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Vol. 80 Commemorative Accounts

Chiral Glycolate Equivalents for the Asymmetric Synthesis of α-Hydroxycarbonyl Compounds

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Chiral glycolic acid equivalents are used extensively for the enantioselective synthesis of α-hydroxycarbonyl compounds. Their efficacy in enolate reactions and their utility in synthetic applications are discussed, highlighting the relevance of these methods to natural product synthesis.

Hydroxycarbonyl compounds are valuable and versatile intermediates in asymmetric synthesis, particularly in the synthesis of complex structures like terpenes, carbohydrates, and alkaloids. The α-hydroxycarbonyl group is found in numerous biologically important natural products, such as okadaic acid[1] which is a potent inhibitor of serine/threonine-specific protein phosphatases, and the cytotoxic macrolide peloruside A[2] amongst many others. (Fig. 1). Methods to install asymmetrically a hydroxy group α to a carbonyl moiety in organic synthesis are therefore a useful goal.[3]

A widely used preparative procedure involves the direct oxidation of enolates.[4] Less common methods for making α-hydroxy acids and their derivatives include diazotisation chemistry,[5] asymmetric dihydroxylation methods,[6] or oxidation of terminal alkenes.[7] However, the majority of α-hydroxycarbonyl compounds are made using multi-step transformations of carbonyl groups. These routes include: α-hydroxylation of enolates with *N*-sulfonyloxaziridines;[8] reduction of α-keto esters;[9] cyanohydrin formation;[10] enzymatic methods using *Candida antarctica* or *burkholderi*[11] and *Candida parapsilosis*;[12] chromatographic resolution;[13] and recently phase-transfer methods, exemplified by the synthesis of farnesyltransferase inhibitor kurasoin A[14] and the anti-diabetes drug (−)-ragaglitazar[15] (Fig. 2).

For the purpose of this article, we have confined our discussion to the preparation and use of chiral glycolic acid (glycolate) equivalents for the synthesis of α-hydroxycarbonyl compounds.

The simplicity of the approach is attractive; attachment of a chiral protecting group to the hydroxy group of either an alcohol or the acid (or indeed both) results in a chiral glycolate equivalent **1**, which can then undergo diastereoselective enolate reactions with electrophiles (Scheme 1). Separation of the diastereomers **2** by conventional chromatographic techniques or preferably, recrystallisation, furnishes a pure diastereoisomer that can be deprotected to enantiopure α-hydroxy acids or

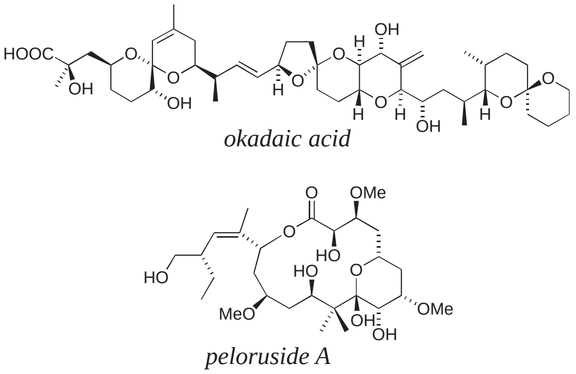


Fig. 1. Natural products containing the α-hydroxycarbonyl motif.

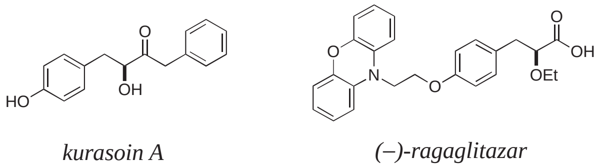
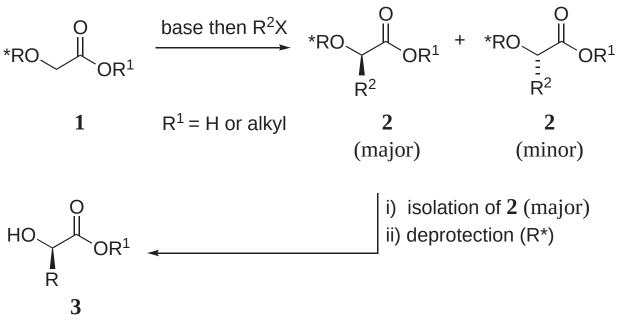


Fig. 2. α-Hydroxycarbonyl-containing pharmaceutical agents.



Scheme 1. Chiral glycolic acid (glycolate) equivalents for the synthesis of α-hydroxycarbonyl compounds.

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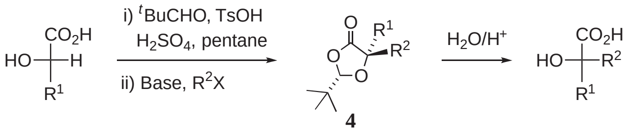


Scheme 2. Diastereoselective alkylation of enolates with alkyl halides.

α-hydroxyesters **3**. Aside from operational simplicity, this approach possesses a number of other favourable features including the broad scope associated with enolate chemistry, as well as the large variety of electrophiles that can be used to quench the enolate reactions.

Selective enolisation can be difficult in acyclic systems as the metal centre of the base (which is often lithium) tends to associate with other functional groups in the enolate, thereby distorting its geometry. For this reason the preference is for cyclic protecting groups, owing to their ability to produce rigid glycolate systems that exert complete control on enolate geometry resulting in superior diastereoselective alkylations. Careful evaluation is required when selecting an appropriate glycolate equivalent, and the pros and cons of the various systems need to be balanced. The optimum choice should possess a low molecular weight, undergo deprotection without interfering with the newly formed stereogenic centre and be efficiently separated from the products. Ideally, it should also be cheap and easy to synthesise in both enantiomeric forms, crystalline and be capable of undergoing reactions with a range of electrophiles in good yields and with excellent diastereoselectivity.

1. Chiral Dioxolanones

In terms of historical perspective, Seebach was one of the first to develop practical procedures for the asymmetric synthesis of α-hydroxy acids.[16] His ground-breaking method involved self-regeneration of the stereogenic centres of protected chiral α-hydroxy acids, such as lactic acid and mandelic acid. Simple chiral acids were protected as cyclic acetals, embedding a chiral memory into the acetal. On enolisation the original chirality associated with the acid is lost but owing to the embedded chirality in the acetal, subsequent alkylation is facially selective.

