1. BDA-protected quinic acid

The rich functionality present in (−)-quinic acid (**22**), as well as its relatively low cost and ease of isolation from plants in its enantiopure form, make it an attractive optically active precursor for the synthesis of a wide range of compounds.[21] Quinic acid (**22**) has two equatorial hydroxyl groups and these can be selectively protected as butane-1,2-diacetals (Scheme 4). Initially, protection was reported from methyl quinate by treatment with tetramethoxybutane, trimethyl orthoformate and methanol in the presence of a catalytic amount of camphorsulfonic acid.[13] However, it was subsequently shown that protection of the 4,5-diequatorial hydroxyl groups of (−)-quinic acid (**22**) with concomitant esterification of its carboxylic acid could be carried out in one pot under similar reaction conditions to afford diacetal **23** in excellent yield.[22]

The protected BDA quinic acid derivative **23** proved to be a useful starting material in the synthesis of several competitive inhibitors of 3-dehydroquinate (DHQ) synthase and dehydroquinase (DHQase) (Scheme 5).[23] These enzymes operate in the shikimic acid pathway, which is the biosynthetic route to the aromatic amino acids L-phenylalanine, L-tryptophan and L-tyrosine, as well as the precursors to the folate coenzymes, alkaloids and vitamins.[24] This pathway is present in bacteria, fungi, plants, and has recently been discovered in apicomplexan parasites, but is absent in mammals, and has been considered an attractive target for the development of new herbicides and antimicrobial agents.

Frost and co-workers[23] synthesized a series of potent competitive inhibitors of the enzyme 3-dehydroquinate synthase, the C-3 quinic acid derivatives **28**, **31**, **34–35** and **37** (Scheme 6), using ketone **25** as the key intermediate, which is readily prepared by oxidation of the remaining secondary alcohol of BDA-protected quinic acid **23**. Conversion of ketone **25** into the designed 3*S* inhibitors **28**, **31**, **34–35** and **37** was achieved by diastereoselective reduction of the rigid ketone **25** or its malonic acid derivative **32** as the key step. The diastereoselectivity of the reduction is controlled by complexation of the reducing agent with the free C-1 tertiary hydroxyl group, which causes the reduction to take place from the same side.

The versatility of the protected quinic acid derivatives **25** and **29** was further demonstrated with the synthesis of several competitive inhibitors of dehydroquinase (DHQase), derivatives **41–42** and **45–46** (Scheme 7).[25] For example, vinyl fluoride **41** and difluoride **42** were prepared from protected ketone **38**,[23] which was obtained by protection of the tertiary hydroxyl group of **25** as the methoxymethyl (MOM) ether.[26] Reaction of ketone **38** with DAST afforded a mixture of vinyl fluoride **39** and difluoride **40**. Deprotection and hydrolysis of the fluorinated derivatives **39** and **40** led to vinyl fluoride **41** and difluoride **42**, respectively. On the other hand, the synthesis of C-3 derivatives **45** and **46** was achieved from allyl ether **43**, which was obtained from epimeric BDA-protected quinic acid **29**.[27] Regioselective allylation of the equatorial alcohol of **29** by treatment with allyl methyl carbonate and a catalytic amount of Pd(0) gave the allyl ether **43**.

Dihydroxylation of alkene **43** using a catalytic amount of osmium tetroxide with concomitant lactonization afforded lactone **44** as a 1.2 : 1 mixture of diastereoisomers. Acidic removal of the bismethoxyacetal group and subsequent hydrolysis of the lactone under basic conditions, followed by protonation using Amberlite IR-120 (H^+) provided dihydroxylated acid **45** as a 1.2 : 1 mixture of epimers at C-2′. The deprotection and hydrolysis of **43** in a similar way to obtaining compound **45** from **44** afforded allyl derivative **46**.

The BDA-protected ketone **25** was also the starting material in the synthesis of various conformationally restricted spiro carba-sugars **49** (Scheme 8).[28] The spirocyclic framework of these compounds was constructed by ring-closing metathesis from compound **47**, a readily available diallyl keto derivative

Table 1 Protection of several monosaccharides and inositols with dispoke, CDA and BDA

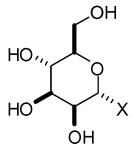
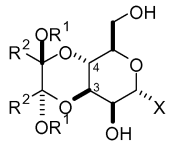
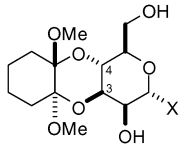
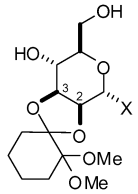
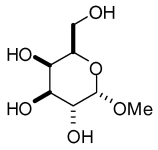
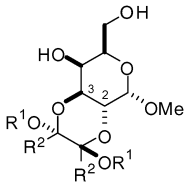
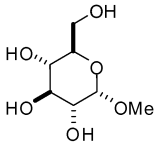
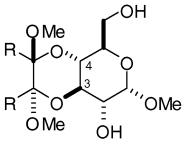
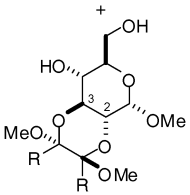
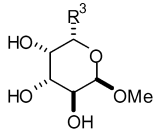
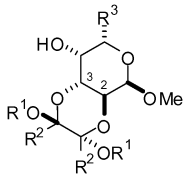
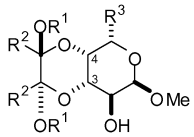
Entry	Substrate	Protected products *trans*	*cis*	Yield (%)	Ratio *trans* : *cis*	Ref.
1	 *D-Manno*		—	36 [X = SEt; R^1, R^2 = –$(CH_2)_4$–] 45 [X = OPent; R^1, R^2 = –$(CH_2)_4$–] 95 (X = OMe; R^1 = R^2 = Me)	1 : 0 1 : 0 1 : 0	16 16 15
				59 (X = OMe) 63 (X = SEt)	4.4 : 1 5.3 : 1	11 11,12
2	 *D-Galacto*		—	46 [R^1 = Me; R^2, R^2 = –$(CH_2)_4$–] 54 [R^1 = R^2 = Me (α : β 10 : 1)] 76 [R^1 = R^2 = Me]	1 : 0 1 : 0 1 : 0	11 13 10
3	 *D-Gluco*	 	—	80 [R, R = –$(CH_2)_4$–] (3 : 5) 82 (R = Me) (1 : 1)	1 : 0 1 : 0	11,12 13
4	 *L-Fuco* (R^3 = Me)/ *L-Arabino* (R^3 = H)			76 [R^1, R^2 = –$(CH_2)_4$–; R^3 = Me] 98 [R^1, R^2 = –$(CH_2)_4$–; R^3 = H]	1 : 0 3 : 2	16 16

Table 1 (*Continued*)

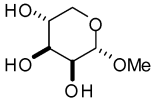
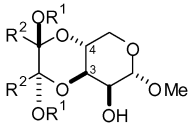
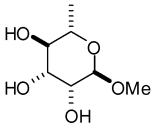
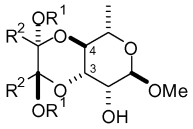
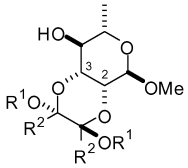
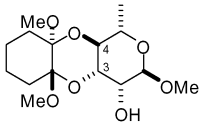
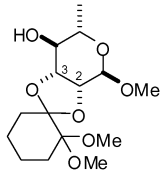
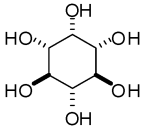
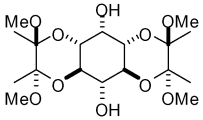
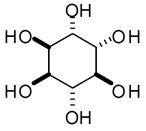
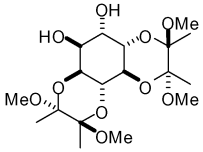
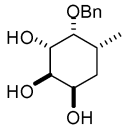
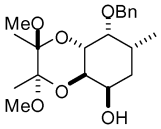
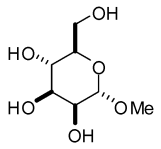
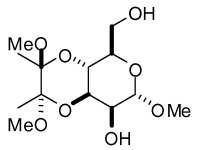
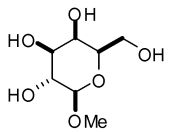
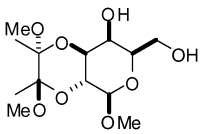
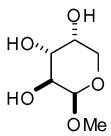
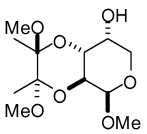
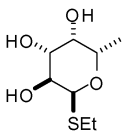
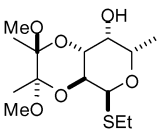
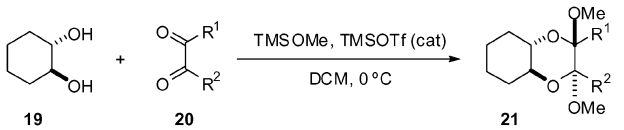
Entry	Substrate	Protected products *trans*	*cis*	Yield (%)	Ratio *trans* : *cis*	Ref.
5	 *D-Lyxo*		—	62 [R^1, R^2 = –$(CH_2)_4$–] 83 (R^1 = R^2 = Me)	1 : 0 1 : 0	16 13
6	 *L-Rhamno*			79 [R^1, R^2 = –$(CH_2)_4$–] 81 (R^1 = R^2 = Me)	3 : 2 1 : 0	16 13
				82	9.3 : 1	11,12
7			—	79	1 : 0	13,17
8			—	97	1 : 0	18
9			—	94	1 : 0	19

Table 2 $BF_3{\cdot}OEt_2$-catalyzed BDA protection[a15]

Entry	Starting material	Product	Method, Yield (%)
1	 **12**		A, 95% B, 99%
2	 **16**		A, 80% B, 85%
3	 **17**		B, 42%
4	 **18**		A, 80% B, 14%

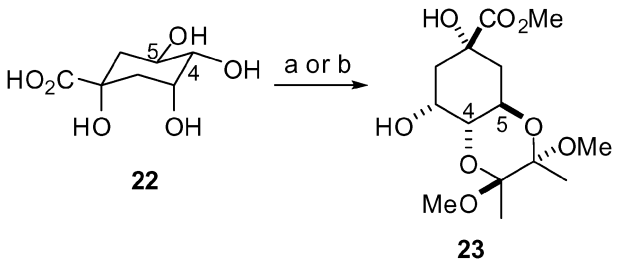
[a] Method A: $(MeCO)_2$ (**8**), $CH(OMe)_3$, CSA (cat.), MeOH, Δ; Method B: $(MeCO)_2$ (**8**), $BF_3{\cdot}OEt_2$ (cat.), $CH(OMe)_3$, MeOH, RT.

Table 3 The TMSOTf-catalyzed formation of 1,2-diacetals from various α-diketones[20]



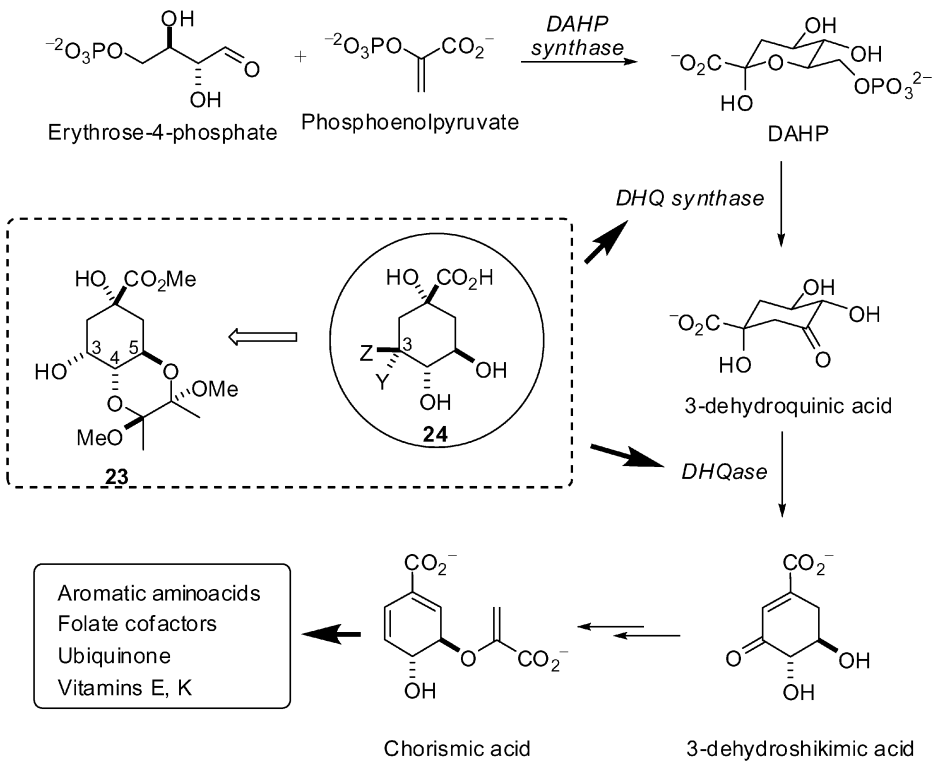
19 **20** **21**

Entry	Ketone	R^1	R^2	**21**, Yield (%)
1	**8**	Me	Me	97
2	**20a**	Et	Me	97
3	**20b**	Me	$-(CH_2)_2OBn$	83
4	**20c**	Me	$-(CH_2)_2OBz$	95
5	**20d**	Me	$-(CH_2)_3OBn$	93
6	**20e**	Me	$-(CH_2)_3OBz$	85
7	**20f**	Me	Ph	86
8	**20g**	Ph	Ph	99
9	**5**	$-(CH_2)_4-$		70

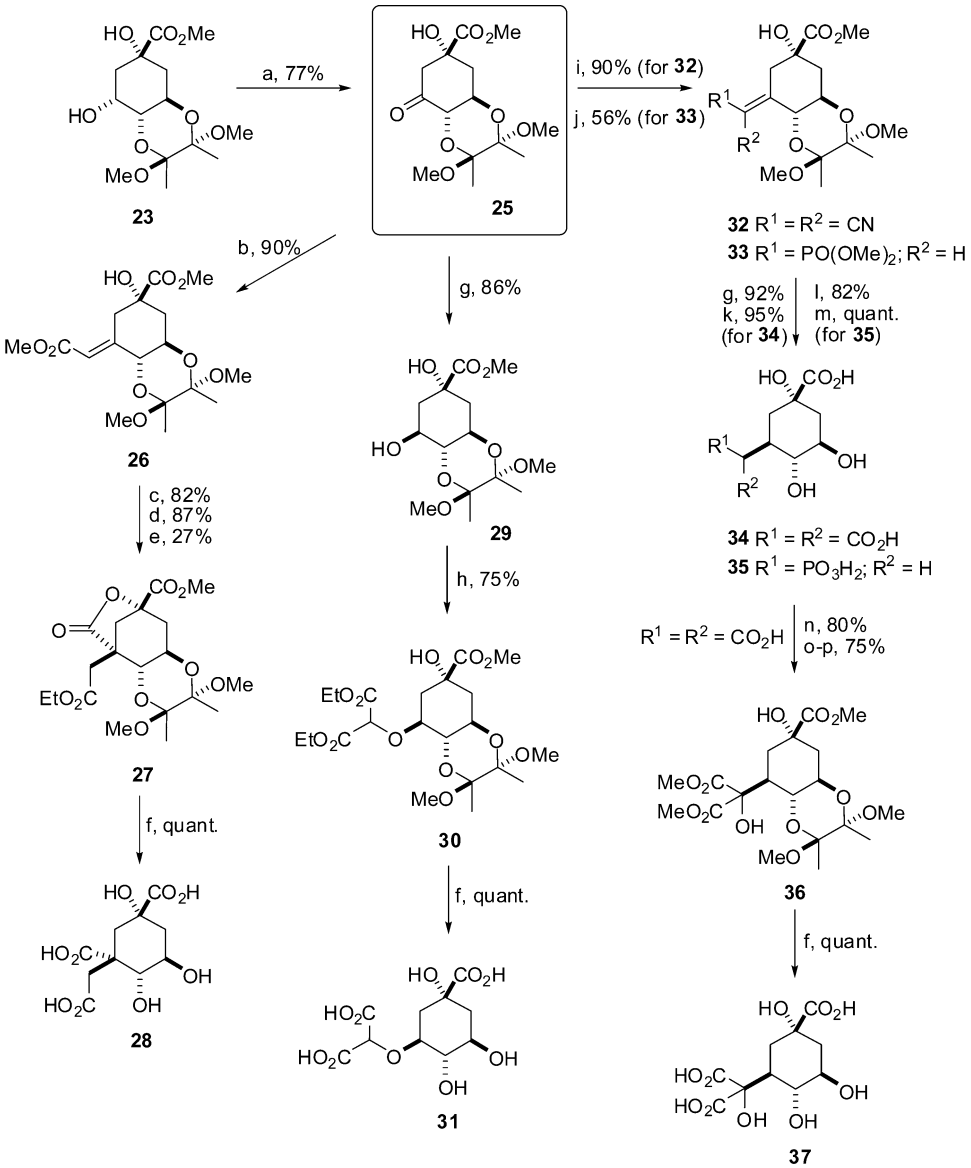


22 **23**

Scheme 4 *Reagents and conditions*: (a) 1. MeOH, Dowex 50 (H^+), Δ (87%); 2. TMB (**7**), CSA (cat.), MeOH, $CH(OMe)_3$, Δ (79%); (b) $(MeCO)_2$ (**8**), CSA (cat.), MeOH, $CH(OMe)_3$, Δ (90%).



Scheme 5 The shikimic acid pathway. DHAP = 2-deoxy-D-arabino-heptulosonic acid-7-phosphate.

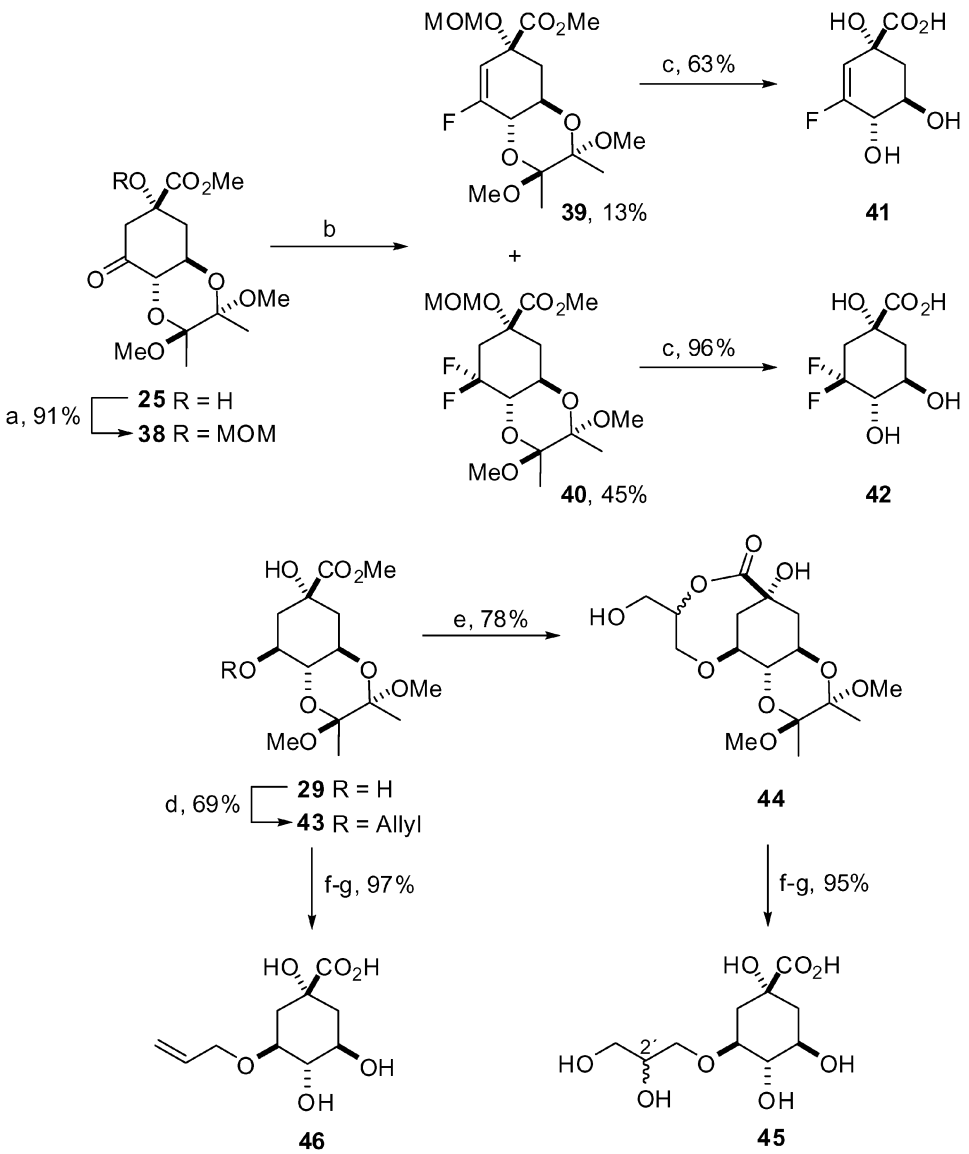


Scheme 6 *Reagents and conditions*: (a) KIO_4, K_2CO_3, $RuCl_3$, H_2O, $CHCl_3$; (b) $Ph_3P{=}CHCO_2Et$, MeCN, Δ; (c) Im_2CO, DCE, Δ; (d) PhSeH, DCE, Δ; (e) Bu_3SnH, AIBN, PhH, Δ; (f) 1. TFA–H_2O; 2. NaOH, THF; 3. Dowex 50 (H^+); (g) $NaBH(OAc)_3$, MeCN, HOAc, RT; (h) $N_2{=}C(CO_2Et)_2$, $Rh_2(OAc)_4$, PhH, Δ; (i) $CH_2(CN)_2$, NH_4OAc, HOAc, PhH; (j) ^{n}BuLi, $CH_2(PO(OMe)_2)_2$, THF, −78 °C to RT; (k) 1. TFA–H_2O; 2. HCl, Δ; 3. NaOH, THF; 4. Dowex 50 (H^+); (l) H_2, 10% Pd/C, EtOAc; (m) HCl, Δ; (n) 1. CH_2N_2, Et_2O, MeOH; 2. TMB, CSA (cat.), MeOH, $CH(OMe)_3$, Δ; (o) ^{t}BuOK, THF, 0 °C; (p) 2-(benzenesulfonyl)-3-phenyloxaziridine, THF, −78 °C.

of (−)-quinic acid. The rich functionality of the resulting spiro ketone **48** was exploited for the diastereoselective synthesis of various spiro carba-sugars **49**, four of which are polyhydroxylated and two aminopolyhydroxylated.

The strategy involved the preparation of diallyl ketone **47**, which was initially carried out *via* ketone **51**[29] to afford diallyl ketone **47** in 56% yield (Scheme 9). It was observed that ketone **25** easily undergoes β-elimination reactions without the need for conversion of the tertiary hydroxyl group into a good leaving group. Therefore, the synthesis of diallyl ketone **47** was carried out by adding allyl bromide to the enolate generated *in situ* using trimethylsilyloxy ketone **50**,[23] an approach that afforded cleaner reaction mixtures than ketones **25** and **51** and a better overall yield of diallyl ketone **47**. Ring-closing metathesis of diallyl ketone **47** with second-generation Grubbs' catalyst afforded an almost quantitative yield of spiro ketone **48**. Reduction of the C=C double bonds and methyl ester and replacement of the ketone group with a hydroxy or amino group led to target compounds **49a–d**, while compounds **49e–g** were obtained by diastereoselective *cis*-dihydroxylation of the cyclopentene double bond, reduction of the cyclohexene double bond (**49e** only) and the ketone group. These compounds were studied for inhibition against various commercially available glycosidases and the results showed that amino spiro carba-sugar **49c** is a moderate inhibitor of *β*-galactosidase.