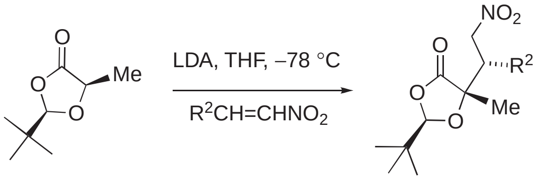
For example, the diastereoselective alkylation of enolates with alkyl halides proceeds especially well (Scheme 2 and Table 1). Symmetrical ketones, unsymmetrical ketones, and aldehydes react readily to afford compounds in which the hydrogen α to the carbonyl group is replaced enantioselectively by an alkyl group. The alkylation of enolates derived from lactic ($R^1 = Me$), phenyl lactic ($R^1 = PhCH_2$), mandelic ($R^1 = Ph$), and malic ($R^1 = CH_2CO_2H$) acids with alkyl halides proceeded in good yield and with excellent diastereoselectivity for both activated and unactivated alkyl halides.[17a]

Yields for the formation of the phenyl lactic acid derivatives were improved from 30–45 to 76–84% (not shown) when LHMDS was used for enolate generation.[17a] The dioxolanones gave chiral enolate derivatives from pivaldehyde, lactic acid, and mandelic acid which were reacted with symmetric and non-symmetric ketones or aldehydes to provide the corresponding aldol products in yields of 81–87% and with diastereoselectivities ranging from 82–95%.[17b]

Table 1. Alkylation Reactions of Dioxolanones

R^1	R^2	Yield of **4**/%	de of **4**/%
Me	EtI	82	97
Me	PrI	72	97
Me	BuI	68	97
Me	$C_7H_{15}I$	84	96
Me	$CH_2=CHCH_2Br$	77	98
Me	$PhCH_2Br$	81	96
Ph	PrI	84	95
$PhCH_2$	MeI	30	>95
$PhCH_2$	EtI	45	>95
$PhCH_2$	PrI	40	>95
$PhCH_2$	$CH_2=CHCH_2Br$	40	>95
CH_2CO_2H	Me	79[a)]	>95
CH_2CO_2H	$CH_2=CHCH_2Br$	76[a)]	>95
CH_2CO_2H	$PhCH_2Br$	77[a)]	>95

a) LHMDS was used as base. LDA was used in the remaining experiments.



Scheme 3. Michael additions of dioxolanones to nitro-olefins.

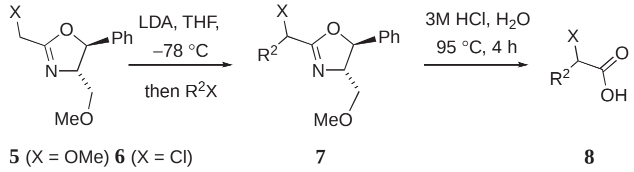
Stereocentres can also be generated by the Michael addition of dioxolanones to nitro-olefins to give adducts in moderate to good yield (40–80%) with diastereoselectivities ranging from 85–95% (Scheme 3).[17c]

These pioneering methods have been applied widely in organic synthesis; including in the preparation of β-lactams by the addition reactions of 1,3-dioxalan-4-one derived enolates to imines;[18] in performing key transformations towards the synthesis of the natural products such as eremantholide A[19] and the antitumour pyrrolizidine alkaloid indicine *N*-oxide[20] and achieving an enantioselective synthesis of asymmetric benzoins.[21] These methods have likewise underpinned research into diastereoselective radical reactions[22] and synthetic approaches to natural products.[23] However, the range of easily accessible enantiopure α-hydroxy acids (by synthesis or commercial availability) remains a limiting factor.

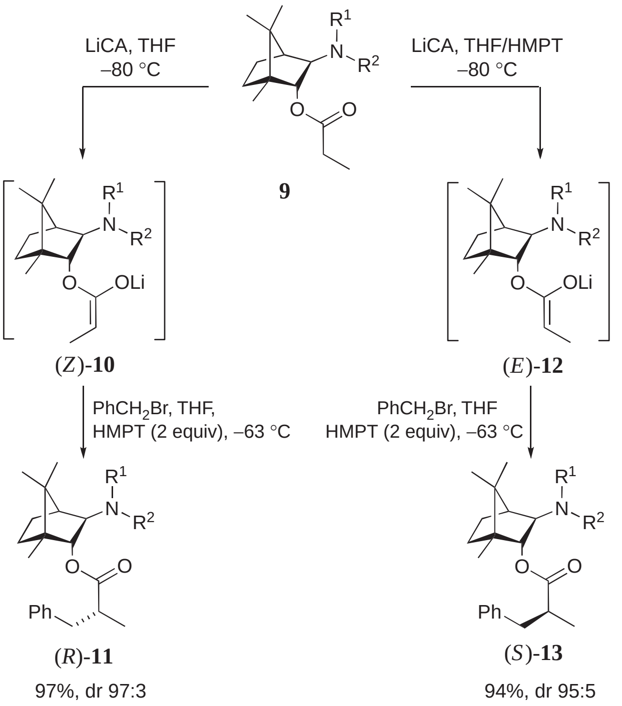
2. Carbonyl-Tethered Auxiliaries

The majority of chiral glycolate equivalents to emerge from the literature involve the tethering of an appropriate chiral auxiliary to the carbonyl group of the glycolic acid moiety with additional protection of its hydroxy group. Procedures describing their use vary according to the control of enolate geometry and the inability to predict the control exerted by the chiral auxiliary.

2.1 Oxazolines. The chiral oxazolines **5** and **6** have been used for the asymmetric synthesis of α-methoxy and α-chloroalkanoic acids **8**.[24] They can be alkylated using simple alkyl



Scheme 4. Asymmetric synthesis of α-methoxy and α-chloroalkanoic acids.



Scheme 5. Camphor sulfonamide glycolate equivalents as carbonyl-tethered auxiliaries.

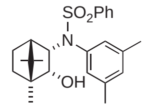
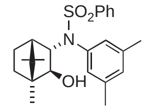
iodides, sulfates, and tosylates to afford products in good yields; 90–97% starting from **5** and 85–94% from **6**. Acid-catalysed cleavage of the auxiliary gave products with generally poor ee's. After conversion to methyl esters, the ee's of the α-methoxy acids ranged from 12–42% while those of the α-chloro acids where high reaction temperatures were used ranged from 2–28% (Scheme 4).