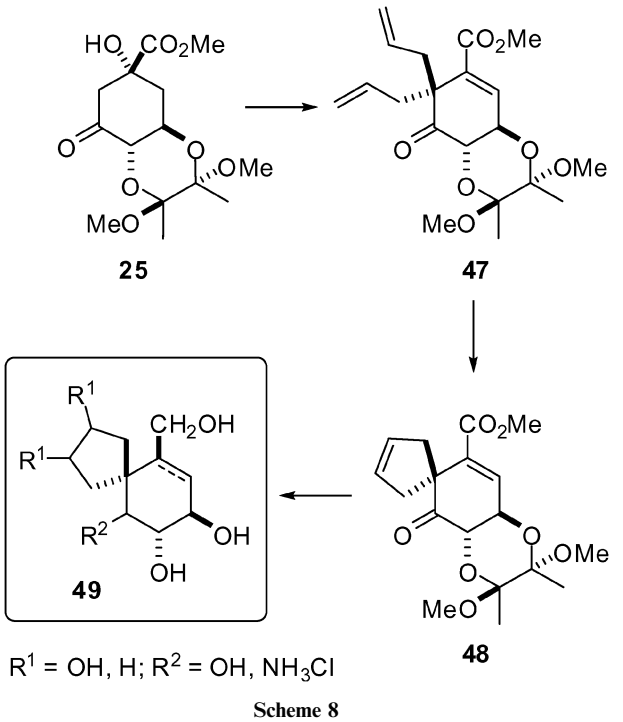
The conformationally rigid *trans*-1,2-diol protected alkene **53** derived from (−)-quinic acid (**22**) proved to be a useful



Scheme 7 *Reagents and conditions*: (a) $CH_2(OMe)_2$, P_2O_5, $CHCl_3$, RT; (b) DAST, DME, Δ; (c) 1. TFA–H_2O, 60 °C; 2. NaOH, RT; 3. Amberlite IR-120 (H^+); (d) allylOCO_2Me, $Pd_2(dba)_3$, dppb, THF, Δ; (e) OsO_4 (cat.), NMO, dioxane–H_2O, RT; (f) TFA–H_2O (20 : 1), RT; (g) 1. LiOH, RT; 2. Amberlite IR-120 (H^+).

synthetic building block in the regio- and diastereoselective synthesis of amino carba-sugar **55a**, a positional stereoisomer of a potent glycosidase inhibitor, valiolamine, its corresponding polyhydroxy-γ-amino acid **55b** as well as polyhydroxycyclohexanes **55c–d** (Scheme 10).[30–32] The synthesis of these compounds was achieved by diasteroselective epoxidation of a double bond and subsequent azidolysis or hydrolysis. Thus, BDA protection of diol **52**, readily prepared in four steps from (−)-quinic acid (**22**), followed by epoxidation of the resultant alkene **53** at the *Re* face—the less hindered face—led to oxirane **54**. The opposite regioselectivity can be obtained by blocking the *Re* face as in lactone **56**, in which case the epoxidation takes place from the *Si* face as it is the less hindered face and also due to the orientating effect of the hydroxyl group. In both cases, the nucleophilic ring opening of oxiranes **54** and **57** occurs diastereoselectively from the less hindered side of both oxiranes, at C-7 and C-3, respectively.

O'Brien and co-workers reported another good example of the advantages of the conformational rigidity induced by the BDA protecting group and they successfully employed this in the synthesis of the core of scyphostatin, a potent inhibitor of neutral sphingomyelinase (Scheme 11).[33] Their synthetic approach starts from BDA-protected (−)-quinic acid **23**. Reduction of **23** and subsequent oxidative cleavage of the corresponding 1,2-diol followed by β-elimination afforded enone **59** in good yield.[34] The conformationally rigid enone **59** led to the diastereoselective incorporation of diverse electrophiles in the α-position.[33,35] Indeed, treatment of the silyl enol **60** with NBS afforded the bromo derivative **63** as a single diastereoisomer and subsequent radical allylation with allyltributyltin gave mainly α-allylated enone **64** together with

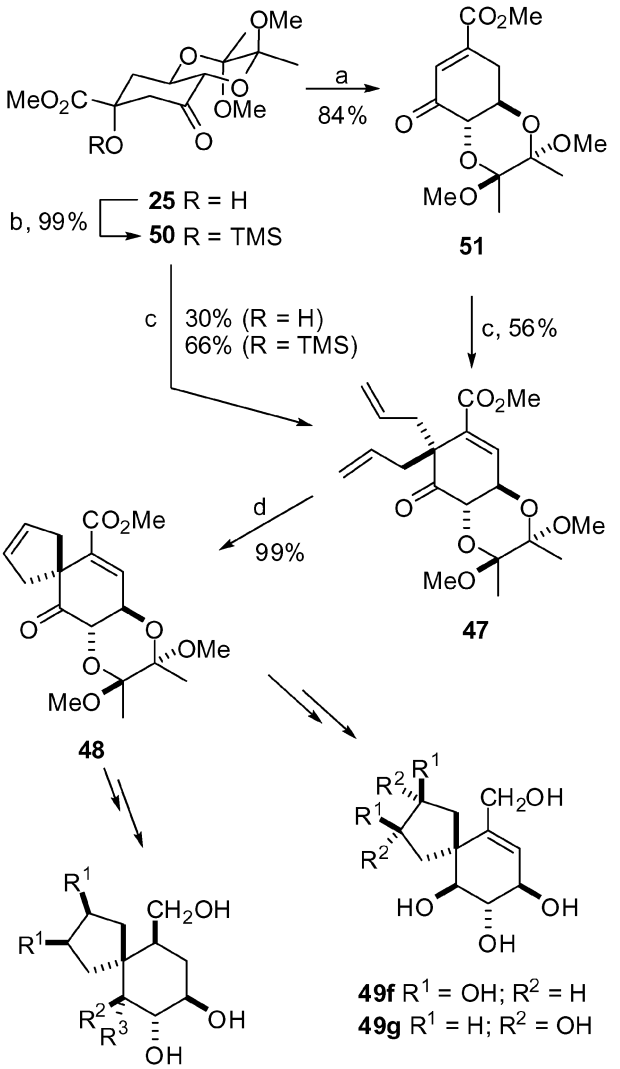


Scheme 8

a small amount of its epimer **65**.[33] The major allylated enone **64** has the opposite stereochemistry for the side chain of scyphostatin. This drawback was overcome by epimerization of the axially allylated enone **64** with DBU to give the thermodynamic equatorial compound **65**. Finally, Rubottom oxidation[36] of **65** with MCPBA followed by treatment with TBAF furnished a single diastereomer of α-hydroxy enone **66**, in which the hydroxyl group is again located in the axial position. Finally, conversion of enone **66** into core compound **67** was carried out by deprotection of the bisketal group and ring-closure of the resulting *trans*-1,2-diol to give an oxirane.

The diastereoselectivity induced by the conformationally rigid silyl enol ether **60**, derived from enone **59**, was also exploited by Mulzer and co-workers[37–39] in the synthesis of *cis*-decalin **62**, an advanced precursor of the natural antibiotic branimycin. Thus, Mukaiyama-type condensation[40] of the silyl enol ether **60** with dimethoxymethane afforded ether **61** as a single diastereoisomer, which was easily converted to *cis*-decalin **62**.

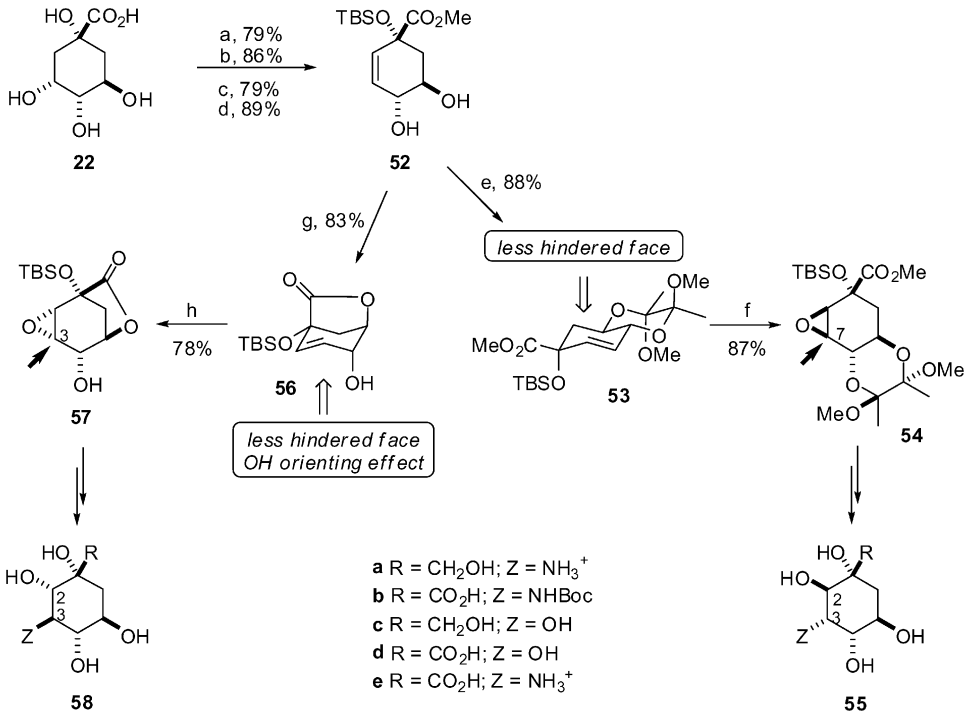
The total synthesis of altenuene and isoaltenuene toxins produced by various *alternaria* fungi was achieved using enone **59** as the key intermediate (Scheme 12).[41] The synthesis starts with the iodination of enone **59**,[34] treatment of which with methylmagnesium bromide yielded mainly addition from the *Re* face to afford alcohol **69a**. Suzuki cross-coupling between iodide **69a** and boronate **70** provided compound **71a**, in which the formation of the carbon–carbon bond and lactonization had occurred. Finally, acidic deprotection of the diacetal protecting group of **71a** provided the isoaltenuene *alternaria* toxins. A similar reaction sequence with the minor alcohol **69b** afforded the altenuene toxin.



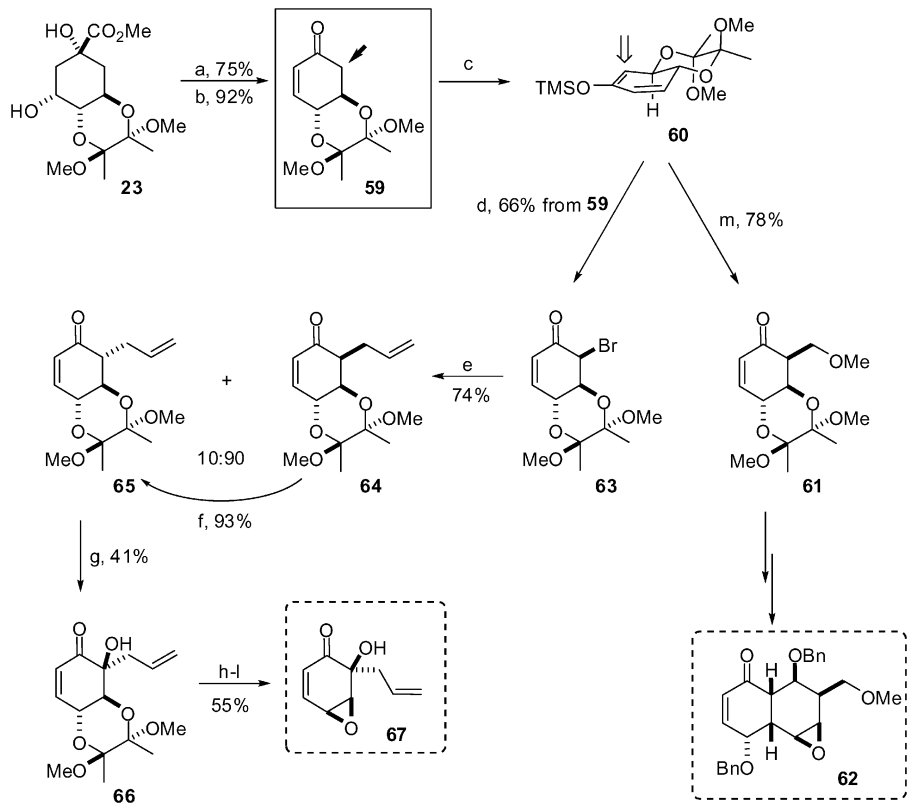
Scheme 9 *Reagents and conditions*: (a) Ac_2O, Py, RT; (b) TMSCl, HMDS, Py, RT; (c) 1. KHMDS, DMF, −78 °C; 2. allyl bromide, −78 °C → −60 °C; (d) 5% 2nd generation Grubbs' catalyst, DCM, Δ.

2. BDA-protected shikimic acid

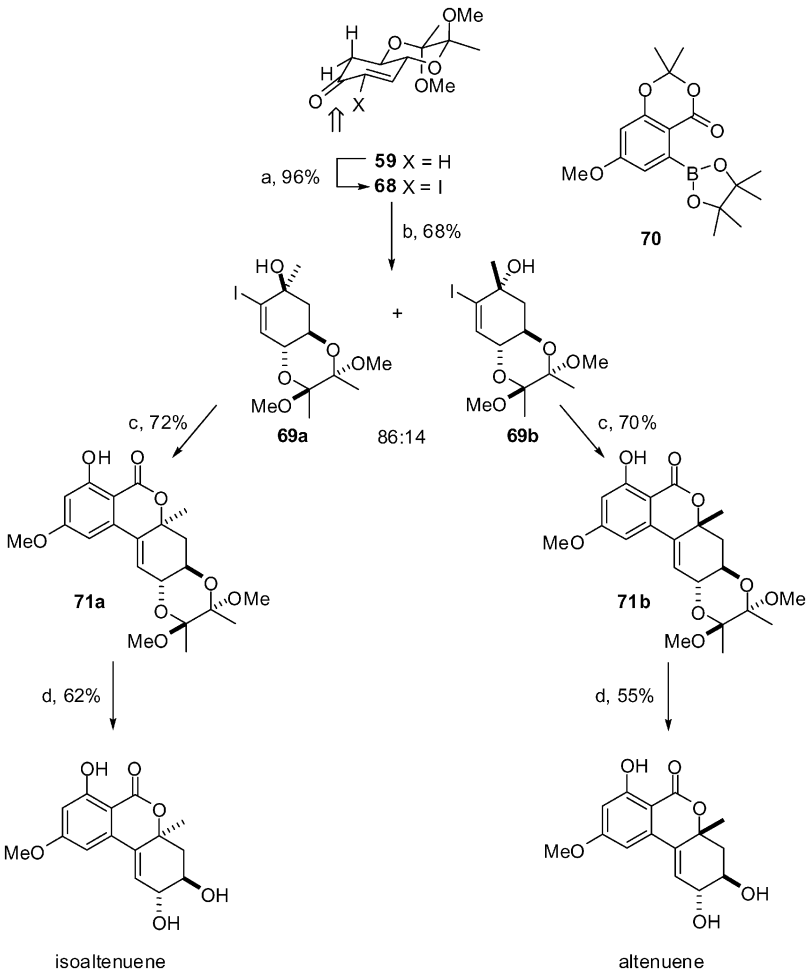
Shikimic acid is also a key intermediate in the biosynthesis of the aromatic amino acids.[24] In recent years there has been a great deal of interest in the synthesis of analogues of shikimic acid due to their biological significance as potential antifungal, antibacterial and antiparasitic agents.[24] In this context, the use of BDA protection in the synthesis of shikimic acid derivatives has led to more efficient synthetic approaches. For instance, the synthesis of (−)-shikimate 3-phosphate (**78**), a key intermediate in the shikimic acid pathway, was achieved in fewer steps than previously reported approaches[42,43] by BDA protection of its *trans*-1,2-diol **72** (Scheme 13). It was found that the reaction time under reflux strongly affected the *cis* : *trans*



Scheme 10 *Reagents and conditions*: (a) PhCHO, *p*-TSOH (cat.), PhMe, Δ; (b) NBS, AIBN (cat.), PhH, Δ; (c) TBSCl, DBU, MeCN, Δ; (d) KCN, MeOH, RT; (e) $(MeCO)_2$ (**8**), $CH(OMe)_3$, MeOH, CSA (cat.), Δ; (f) UHP, TFAA, Na_2HPO_4, DCM, 0 °C; (g) NaH, THF, 0 °C; (h) MCPBA, $NaHCO_3$, DCM, Δ.



Scheme 11 *Reagents and conditions*: (a) 1. DIBAL-H, Et_2O, −78 °C; 2. H_2O then filtration; 3. $NaIO_4$, RT; (b) $^iPr_2EtN$, DMAP, Ac_2O, DCM, 0 °C; (c) 1. LHMDS, THF, −78 °C; 2. TMSCl; (d) NBS, THF, 0 °C; (e) allylSnBu$_3$, AIBN, PhMe, 80 °C; (f) DBU, TMSCl, PhMe, 80 °C; (g) 1. Et_3SiOTf, Et_3N, DCM, RT; 2. MCPBA, DCM, −20 °C; 3. TBAF, 0 °C; (h) TFA–H_2O, RT; (k) Et_3N, MsCl, 0 °C; (l) NaOH, RT; (m) $CH_2(OMe)_2$, 2,6-DTBP, TMSOTf, DCM, 0 °C.



Scheme 12 *Reagents and conditions*: (a) I_2, DMAP, Py–CCl_4, 0 °C to RT; (b) MeMgBr, THF, −40 °C to RT; (c) **70**, $Pd(OAc)_2$, S-Phos, Cs_2CO_3, dioxane–H_2O, 80 °C; (d) TFA–H_2O, RT.

protection ratio.[44] Thus, a short reaction time (3 h) favoured *cis*-diol protection (ratio 1.5 : 1) but longer reaction times (48 h) provided the *trans*-diol protected product **74** as the only isolated compound in 77% yield. Phosphorylation of the C-3 position afforded compound **77**, deprotection of which with trimethylsilyl bromide followed by basification with sodium hydroxide gave the required (−)-shikimate 3-phosphate (**78**) in good yield. The efficient synthesis of (3*S*)- (**76**) and (3*R*)-3-fluoroshikimic acids (**81**) recently reported by Whitehead and co-workers was also achieved starting from BDA-protected shikimic acid **74** (Scheme 13).[45,46] Thus, allylic alcohol **74** underwent smooth fluorodeoxygenation to give fluoro derivative **75**, which was deprotected to afford (3*S*)-3-fluoroshikimic acid (**76**). Mitsunobu inversion of allylic alcohol **74** followed by methanolysis of the resulting benzoate ester gave the *epi*-BDA-protected shikimic acid **79**. Subsequent fluorodeoxygenation and deprotection afforded (3*R*)-3-fluoroshikimic acid (**81**).

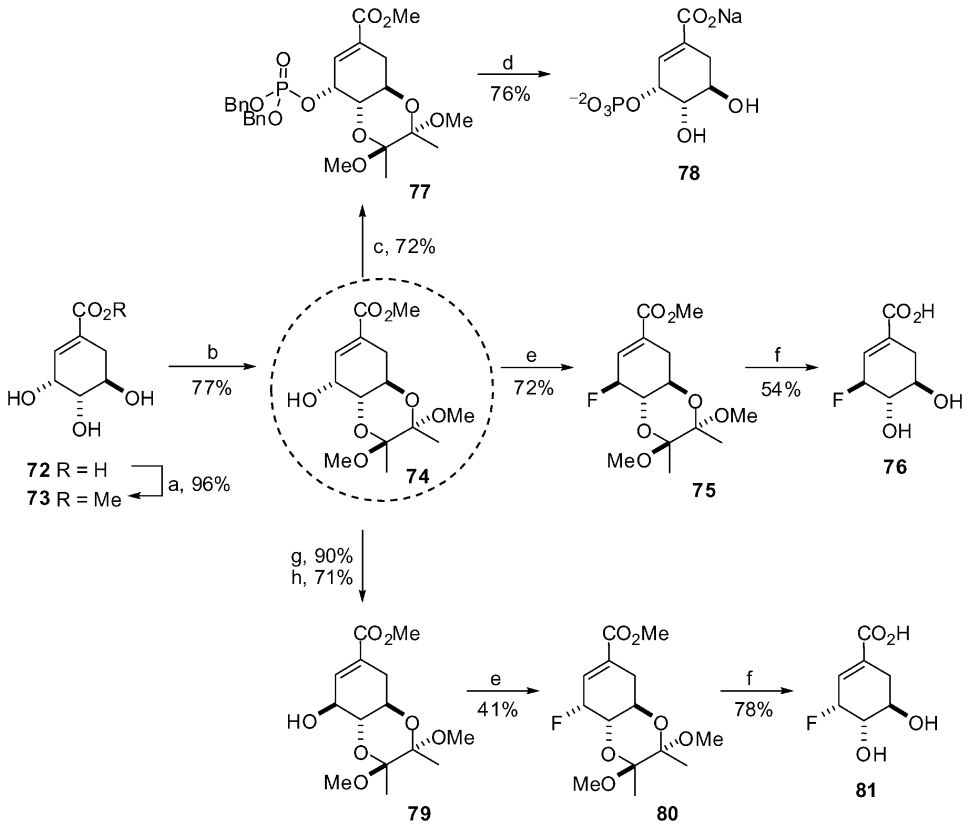
Recently, the synthesis of the antimicrobial (6*S*)-6-fluoroshikimic acid (**88**)[47,48] has been achieved from diacetal **84**, which is readily prepared from commercially available diol **82** (Scheme 14).[49] Selective benzylation of the allylic hydroxyl group of **82** and subsequent exposure to the standard BDA protecting conditions afforded the desired diacetal **84** in 48% yield.[50] Halogen exchange of vinyl bromide **84** and subsequent fluorodeoxygenation of **85** using DAST gave the allylic fluoride **86**. Palladium(0)-mediated carbonylation of **86** gave the α,β-unsaturated ester **87**. Finally, acidic removal of the protecting groups afforded the desired (6*S*)-6-fluoroshikimic acid (**88**).

The protected BDA shikimic acid derivative **74** proved to be a useful intermediate in the first total stereoselective synthesis of the antitumoral natural product (−)-zeylenone (**92**) (Scheme 15).[51] The key steps in this synthesis are the diastereoselective *cis*-dihydroxylation of alkene **89**, which is readily prepared in three steps from protected BDA shikimic acid **74**, and the allylic selenium dioxide oxidation of alkene **91**.

Building blocks derived from BDA

1. BDA-protected glyceraldehyde derivatives

D-Glyceraldehyde acetonide **93** has been extensively used as a three-carbon building block for organic synthesis (Scheme 16). However, this compound must always be freshly prepared due to its propensity to polymerize, to racemize and to form hydrates. Alternatively, Ley and Michel[52] have shown that butane-2,3-diacetals of glyceraldehydes, **94** and **96**, and their



Scheme 13 *Reagents and conditions*: (a) MeOH, CSA (cat.), Δ; (b) TMB (**7**), CSA (cat.), MeOH, $CH(OMe)_3$, 48 h, Δ; (c) 1. $(^{i}Pr)_2NP(OBn)_2$, tetrazole; 2. MCPBA; (d) 1. TMSBr; 2. NaOH; (e) Et_2NSF_3, DCM, 0 °C to RT; (f) 1. LiOH, H_2O, MeOH, RT; 2. TFA, H_2O, RT; (g) Ph_3P, diisopropylazodicarboxylate, $PhCO_2H$, THF, RT; (h) K_2CO_3, MeOH, RT.

corresponding methyl esters, **95** and **97**, are considerably more stable glyceraldehyde derivatives than the acetonide. More importantly, these conformationally rigid BDA-protected glyceraldehyde derivatives (**94–97**) show excellent facial stereoselectivity in alkylation or nucleophilic addition reactions.[52–55] For example, alkylation of the ester (*R*)-glycerate **95** with various electrophiles affords mainly the equatorial derivatives **98** (Scheme 16).[54] The reaction seems to be under thermodynamic control. This facial stereoselectivity was used to prepare enantiomerically pure methyl (*S*)-2-allylglycerate **99**.[54] On the other hand, aldehyde **96**, which contains an axial aldehyde, proved to have strong *anti* selectivity in nucleophilic additions with diverse Grignard reagents, leading to protected 1,2,3-triols **101** with a 2,3-*anti* relationship (Table 4).[52] This excellent stereofacial selectivity seems to be controlled by β-chelation of the aldehyde, located in an axial position, with the methoxy group of the diacetal group.