2.2 Camphor Sulfonamide Glycolate Equivalents. The lithium enolates of **9** underwent alkylation in the presence of benzyl bromide with very high diastereoselective control but with markedly different preferences depending on the initial enolate geometries (Scheme 5 and Table 2).

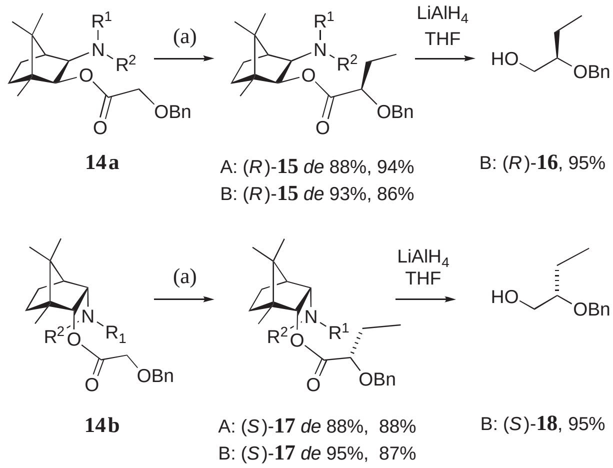
On low-temperature metallation with lithium cyclohexylamide (LiCA) in THF the esters **9** selectively formed the (*Z*)-enolate **10** which gave preferentially the (*R*)-product **11** in a 97:3 ratio, while the addition of hexamethylphosphoric acid triamide (HMPT) to the solvent system resulted in predominantly the (*E*)-form of the enolate **12** which gave the (*S*)-products **13** in a 95:5 diastereomeric ratio.[25a]

By contrast, alkylation reactions involving the lithium enolates of the *cis*-*O*-benzyl glycolates **14** were shown to proceed via an alternative mechanism, as almost identical product ratios were obtained under both sets of conditions (Scheme 6).[25]

Table 2. Alkylation of Camphor Sulfonamide Derivatives

ROH	Solvent[a)]	dr (%) **11**:**13**	Combined yield/%
	A	97:3	97
	B	5:95	98
	A	2:98	90
	B	76:24	98

a) Solvent system: A. LiCA in THF; B. LiCA in THF/HMPT.



(a) i) LiCA, −80 °C, THF (A) or THF/HMPT (B). ii) EtI, −63 °C

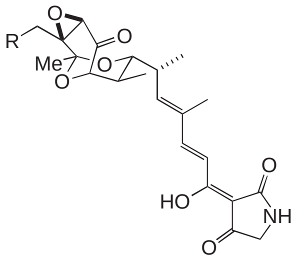
Scheme 6. Alkylation reactions involving the lithium enolates of the *cis*-*O*-benzyl glycolates.

Intermediate compounds **15** and **17** were formed in good to excellent yields ranging from 87–97% and with good diastereoselectivities of 88–95%. Subsequent hydride reduction to the respective alcohols **16** and **18** also proceeded in excellent yield (95%) with complete preservation of the newly formed stereogenic centre.

This method appears promising for stereochemical control in acyclic systems, but the relatively small number of examples reported to date detracts from the generality of the approach. A further drawback is the large-scale synthesis of the high molecular weight auxiliary from (+)-camphor that requires the use of the oxidant SeO_2.[25b] Although camphor sulfonamide auxiliaries **7** and **8** are now commercially available, they have yet to inspire wider use as chiral glycolate equivalents.

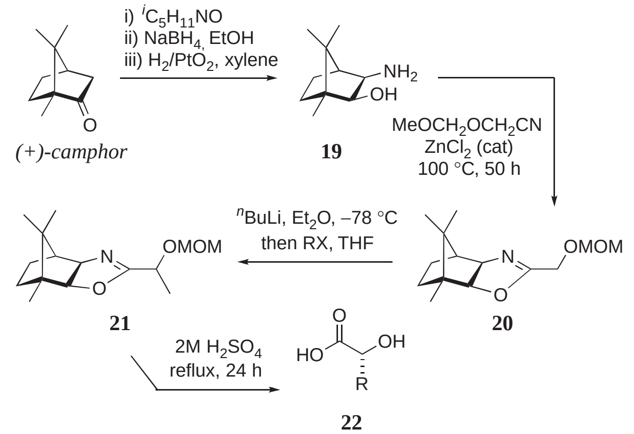
2.3 Camphor-Derived Oxazolines. A conceptually better approach involves a chiral glycolate equivalent based on a camphor-derived oxazoline. These methods were devised to enable access to antibiotic natural products tirandamycin A and B (Fig. 3).[26]

The oxazoline **20** was obtained in four steps from (+)-camphor, first by reaction of camphor with isoamyl nitrite then by using successive reduction steps with $NaBH_4$ and H_2/PtO_2 which gave **19** in yields (72–76%). Heating amine **19** with an



tirandamycin A (R = H)
tirandamycin B (R = OH)

Fig. 3.



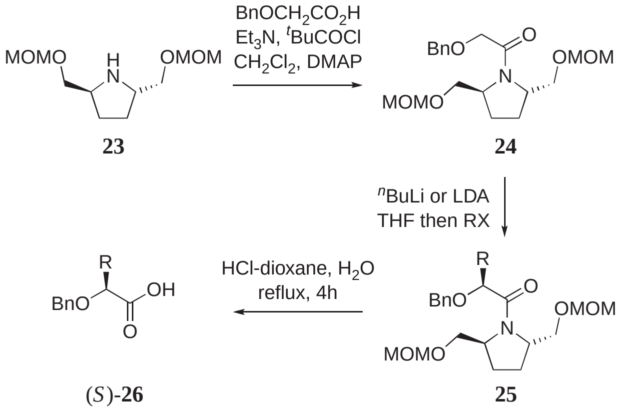
Scheme 7. Camphor-derived oxazoline employed in the synthesis of tirandamycin A and B.

Table 3. Synthesis of Enantio-Enriched α-Hydroxy Acids **22** via a Camphor-Derived Oxazoline

RX	ee of **22**/%	Yield of **22**/%
$PhCH_2Br$	92	70
$(CH_3)_2CHCH_2I$	88	72
^{i}PrI	87	26
^{n}PrI	86	57
EtI	77	42

appropriate nitrile in the presence of catalytic amount of $ZnCl_2$ led to the oxazoline **20** in 48% yield (Scheme 7).