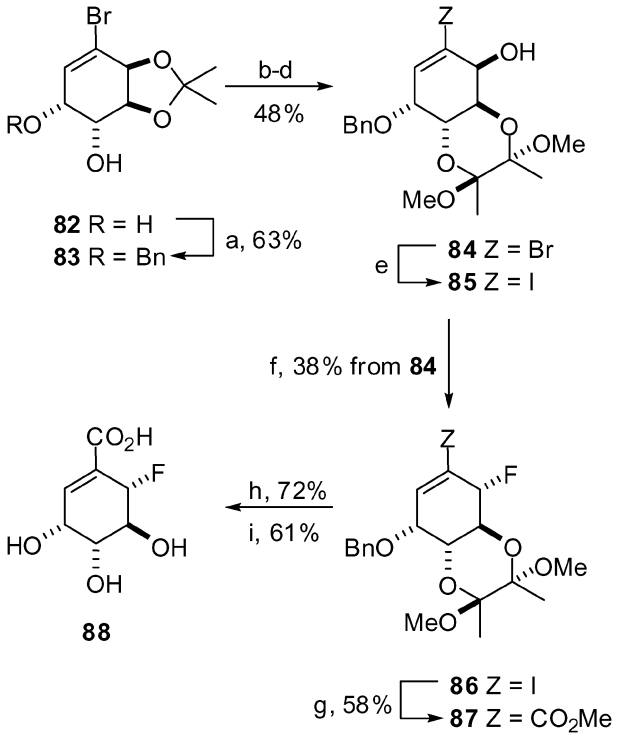
Alternatively, García and co-workers[55] showed that the addition of zinc alkynylides, prepared *in situ* with $Zn(OTf)_2$, (−)-*N*-methylephedrine (NME) and triethylamine, to the equatorial aldehyde **94** affords the corresponding *syn*-derivatives **102** in high yields and with excellent diastereoselectivities (up to $>80:1$) (Table 5, entries 1–4). They also showed that although aldehyde **94** favours the *syn* addition, the chiral ligand overcomes the stereochemical bias of **94**. In fact, the stereoselectivity of the reaction can be reversed in the presence of (+)-*N*-methylephedrine (Table 5, entries 5–8).

This methodology was applied to the efficient synthesis of a 1,2,3-triol with a 2,3-*syn* relationship, *i.e.* the (−)-polyoxamic acid derivative **106** (Scheme 17).[55] Partial reduction of the triple bond of *syn*-**102** (R = CH_2OBz) followed by treatment with tosyl isocyanate efficiently yielded the allylic tosylcarbamate **103**. Pd(II)-catalyzed cyclization of **103** stereoselectively gave the *trans*-oxazolidione **104** in 85% yield. Ozonolysis of alkene **104** followed by oxidation of the resulting aldehyde gave acid **105**, which was readily transformed into the required (−)-polyoxamic acid derivative **106** in 63% yield.

The (*R*)-BDA-protected glyceraldehyde derivatives **94** and **95** can be prepared on a large scale from D-mannitol (**107**) and the only purification is a single distillation under vacuum at the final stage (Scheme 18). On the other hand, (*S*) derivatives **96** and **97** can be easily obtained from L-ascorbic acid (**109**).[52]

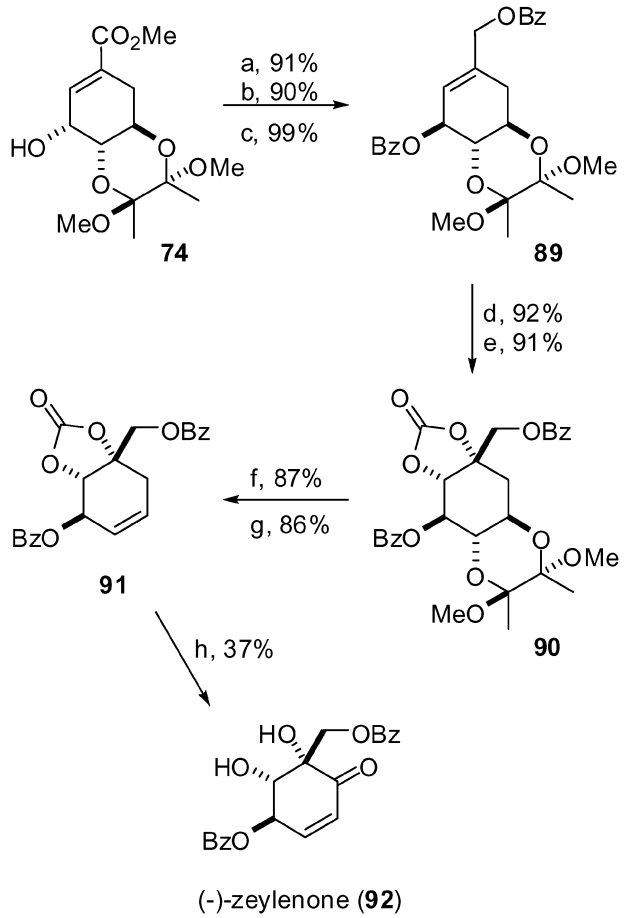
2. BDA-protected tartaric acid derivatives

Protected tartrate derivatives are excellent building blocks as they are easily available from cheap starting materials and they can lead to highly enantiopure polyhydroxylated compounds. As a result of the rigid chair conformation of the diacetal group, BDA-protected tartaric acid derivatives have been shown to be, in a similar way to BDA-protected glyceraldehydes, useful building blocks in the stereoselective synthesis of polyhydroxylated natural products. Excellent examples

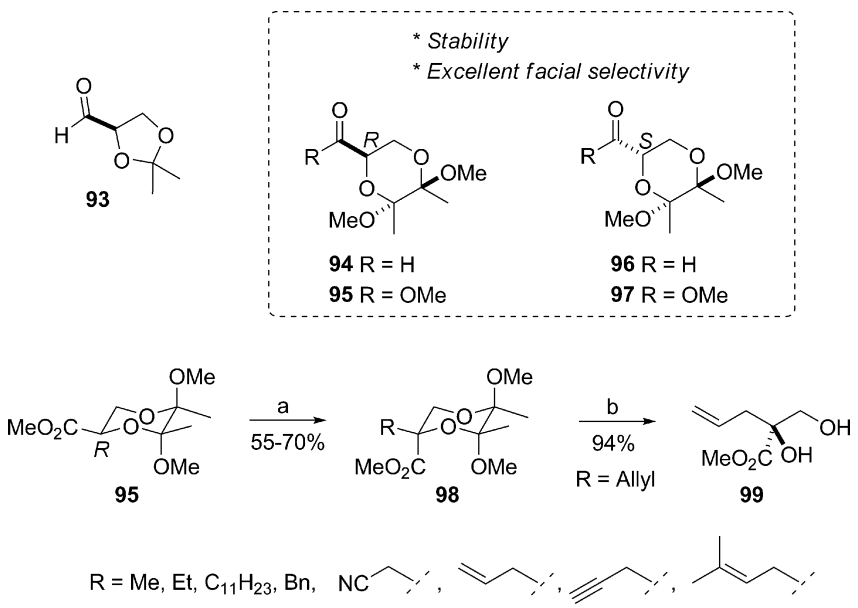


Scheme 14 *Reagents and conditions*: (a) 1. Bu_2SnO, C_6H_6, Δ; 2. CsF, BnBr, DMF, RT; (b) $(MeCO)_2$ (**8**), $CH(OMe)_3$, CSA (cat.), MeOH, Δ; (c) Ac_2O, Py, DMAP, DCM; (d) K_2CO_3, MeOH; (e) CuI, KI, $(CH_2NMe_2)_2$, ^{n}BuOH, 130 °C; (f) Et_2NSF_3, DCM, −78 °C to RT; (g) $Pd(OAc)_2$, $^i Pr_2EtN$, tri-2-furylphosphine, MeOH, CO, DMF, RT; (h) TFA, H_2O, RT; (i) HCl (conc.), H_2O, 60 °C.

of the synthetic utility of building blocks of this type have been reported by Ley's group in the total synthesis of structurally complex macrolides, such as antascomicin B[56] or (+)-aspicilin.[57,53] Indeed, the synthesis of the polyhydroxylated fragment of antascomicin B was efficiently achieved from epoxide **113**, which was prepared from BDA-protected D-tartrate **114**[58]

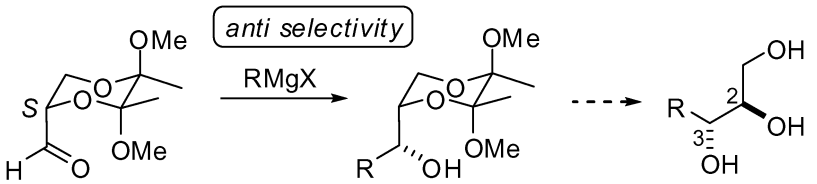


Scheme 15 *Reagents and conditions*: (a) 1. Ph_3P, DEAD, p-$O_2NC_6H_4CO_2H$, THF, RT; 2. MeONa, MeOH, RT; (b) DIBAL-H, PhMe, −78 °C; (c) BzCl, DMAP, Py, RT; (d) OsO_4 (cat.), NMO, THF–H_2O; (e) triphosgene, Py, DCM, −78 °C; (f) TFA, DCM, RT; (g) Ph_3P, Im, I_2, Δ; (h) 1. SeO_2, THF, Δ; 2. Py–H_2O (1 : 1), Δ.



Scheme 16 *Reagents and conditions*: (a) 1. LDA, THF, −78 °C; 2. RX, HMPA; (b) p-TSA, MeOH, Δ.

Table 4 Stereoselective addition of Grignard reagents to aldehyde **96**[52]



96 **100** **101**

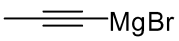
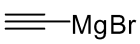
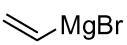
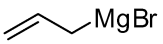
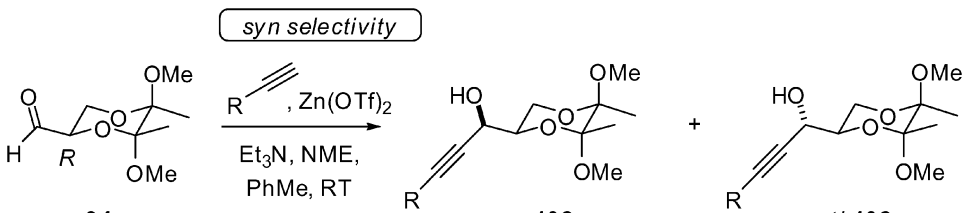
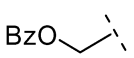
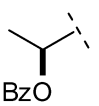
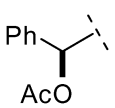
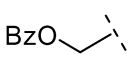
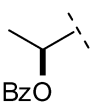
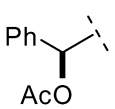
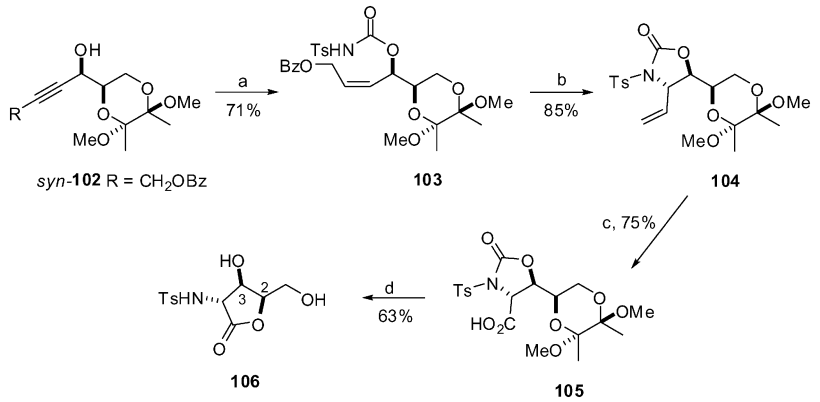
Entry	RMgX	Yield (%)	Ratio *anti* : *syn*
1	MeMgCl	81	25 : 1
2		93	15 : 1
3		95	15 : 1
4		80	15 : 1
5		88	15 : 1

Table 5 Stereoselective addition of zinc alkynylides to aldehyde **94**[55]

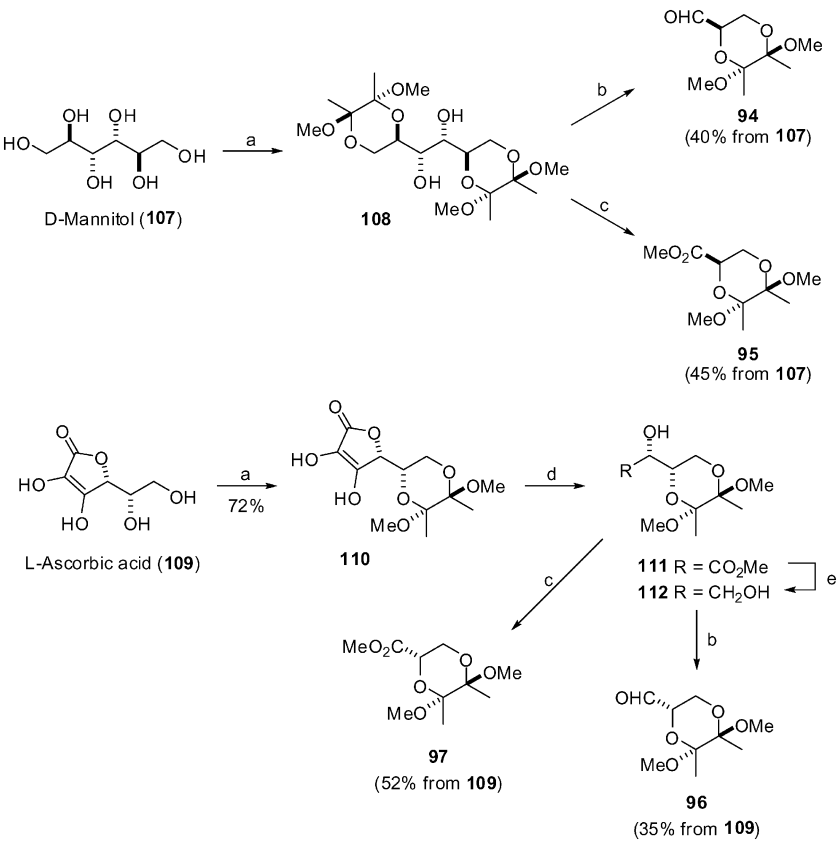


94 *syn*-**102** *anti*-**102**

Entry	NME	R	Yield (%)	Ratio *syn* : *anti*
1	–		95	>80 : 1
2	–		89	50 : 1
3	–		100	>80 : 1
4	–	Ph	88	19 : 1
5	+		83	1 : 16
6	+		79	1 : 13
7	+		98	1 : 50
8	+	Ph	98	1 : 11



Scheme 17 *Reagents and conditions*: (a) H_2, Lindlar's catalyst, quinoline, EtOAc, RT, then TsNCO, THF, RT; (b) $Pd(OAc)_2$, LiBr, THF, Δ; (c) 1. O_3, DCM, −78 °C; 2. Me_2S; 3. $NaClO_2$, H_2O_2, NaH_2PO_4, MeCN–H_2O; (d) 1. LiOH (aq), Δ; 2. HCl (2M), THF, 60 °C.



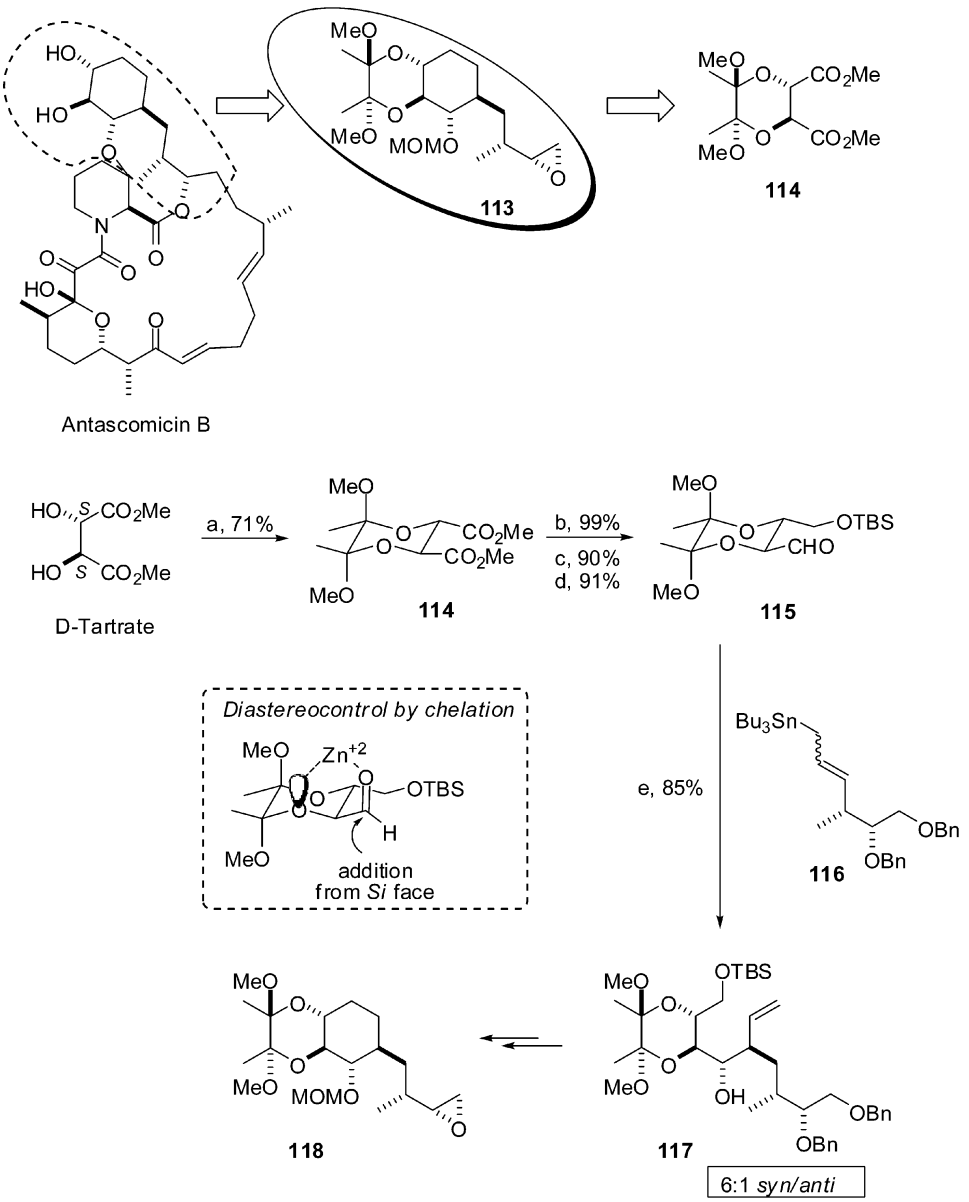
Scheme 18 *Reagents and conditions*: (a) $(MeCO)_2$, $HC(OMe)_3$, $BF_3{\cdot}Et_2O$, MeOH; (b) $NaIO_4$, DCM; (c) $NaIO_4$, MeOH–H_2O, then $NaHCO_3$, Br_2; (d) 1. H_2O_2, K_2CO_3; 2. Me_2SO_4; (e) $LiAlH_4$.

(Scheme 19). Thus, diacetal **114**, easily obtained from dimethyl D-tartrate and now commercially available, was converted into aldehyde **115** by a three-step procedure (reduction, selective TBS monoprotection and oxidation of the free hydroxyl group) to afford enantiopure aldehyde **115** in an efficient manner. The key step of the approach was the diastereoselective *syn*-addition to aldehyde **115** of allyl stannane **116**, catalyzed by $ZnCl_2$. The diastereoselectivity is controlled by chelation of Zn^{2+} to the equatorial carbonyl group and the axial lone pair of electrons on the α-oxygen atom of the diacetal, forcing the allyl stannane to attack in an antiperiplanar orientation.

Maycock and co-workers have also shown that (*S,S*)-**118** and (*R,R*)-diethyldithioester **121**, derived from D- and L-tartrate, respectively, are good starting materials for the synthesis of (+)-*O*-methylpiscidic acid dimethyl ester (**120**) and (+)-neophrosteranic acid (**124**), respectively (Scheme 20).[59–61] The key step in both approaches was a highly stereoselective reaction between the dithioenolate of **118** or **121** and an electrophile, either *p*-methoxybenzyl bromide or decanal, respectively.

3. BDA-protected glycolic derivatives

The enantioselective synthesis of α-hydroxy acids and 1,2-diols has been extensively studied, not only because they are

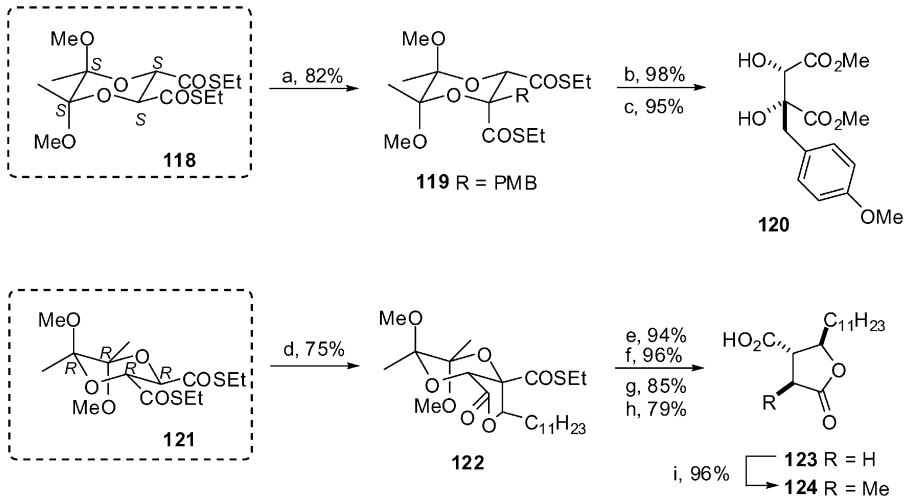


Scheme 19 *Reagents and conditions*: (a) $(MeCO)_2$, $CH(OMe)_3$, CSA (cat.), MeOH, Δ; (b) LAH, THF, 0 °C to RT; (c) NaH, THF, RT then TBSCl; (d) $(COCl)_2$, DMSO, DCM, −78 °C then Et_3N, −78 °C to RT; (e) ZnI_2, DCM, −78 °C to RT.

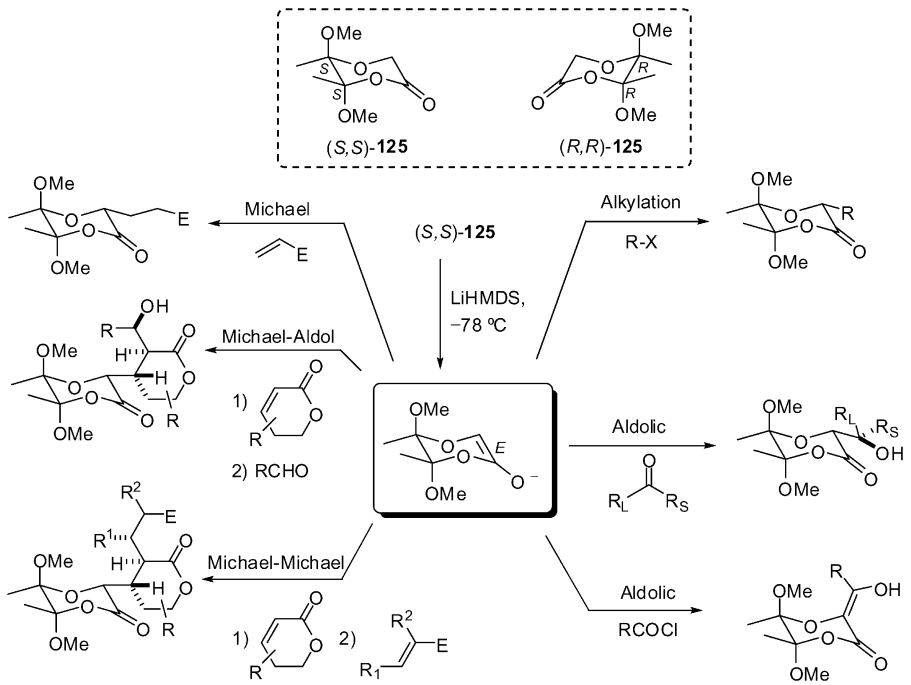
remarkable moieties in biologically active compounds but also because they are excellent building blocks for the total synthesis of natural products. The synthesis of chiral α-hydroxy acids and 1,2-diols has essentially been carried out by α-alkylation of either acyclic chiral derivatives bearing an ester or cyclic glycols containing a chiral acetal. The latter glycols are remarkable because they provide a constrained cyclic enolate with the *E*-configuration, which favours good facial stereocontrol. This is the case for enolates derived from BDA-protected glycolic derivatives, *e.g.* compounds (*S*,*S*)- and (*R*,*R*)-**125** (Scheme 21), that have a rigid chair conformation and induce excellent diastereoselectivities in a wide range of reactions, from alkylations with alkyl halides,[62,63] aldol reactions with aldehydes,[64] ketones[65] or acid chlorides,[66] Michael additions,[67] Michael-aldol reactions[68] and Michael–Michael additions.[68,69] For instance, an efficient synthesis of enantiopure α-aryl-α-hydroxy esters (*S*)- and (*R*)-**128** was achieved from diacetals (*R*,*R*)- and (*S*,*S*)-**125**, respectively, by diastereoselective palladium-catalyzed α-arylation reactions of the corresponding silylenol ether **126** (Scheme 22).[70]