Glycolate alkylation reactions of **20** and subsequent acid-catalysed cleavage of the auxiliary were carried out sequentially in a one-pot procedure to provide the (*R*)-hydroxy acids **22** with good enantiomeric excesses (72–92%) (Scheme 7). This system has desirable features for stereoselective anion generation and provides a good opportunity for diastereofacial selectivity during alkylation. However, the yields for hydrolysis to the acids were often low (26–72%) (Table 3). Moreover, effective separation of diastereoisomers at the intermediate stage without chromatography was not possible and would therefore be problematic on scale-up.

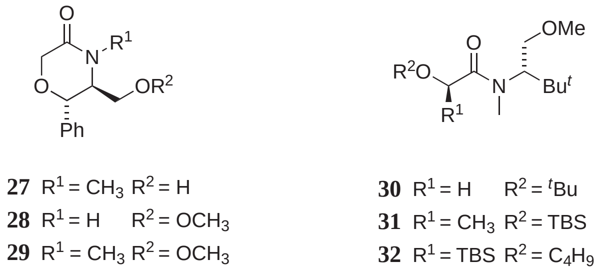


Scheme 8. Alkylation of pyrrolidine auxiliary **24**.

Table 4. Alkylation of Pyrrolidine Auxiliary **24**

RX	Yield of **25**/%	de of **25**/%	Yield of **26**/%
CH_3I	92[a)]	97	88
$PhCH_2Br$	91[a)]	98	89
BuI	77[a)]	96	83
$C_8H_{17}I$	72[b)]	96	73
$PhCH_2O(CH_2)_6I$	65[b)]	96	84
$(CH_3)_2CHOTf$	76[c)]	97	65

Alkylation additions: a) −78 °C; b) base at −78 °C then add RX at −78 °C and allow to warm to −20 °C; c) −20 °C.



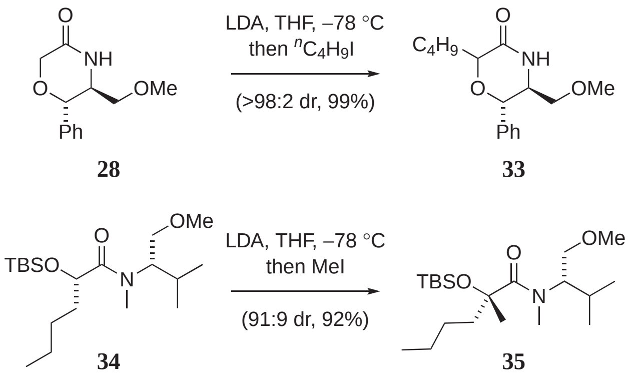
Scheme 9. Cyclic and acyclic chiral amide auxiliaries.

2.4 Pyrrolidine Auxiliaries. The asymmetric synthesis of α-hydroxy acids via alkylation of chiral *N*-(benzyloxyacetyl)-*trans*-2,5-bis(methoxymethoxymethyl)pyrrolidine (**24**) and subsequent hydrolysis was a particularly effective method that produced some of the highest literature reported de's for the asymmetric alkylation of glycolate derivatives (Scheme 8).[27]

For the alkylation reactions of **24**, methyl iodide and benzyl bromide reacted smoothly at −78 °C while other primary iodides required slightly elevated temperatures (−20 °C) to ensure the reaction went to completion and although isopropyl iodide was a poor electrophile, alkylation could be achieved using isopropyl triflate (Table 4).

In general, the alkylation of the glycolate **24** proceeded in good yield (65–92%) and with very high diastereoselectivity (96–98%). The compounds were hydrolysed to the corresponding acids **26** by refluxing in aqueous HCl–dioxane, again with respectable yields (65–89%) and without detectable racemisation. It should be noted that **23** is not yet a commercially available starting material.

2.5 Amide Auxiliaries. Cyclic and acyclic chiral amide derivatives, **27**–**29** and **30**–**32** respectively, including *tert*-butyl and trialkylsilyl-protected glycolic and lactic acids, provide efficient access to α-hydroxy acid compounds (Scheme 9; see also Section **4.1**).[28]



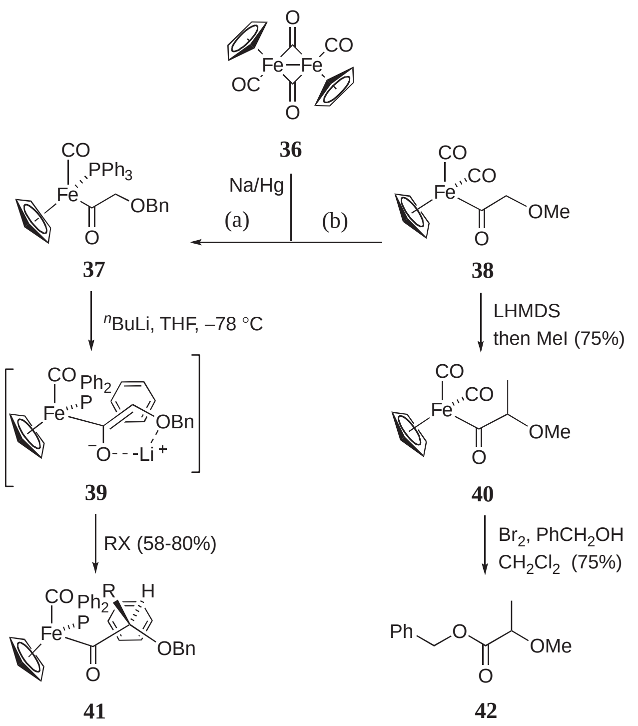
Scheme 10.

For example, chiral glycolic amides **28** and **34** have been used to prepare derivatives **33** and **35** respectively with yields of 99 and 92% and de's of 96 and 82% (Scheme 10). These compounds could then be hydrolysed by refluxing in dilute HCl to afford the corresponding α-hydroxy compounds, without any observable racemisation of the newly formed chiral centre. Removal of the auxiliary using triethyloxonium tetrafluroborate followed by hydrolysis enabled deprotection under milder conditions, but with the formation of amide by-products.

2.6 Acyl Iron Complexes. The chiral iron complex **37** $[\eta^5$-$(C_5H_5)Fe(CO)$-$(PPh_3)COCH_2OBn]$ is a novel chiral glycolate equivalent which has been used in the stereoselective synthesis of α-hydroxy acid derivates (Scheme 11).[29] It undergoes stereoselective alkylation, deuteration, and aldol reactions via the corresponding (*E*)-enolate, in addition to hydrogenation to form the corresponding hydroxy acetal complex. This iron complex **37** was prepared by first reducing iron dimer complex **36** with sodium amalgam, then treating the resulting nucleophilic iron anion with chloromethyl benzyl ether. Complex **37** arises from the treatment of triphenylphosphine in the presence of calcium hydroxide in refluxing acetonitrile.

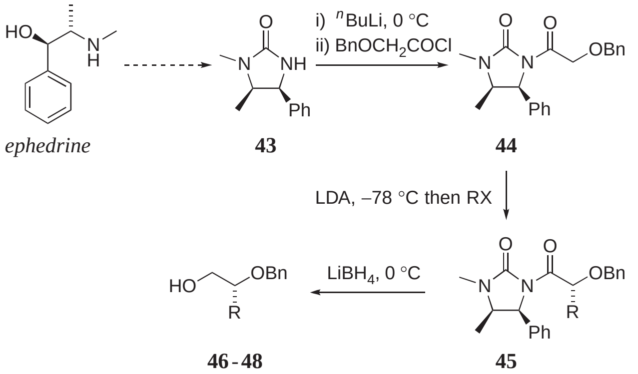
Alkylation reactions of **37** with ethyl iodide, isopropyl iodide, allyl bromide, and benzyl bromide using butyllithium all proceeded with excellent 100:1 diastereomeric ratios in yields ranging between 58–80% (Scheme 11). Methyl iodide resulted in a reduced diastereomeric ratio (60:1).

The ferrate anion produced after reduction of **36** could also be quenched with methoxyacetyl chloride to give complex **38**. After formation of the enolate with lithium hexamethyldisilazide (LHMDS), this alternative complex was alkylated with methyl iodide. On deprotection by oxidative decomplexation with bromine in benzyl alcohol, the corresponding α-methoxy ester **42** was liberated in 75% yield. While the stereoselectivity using the iron acyl derivatives can be excellent, the high molecular weight, cost and thermal stability of these complexes can be issues.



(a) i) $ClCH_2OBn$; ii) PPh_3, $Ca(OH)_2$, MeCN (45%)
(b) $ClCOCH_2OMe$ (67%)

Scheme 11. An unusual chiral glycolate equivalent used in stereoselective synthesis of α-hydroxy acids.

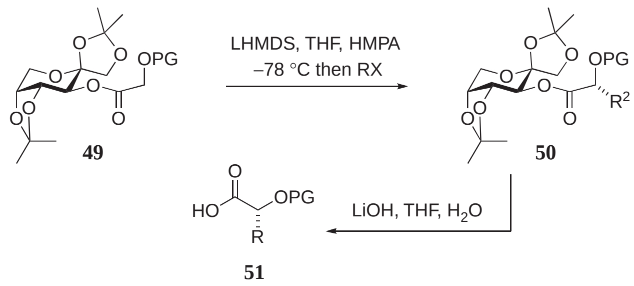


Scheme 12. Ephedrine-derived glycolate imides used for preparing 2-benzyloxy alcohols and 1,2-diols.

Table 5. Alkylation of Ephedrine-Derived Imides **43**

R	Yield of **44**/%	de/%	Yield of ROH/%
$PhCH_2$	87	92	(**46**) 84
$MeCH{=}CH_2CH_2$	75	92	(**47**) 82
$BnOCH_2$	68	94	(**48**) 85

2.7 Ephedrine-Derived Imides. Chiral glycolate imides derived from ephedrine have been used for the enantioselective synthesis of 2-benzyloxy alcohols and 1,2-diols.[30] This arises from the condensation of ephedrine to give the cyclic urea building block **43**.[31] This was converted into glycolate imide **44** by reaction of it lithium anion with an equimolar amount of benzyloxyacetyl chloride (Scheme 12). Deprotonation of the glycolate imide with LDA furnished a chiral enolate that underwent alkylation with alkyl halides to give **45** (Table 5). Three examples of the alkylated product **45** prepared by this method were reported with excellent de's (92–94%) and in reasonable yields (68–87%). Subsequent reduc-



Scheme 13. Fructose bis-acetonide as the chiral auxiliary.

Table 6. Alkylation of Fructose Derivatives **49**

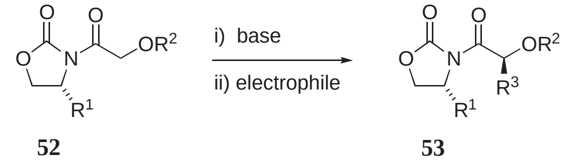
PG	RX	Yield of **50**/%	de of **50**/%
Bn	$PhCH_2Br$	58	98
Bn	EtI	74	76
Bn	$PhCH_2CH_2Br$	52	79
TES	$CH_2{=}CHCH_2I$	71	91
TES	$PhCH_2Br$	75	96
TES	EtI	83	88
TES	$PhCH_2CH_2I$	61	60
TES	BuI	58	83
TES	2-Bromomethylnaphthalene	71	91

tive cleavage of the intermediates with lithium borohydride gave 2-benzyloxy alcohols (**46**–**48**) in yields ranging between 82–85%.

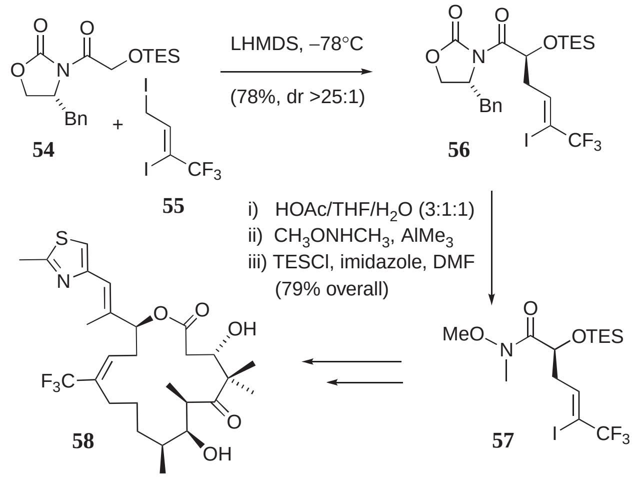
Diols were also prepared using either a single hydrogenolysis step (palladium on carbon) as in the case of **46**, or preceding hydrogenolysis by oxidative cleavage with ozone followed by borohydride reduction in the case of **47**, or with prior acylation with propanoyl chloride in the case of **48**. All three known chiral diols were obtained in very high yields (92–95%) and ee's of 91–92%. Application of this methodology to the other enantiomer revealed similarities in yield and selectivity. The relatively cheap chiral auxiliaries were also readily recycled without any loss of activity.