BDA derivatives as chiral auxiliaries for asymmetric catalysis

The most challenging applications of the BDA derivatives have involved the use of the chiral information stored in the diacetal function to induce chirality in asymmetric catalysis. Berens and co-workers[71] were the first to develop chiral ligands based on BDA-protected tartaric acid derivatives as an alternative to the structurally related TADDOLs and



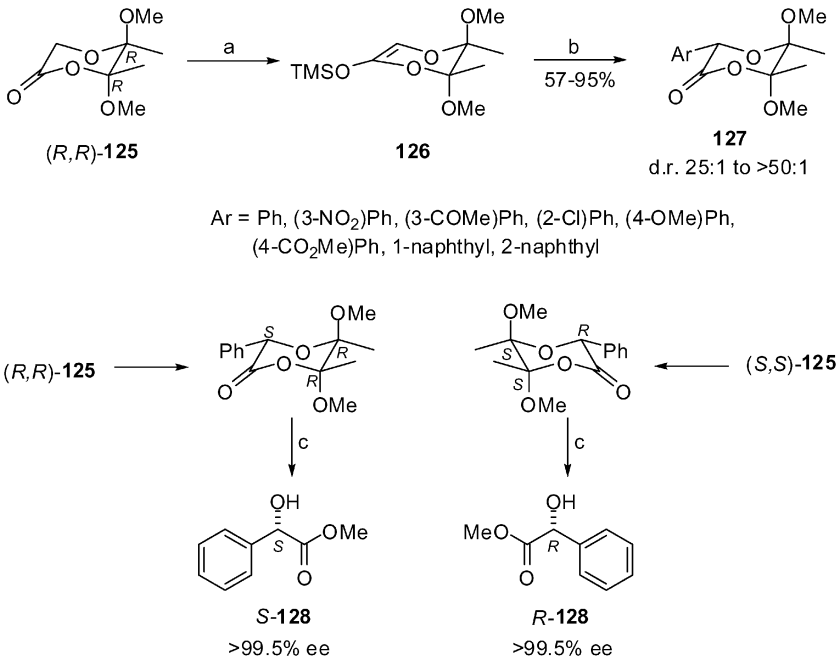
Scheme 20 *Reagents and conditions*: (a) LDA, THF, PMBBr, HMPA, −78 °C to 0 °C; (b) TFA, DCM, H_2O, Δ; (c) NaOMe, MeOH, RT; (d) LDA, THF, $C_{11}H_{23}CHO$, −78 °C; (e) $BF_3{\cdot}Et_2O$, 1,2-ethanedithiol, DCM, 80 °C; (f) NaOEt, EtOH, THF, 0 °C; (g) MsCl, DIPEA, DCM, 0 °C; (h) 1. H_2, Pd/C, NaOAc, MeOH, EtOAc, RT; 2. DBU, DCM, RT; 3. HCl (6 M), dioxane, Δ; (i) NaHMDS, MeI, THF, −78 °C.



Scheme 21

DIOP ligands. They developed various bisphosphine ligands **129–132** in which the diacetal group was introduced to fix the conformation of the phosphines (Fig. 2).[71,72] Unfortunately, the enantiomeric excess induced by the ligands **129–132** in the asymmetric catalytic hydrogenolysis of the studied enamine **134** was moderate (Scheme 23).[72] However, excellent enantioselectivities were obtained with enamides **136**, which furnished chiral amines or β-amino alcohols **137** (Scheme 24).[73] It is believed that the 1,4-dioxane backbone in the ligands plays an important role in stabilizing the metal–ligand chelate conformation. Other structurally related ligands derived from BDA-protected tartaric acid derivatives have also been reported (Fig. 3). For instance, monophosphonite **138** was used in the enantioselective hydrosilylation of ketones,[74] phosphite **139** in asymmetric cross silyl benzoin reactions,[75] bisoxazolines **140** in the enantioselective copper-catalyzed conjugate addition of diethylzinc to enones,[76] monooxazolines **141** in the asymmetric alkylation of benzaldehyde by diethylzinc,[77] diamine **142** in the enantioselective reduction of acetophenone, *etc.*[78] However, the enantiomeric excesses obtained were moderate in all of these cases, ranging between 30% and 50%.

On the other hand, Shing and co-workers[79,80] recently reported that bisketal-protected ketones derived from



Scheme 22 *Reagents and conditions:* (a) 1. LDA, THF, −78 °C; 2. TMSCl, −78 °C to RT; (b) ArBr, 5% $Pd(dba)_2$, 10% $P(^tBu)_3$, ZnF_2 or $Zn(O^tBu)_2$ (0.25–1 equiv.), DMF, RT or 80 °C; (c) TMSCl, MeOH.

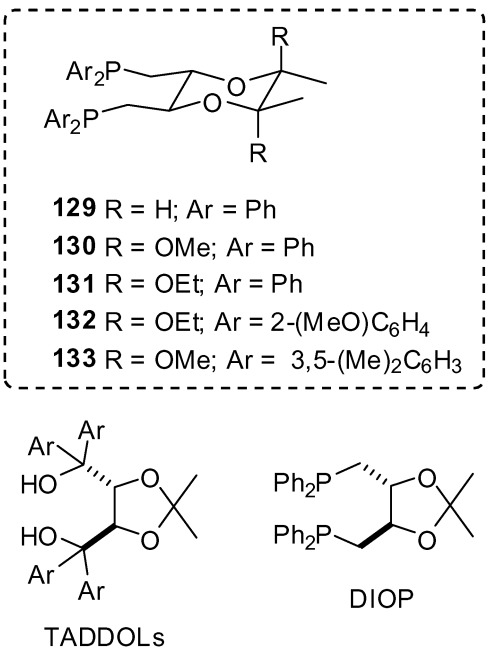
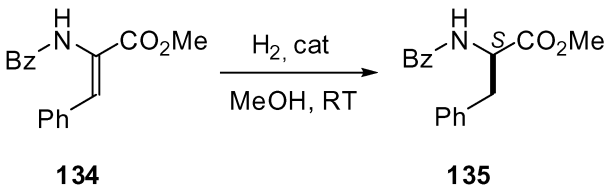
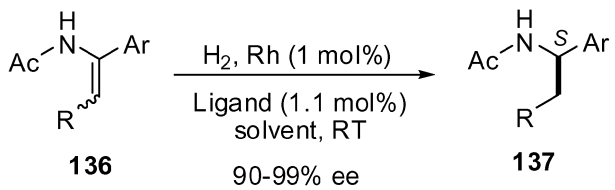


Fig. 2 BDA-protected bisphosphine ligands.

L-arabinose (**143**) successfully catalyzed the enantioselective epoxidation of di- and trisubstituted alkenes (Scheme 25). The best enantiomeric excesses (between 68 to 90%) were achieved with ketones protected as diisobutoxy- and dineopentoxyacetals **148** and **149**, respectively, which were obtained by transacetalization of the corresponding bismethoxyacetal **144**. For *trans*-disubstituted alkenes, ketone catalyst **149** displayed the best chiral induction.



Scheme 23



Scheme 24 COD = cyclooctadiene; NBD = norbornadiene.

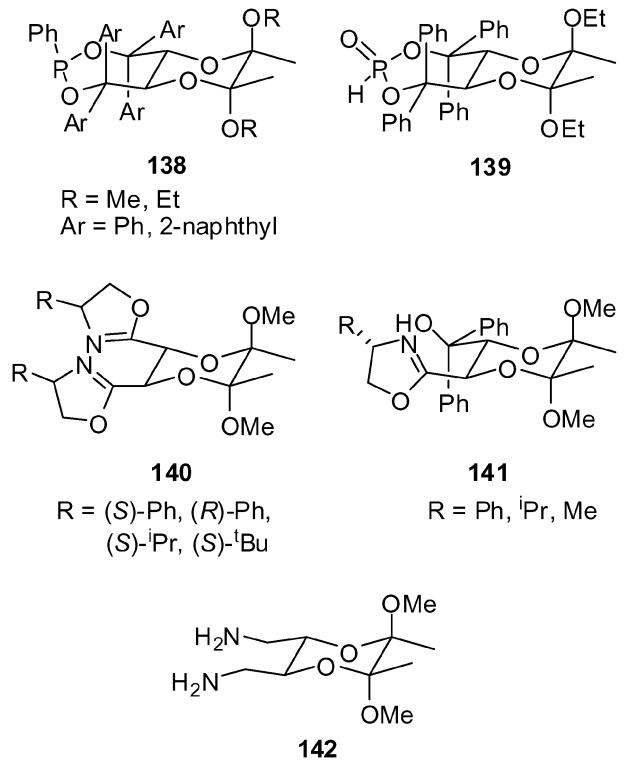
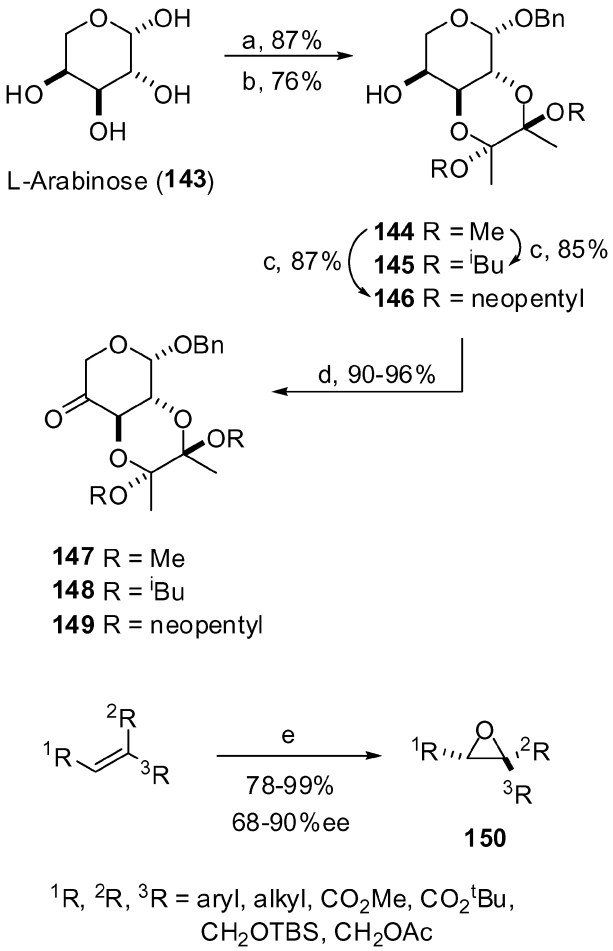


Fig. 3 Other BDA derivatives used as chiral ligands for asymmetric catalysis.



Scheme 25 *Reagents and conditions*: (a) BnOH, AcCl, RT; (b) TMB (**7**), $CH(OMe)_3$, CSA(cat.), Δ; (c) ^{t}BuOH or neopentyl alcohol, *p*-TsOH, PhH_{lit}, Δ; (d) PDC, 3 Å MS, DCM, RT; (e) 10% mol **148** or **149**, Oxone®, MeCN, H_2O, RT, pH = 7–7.5.

Conclusions and final remarks

Diacetals were initially developed by Ley's group as selective protecting groups for *trans*-1,2-equatorial diols. However, these materials stood out due to their diastereoselectivity in glycosidation reactions as well as their donor/acceptor reactivity in oligosaccharide chemistry. The scope of diacetal chemistry, particularly butane-1,2-diacetal, has been rapidly extended to other synthetic areas as a consequence of the excellent diastereoselectivity control that can be achieved through the strong conformational rigidity induced by the butane-1,2-diacetal group. The chiral information stored in the diacetal backbone provides excellent opportunities in synthetic chemistry for the synthesis of molecules of biological importance and a wide range of natural products, some of which have been exemplified in this critical review. Particularly remarkable is the use of BDA-protected glycerate, tartrate and glycolic building blocks as they can efficiently lead to highly enantiopure polyhydroxylated compounds. More challenging has been the use of butane-1,2-diacetal ligands in asymmetric catalysis. Unfortunately, the enantioselectivity reported so far on using this type of ligand is still moderate, but hopefully this can soon be improved.

The wide range of reactions performed with this type of diacetal protecting group, some of them shown herein, is excellent evidence of its robustness. It is worth highlighting its enormous practical use because diacetal protected products are usually crystalline materials with simple NMR spectra, particularly butane-1,2-diacetals. This protecting group displays only singlets in the ^{1}H NMR spectra, which helps in the analysis of the reaction products (see ESI)§. In conclusion, their integrity as protecting groups, as well as the chemical properties derived from their conformational rigidity, makes diacetals an extremely useful functional group.