2.8 Fructose Derivatives. Compounds containing different alcohol protecting groups have been prepared from the glycolate system **49**, which exploits the fructose bis-acetonide as the chiral auxiliary. TES and benzyl-protected variants gave the best overall results in terms of yield and diastereoselectivity for subsequent enolate alkylations (Scheme 13 and Table 6).[32]

Modest diastereoselectivities of 60–98% were observed in most cases and yields were moderate (52–75%) even with the addition of HMPA. HMPA appeared to have a negligible effect on the selectivity of alkylations with methyl iodide and allyl iodide, with the exception of the alkylation of the TES-protected auxiliary with ethyl iodide. This produced the corresponding hydroxycarbonyl compound in 83% yield and a better than average de (88%). Reactivity with unactivated alkyl halides was notably lower and the otherwise reactive allyl iodide did not show particularly high conversion. Although cheap, the relatively high molecular weight auxiliary (301 daltons) is a disadvantage. The opposite (*S*)-configuration required a 4-step synthesis from L-sorbose.[33]



Scheme 14. Oxazolidinone-derived auxiliaries.

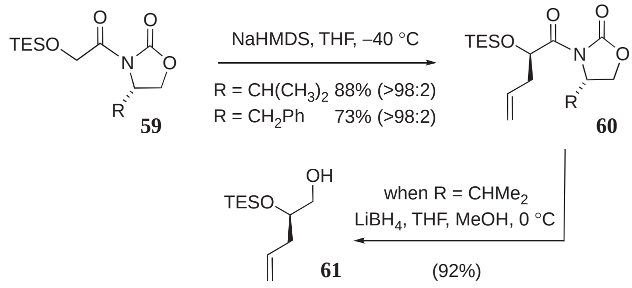


Scheme 15. TES-protected oxazolidinone auxiliaries in the synthesis of epothilones analogues.

2.9 Oxazolidinones and Related Systems. The powerful oxazolidinone-derived auxiliaries introduced by Evans[34] are useful for a wide range of enolate reactions including glycolate enolate chemistry (Scheme 14).[35] They are commercially available and can be removed with ease, recovered and recycled. Despite this, the enolates of glycolate derivatives **52** tend to be unpredictable in simple enolate alkylations, and in order for these to be successful, highly reactive electrophiles such as allylic iodides must be used in the alkylation step. The choice of protecting group for oxygen is also an important consideration, with preference usually given to more robust options.

The epothilones are important natural products offering promising antitumour properties with the synthesis of epothilone analogues providing an excellent example of the use of oxazolidinone auxiliaries **54**.[36] Building on earlier methodology for the epothilones series,[36a] the preparation of epothilone analogue **58** required the introduction of a trifluoromethyl group to one of the fragments.[36b] This was achieved using the TES-protected oxazolidinone derivative **56** (Scheme 15). The choice of silyl *O*-protection meant deprotection would be feasible without adverse effects on the sensitive iodoalkene moiety. However, the final choice of silyl protection required some prior investigation. At first, TMS, TBS, and TBDMS were tried but these led to the auxiliary being cleaved during the alkylation step. Finally, TES-protection permitted scalable asymmetric alkylations and was easy to remove.[37]

The allylic iodide **55** bearing a trifluoromethyl group (generated from the corresponding alcohol) was reacted with the lithium enolate of oxazolidinone **54** using LHMDS as the base. This gave **56** in a 78% yield with a diastereomeric ratio greater than 25:1. Removal of the auxiliary in three steps afforded the



Scheme 16. 4-Substituted oxazolidinones in synthesis.

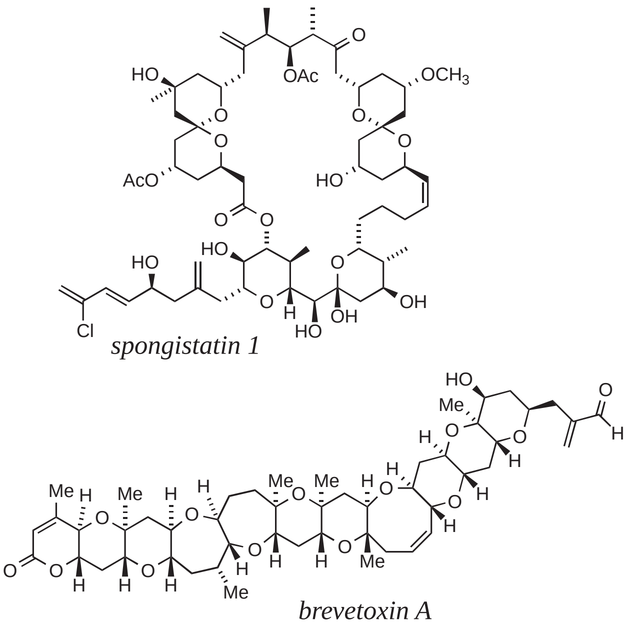


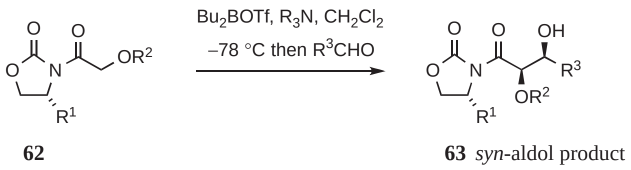
Fig. 4. Complex natural product targets prepared in part using oxazolidinone-based methodology.

corresponding Weinreb amide **57** which was then taken through to the epothilone derivative **58**.

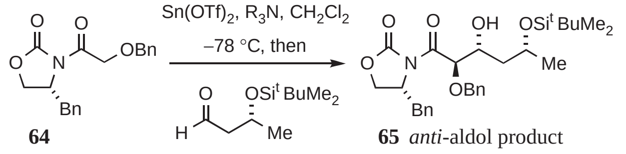
A study of glycolate alkylations of 4-substituted oxazolidinones with allylic iodides and different alcohol protecting groups was published alongside the above work.[38] It demonstrates how a valine-derived oxazolidinone system **59** (where R is CHMe$_2$) displays similar, if not slightly better reactivity towards electrophiles possessing a range of alcohol protecting groups, including TES, when compared to the benzyl-substituted auxiliaries (Scheme 16).

Valine-derived oxazolidinones were used to synthesise selectively protected 1,2-diols. These approaches were later used in the synthesis steps towards a number of complex natural product syntheses, including brevetoxin A,[39] spongistatin (Fig. 4),[40] and (−)-laulimalide.[41] The aldol reactions of oxazolidinone glycolates have also been widely used in asymmetric processes and have been incorporated into a great many natural product syntheses by other researchers.[42]

Under the commonly used boron aldol conditions (dibutylboron triflate plus an amine) the reaction of oxazolidinone **62** favoured the formation of the *syn*-aldol product **63** with excellent diastereoselectivity (Scheme 17). The outcomes and preferences of these reactions were reliable with only a few exceptions.[43] The improved selectivity is attributed to the shorter boron–carbon and boron–oxygen bond lengths when compared with the lithium equivalents[44] and thus the comparatively more compact enolate transition state that is generated.



Scheme 17. Boron aldol conditions favour the formation of the *syn*-aldol products.



Scheme 18. *anti*-Aldol products from the enolate of benzyloxyoxazolidinone.

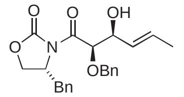
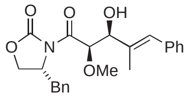
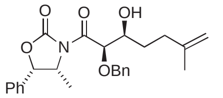
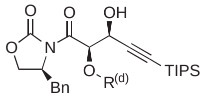
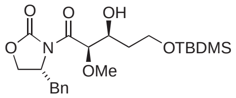
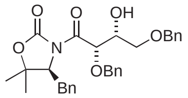
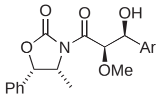
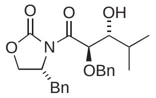
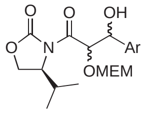
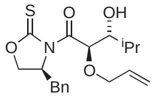
In contrast to what is often referred to as the Evans' aldol conditions above, the complementary titanium-mediated route to *syn*-aldol products attributed to Crimmins, can also be employed.[41,45] Evans later reported how the addition of isobutyl aldehyde to the tin(II) enolate of benzyloxyoxazolidinone resulted in *anti*-aldol products.[46] This was used to good effect in the synthesis of the spiroketal-containing antibiotic griseusin A, where fragment **65** was obtained as the major aldol product in 60% yield (Scheme 18).[47]

anti-Aldol additions have been achieved using the titanium-mediated enolization of an *N*-glycolyloxazolidinethione in combination with (−)-sparteine. Aldehydes activated with TiCl$_4$ are added to the enolates that demonstrate a strong preference for *anti*-aldol products with no observable *syn*-isomer formation. The best results in terms of yield and selection were observed using the allyl-protected glycolates.[48] A selection of results and conditions of such aldol reactions are shown in Table 7.[49] Overall, these versatile methods for the formation of α-hydroxy acids are clearly excellent and have been used extensively owing to their ready availability of starting materials.

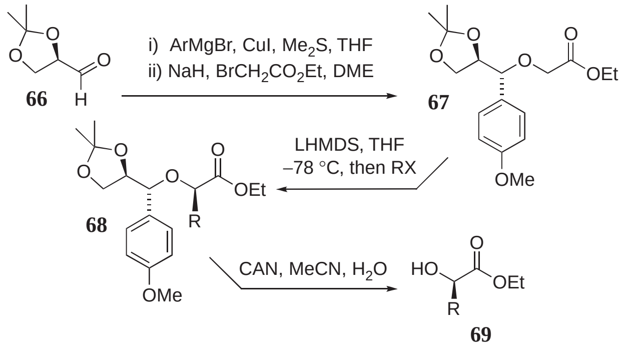
3. Alcohol-Tethered Auxiliaries

3.1 Glyceraldehyde-Derived Systems. (*R*)-Glyceraldehyde acetonide **66** was elaborated first by diastereoselective Grignard addition then by reaction of ethylbromoacetate with the intermediate secondary alcohol to furnish **67** (Scheme 19 and Table 8).[50] Good diastereoselectivities for the alkylation of **67** were obtained but yields of the alkylated product **68** with unactivated and smaller alkyl halides were generally poor. Prolonged reaction times and the use of stronger bases only helped lower the selectivity, presumably by epimerisation. Deprotection of the auxiliary, however, with cerium ammonium nitrate to unveil the α-hydroxycarbonyl compounds **69** was found to proceed in good yield (71–75%) although the same conditions would appear not to suit more labile substrates.

Table 7. Selected Aldol Reactions

Entry	Aldol product	Reaction conditions	de or dr	Yield /%	Entry	Aldol product	Reaction conditions	de or dr	Yield /%
1		Bu$_2$BOTf[a]	—	92	6		Bu$_2$BOTf[a]	3:2:2:1	—
2		Bu$_2$BOTf[a]	>98	78	7		TiCl$_4$, NMP[c]	>20:1	93
3		Bu$_2$BOTf[b]	—	95	8		Bu$_2$BOTf[b]	94	77
4		Bu$_2$BOTf[b]	>92 (15:1)	99	9		Sn(OTf)$_2$ TMEDA[a]	77:23	63
5		LDA	48:29:10	87	10		TiCl$_4$ (−)-sparteine	87:13	61

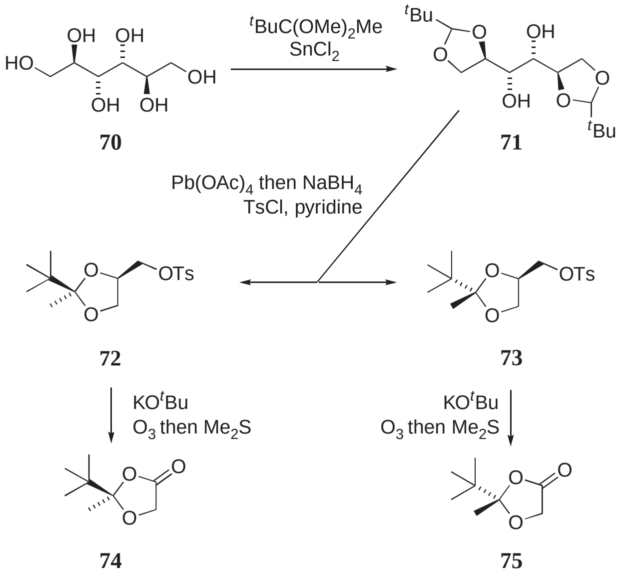
Base: a) Et$_3$N; b) ^{i}Pr$_2$NEt; c) DIPEA; d) R = (*S*)-CH(CH=CH$_2$)CH$_2$OBn.