References

1. K. C. Nicolaou and H. J. Mitchell, *Angew. Chem., Int. Ed.*, 2001, **40**, 1576–1624.
2. K. C. Nicolaou and E. J. Sorensen, *Classics in Total Synthesis*, Wiley-VCH, Weinheim, 1996.
3. K. C. Nicolaou and S. A. Snyder, *Classics in Total Synthesis II*, Wiley-VCH, Weinheim, 2003.
4. P. J. Kocieński, *Protecting Groups*, Thieme, Stuttgart, 3rd edn, 2005.
5. P. G. M. Wuts and T. W. Greene, *Greene's Protective Groups in Organic Synthesis*, Wiley-Interscience, New Jersey, 4th edn, 2006.
6. C. A. A. van Boeckel and J. H. van Boom, *Tetrahedron*, 1985, **41**, 4567–4575.
7. S. V. Ley, M. Woods and A. Zanotti-Gerosa, *Synthesis*, 1992, 52–54.
8. S. V. Ley, D. K. Baeschlin, D. J. Dixon, A. C. Foster, S. J. Ince, H. W. M. Priepke and D. J. Reynolds, *Chem. Rev.*, 2001, **101**, 53–80.
9. T. Ziegler, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2272–2275.
10. S. V. Ley, R. Leslie, P. D. Tiffin and M. Woods, *Tetrahedron Lett.*, 1992, **33**, 4767–4770.

11. S. V. Ley, H. W. M. Priepke and S. L. Warriner, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2290–2292.
12. S. V. Ley, H. M. I. Osborn, H. W. M. Priepke and S. L. Warriner, *Org. Synth.*, 1998, **75**, 170–176.
13. J. L. Montchamp, F. Tian, M. E. Hart and J. W. Frost, *J. Org. Chem.*, 1996, **61**, 3897–3899.
14. N. L. Douglas, S. V. Ley, H. M. I. Osborn, D. R. Owen, H. W. M. Priepke and S. L. Warriner, *Synlett*, 1996, 793–794.
15. A. Hense, S. V. Ley, H. M. I. Osborn, D. R. Owen, J.-F. Poisson, S. L. Warriner and K. E. Wesson, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2023–2031.
16. S. V. Ley, G.-J. Boons, R. Leolie, M. Woods and D. M. Hollinshead, *Synthesis*, 1993, 689–692.
17. S. J. Mills, A. M. Riley, C. Liu, M. F. Mahon and B. V. L. Potter, *Chem.–Eur. J.*, 2003, **9**, 6207–6214.
18. C. Liu, A. M. Riley, X. Yang, S. B. Shears and B. V. L. Potter, *J. Med. Chem.*, 2001, **44**, 2984–2989.
19. M. Carpintero, A. Bastida, E. García-Junceda, J. Jiménez-Barbero and A. Fernández-Mayoralas, *Eur. J. Org. Chem.*, 2001, 4127–4135.
20. E. Lence, L. Castedo and C. González, *Tetrahedron Lett.*, 2002, **43**, 7917–7918.
21. A. Barco, S. Benetti, C. De Risi, P. Marchetti, G. P. Pollini and V. Zanirato, *Tetrahedron: Asymmetry*, 1997, **8**, 3515–3545.
22. N. Armesto, M. Ferrero, S. Fernández and V. Gotor, *Tetrahedron Lett.*, 2000, **41**, 8759–8762.
23. F. Tian, J.-L. Montchamp and J. W. Frost, *J. Org. Chem.*, 1996, **61**, 7373–7381.
24. C. Abell, *Enzymology and Molecular Biology of the Shikimate Pathway*, in *Comprehensive Natural Products Chemistry*, ed. U Sankawa, Pergamon, Elsevier Science Ltd., Oxford, 1999, vol. 1, pp. 573–607.
25. C. González-Bello and L. Castedo, *Med. Res. Rev.*, 2007, **27**, 177–208.
26. M. Frederickson, J. R. Coggins and C. Abell, *Chem. Commun.*, 2002, 1886–1887.
27. M. D. Toscano, M. Frederickson, D. P. Evans, J. R. Coggins, C. Abell and C. González-Bello, *Org. Biomol. Chem.*, 2003, **1**, 2075–2083.
28. C. González-Bello, L. Castedo and F. J. Cañada, *Eur. J. Org. Chem.*, 2006, 1002–1011.
29. C. Alves, M. T. Barros, C. D. Maycock and M. R. Ventura, *Tetrahedron*, 1999, **55**, 8443–8456.
30. C. González, M. Carballido and L. Castedo, *J. Org. Chem.*, 2003, **68**, 2248–2255.
31. M. Carballido, L. Castedo and C. González, *Tetrahedron Lett.*, 2001, **42**, 3973–3976.
32. M. Carballido, L. Castedo and C. González-Bello, *Eur. J. Org. Chem.*, 2004, 3663–3668.
33. L. M. Murray, P. O'Brien and R. J. K. Taylor, *Org. Lett.*, 2003, **5**, 1943–1946.
34. M. T. Barros, C. D. Maycock and M. R. Ventura, *J. Chem. Soc., Perkin Trans. 1*, 2001, 166–173.
35. C. L. Arthus, N. S. Wind, R. C. Whitehead and I. J. Stratford, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 553–557.
36. G. M. Rubottom, J. M. Gruber, H. D. Juve and D. A. Charleson, *Org. Synth.*, 1986, **64**, 118.
37. S. Marchart, J. Mulzer and V. S. Enev, *Org. Lett.*, 2007, **9**, 813–815.
38. J. Mulzer, D. Castagnolo, W. Felzmann, S. Marchat, C. Pilger and V. S. Enev, *Chem.–Eur. J.*, 2006, **12**, 5992–6001.
39. V. S. Enev, M. Drescher and J. Mulzer, *Tetrahedron*, 2007, **63**, 5930–5939.
40. S. Murata, M. Suzuki and R. Noyori, *Tetrahedron*, 1988, **13**, 4259–4275.
41. M. Altemöller, J. Podlech and D. Fenske, *Eur. J. Org. Chem.*, 2006, 684.
42. L. Chahoua, M. Baltas, L. Gorrichon, P. Tisnes and C. Zedde, *J. Org. Chem.*, 1992, **57**, 5798–801.
43. P. A. Bartlett and L. A. McQuaid, *J. Am. Chem. Soc.*, 1984, **106**, 7854–7860.
44. T.-L. Shih and S.-H. Wu, *Tetrahedron Lett.*, 2000, **41**, 2957–959.
45. T. H. Box, L. M. Harwood, J. L. Humphreys, G. A. Morris, P. M. Redon and R. C. Whitehead, *Synlett*, 2002, 358–36.
46. L. Begum, M. G. B. Drew, J. L. Humphreys, D. J. Lowes, P. R. Russi, H. L. Whitby and R. C. Whitehead, *Tetrahedron Lett.*, 2004, **45**, 6249–6253.
47. G. M. Davis, K. J. Barrett-Bee, D. A. Jude, M. Lehan, W. W. Nichols, P. E. Pinder, J. L. Thain, W. J. Watkins and R. G. Wilson, *Antimicrob. Agents Chemother.*, 1994, **38**, 403–406.
48. D. A. Jude, C. D. C. Ewart, J. L. Thain, G. M. Davies and W. W. Nichols, *Biochim. Biophys. Acta*, 1996, **1279**, 125–129.
49. J. L. Humphreys, D. J. Lowes, K. A. Wesson and R. C. Whitehead, *Tetrahedron*, 2006, **62**, 5099–5108.
50. L. Begum, J. M. Box, M. G. B. Drew, L. M. Harwood, J. L. Humphreys, D. J. Lowes, G. A. Morris, P. M. Redon, F. M. Walker and R. C. Whitehead, *Tetrahedron*, 2003, **59**, 4827–4841.
51. Y. Zhang, A. Liu, Z. G. Ye, J. Lin, L. Z. Xu and S. L. Yang, *Chem. Pharm. Bull.*, 2006, **54**, 1459–1461.
52. P. Michel and S. V. Ley, *Angew. Chem., Int. Ed.*, 2002, **41**, 3898–3901.
53. S. V. Ley and A. Polara, *J. Org. Chem.*, 2007, **72**, 5943–5959.
54. S. V. Ley, P. Michel and C. Trapella, *Org. Lett.*, 2003, **5**, 4553–4555.
55. J. Boyer, Y. Allenbach, X. Ariza, J. García, Y. Georges and M. Vicente, *Synlett*, 2006, 1895–1898.
56. D. E. A. Brittain, C. M. Griffiths-Jones, M. R. Linder, M. D. Smith, C. McCusker, J. S. Barlow, R. Akiyama, K. Yasuda and S. V. Ley, *Angew. Chem., Int. Ed.*, 2005, **44**, 2732–2737.
57. D. J. Dixon, A. C. Foster and S. V. Ley, *Can. J. Chem.*, 2001, **79**, 1668–1680.
58. J. S. Barlow, D. J. Dixon, A. C. Foster, S. V. Ley and D. J. Reynolds, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1627–1629.
59. M. T. Barros, A. J. Burke, J. Lou, C. D. Maycock and J. R. Wahnon, *J. Org. Chem.*, 2004, **69**, 7847–7850.
60. M. T. Barros, C. D. Maycock and M. R. Ventura, *Org. Lett.*, 2003, **5**, 4097–4099.
61. A. J. Burke, C. D. Maycock and M. R. Ventura, *Org. Biomol. Chem.*, 2006, **4**, 2361–2363.
62. S. V. Ley, E. Díez, D. J. Dixon, R. T. Guy, P. Michel, G. L. Nattrass and T. D. Sheppard, *Org. Biomol. Chem.*, 2004, **2**, 3608–3617.
63. E. Díez, D. J. Dixon and S. V. Ley, *Angew. Chem., Int. Ed.*, 2001, **40**, 2906–2909.
64. D. J. Dixon, S. V. Ley, A. Polara and T. Sheppard, *Org. Lett.*, 2001, **3**, 3749–3752.
65. D. J. Dixon, A. Guarna, S. V. Ley, A. Polara and F. Rodríguez, *Synthesis*, 2002, 1973–1978.
66. S. V. Ley, D. J. Dixon, R. T. Guy, M. A. Palomero, A. Polara, F. Rodríguez and T. D. Sheppard, *Org. Biomol. Chem.*, 2004, **2**, 3618–3627.
67. D. J. Dixon, S. V. Ley and F. Rodríguez, *Org. Lett.*, 2001, **3**, 3753–3755.
68. D. J. Dixon, S. V. Ley and F. Rodríguez, *Angew. Chem., Int. Ed.*, 2001, **40**, 4763–4765.
69. S. V. Ley, D. J. Dixon, R. T. Guy, F. Rodríguez and T. D. Sheppard, *Org. Biomol. Chem.*, 2005, **3**, 4095–4107.
70. X. Liu and J. F. Hartwig, *J. Am. Chem. Soc.*, 2004, **126**, 5182–5191.
71. U. Berens, D. Leckel and S. C. Oepen, *J. Org. Chem.*, 1995, **60**, 8204–8208.
72. U. Berens and R. Selke, *Tetrahedron: Asymmetry*, 1996, **7**, 2055–2064.
73. W. Li, J. P. Waldkirch and X. Zhang, *J. Org. Chem.*, 2002, **67**, 7618–7623.
74. D. Haag, J. Runsink and H.-D. Scharf, *Organometallics*, 1998, **17**, 398–409.
75. L. Xin, J. R. Potnick and J. S. Johnson, *J. Am. Chem. Soc.*, 2004, **126**, 3070–3071.
76. M. T. Barros, C. D. Maycock and A. M. Faísca Phillips, *Tetrahedron: Asymmetry*, 2005, **16**, 2946–2953.
77. M. T. Barros, C. D. Maycock and A. M. Faísca Phillips, *Eur. J. Org. Chem.*, 2004, 1820–1829.
78. G. A. Grasa, A. Zanotti-Gerosa, J. A. Medlock and W. P. Hems, *Org. Lett.*, 2005, **7**, 1449–1451.
79. T. K. M. Shing, G. Y. C. Leung and T. Luk, *J. Org. Chem.*, 2005, **70**, 7279–7289.
80. T. K. M. Shing, G. Y. C. Leung and K. W. Yeung, *Tetrahedron Lett.*, 2003, **44**, 9225–9228.