Scheme 19.

Table 8. Alkylation of (*R*)-Glyceraldehyde Acetonide Derivative **67**

RX	Yield of **68**/%	dr of **68**	Yield of **69**/%
MeI	86	100:1	71
EtI	25	130:1	73
EtOTf	85	16:1	—
CH$_2$=CHCH$_2$Br	36	180:1	77
PhCH$_2$Br	77	>300:1	85

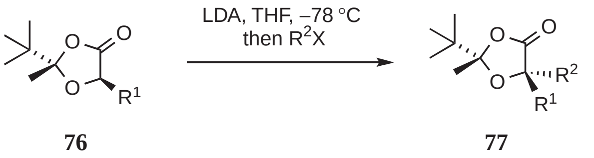


Scheme 20.

3.2 Dioxolanone Auxiliary. A non-racemic glycolic acid equivalent was prepared by reacting the inexpensive D-mannitol (**70**) with pinacolone dimethyl acetal to form the corresponding acetal derivative **71** (Scheme 20). After elaboration through cleavage and tosylation, the crystalline dioxolanone derivatives **72** and **73** were produced and separated by recrystallisation or chromatography.[51] The diastereomers were converted (separately) into the two enantiomers of the chiral glycolate equivalent **74** and **75**.

While the additional methyl group in these auxiliaries provided additional stability during subsequent alkylation reactions, the diastereoselectivity was noticeably poorer. As a result the dioxolanones have found little use (Scheme 21 and Table 9).

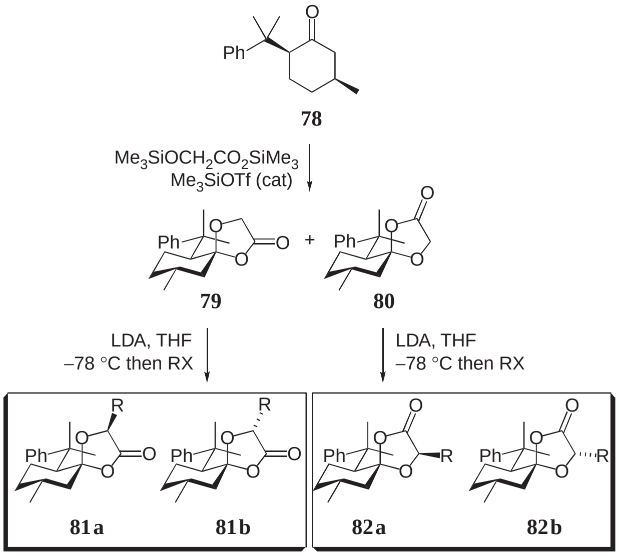
3.3 Phenylmenthone-Based Systems. 8-Phenylmenthone **78** which is readily obtained from pugelone,[52] was a suitable precursor for the preparation of spirocyclic 1,3-dioxolan-4-one-derived chiral glycolate equivalents **79** and **80**, which were prepared from **78** by Lewis acid-catalysed acetal formation.[53] The two dioxolanones were produced in 74% yield in a 1.3:1 ratio (**79**:**80**) which required separation by chromatography (Scheme 22).



Scheme 21.

Table 9. Alkylation of the Mannitol-Functionalised Auxiliary **76**

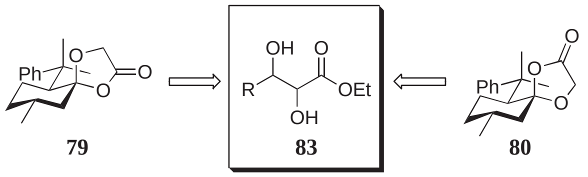
R^1	R^2	Yield of **77**/%	dr of **77**
H	$(CH_2)_3CH{=}CH_2$	69	2.2:1
$(CH_2)_3CH{=}CH_2$	PhSe	79	3:1
H	PhSe	90	1.5:1
SePh	$CH_2C{\equiv}CSiMe_3$	86	2:1
H	$CH_2CH{=}CH_2$	80	3:1
$CH_2CH{=}CH_2$	$(CH_2)_2CH{=}CH_2$	60	2:1
$CH_2CH{=}CH_2$	$CH_2C{\equiv}CH$	60	2.5:1



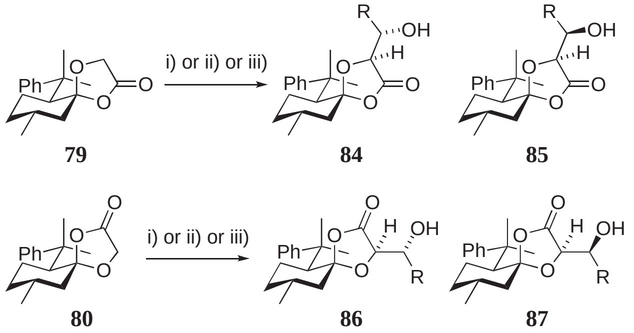
Scheme 22.

Table 10. Alkylation of Phenylmenthone-Based Systems

RX	Yield of **81**/%	dr a:b	Yield of **82**/%	dr a:b
MeI	97	14:1	99	24:1
$CH_2{=}CHCH_2I$	97	42:1	96	123:1
^{n}BuI	96	58:1	92	>123:1
$PhCH_2Br$	85	24:1	82	28:1



Scheme 23.



i) LDA, THF, –78 °C then RCHO; ii) LDA, THF, –78 °C, $MgBr_2$ then RCHO; iii) LDA, THF, –78 °C, Cp_2ZrCl_2 then RCHO

Scheme 24.

Table 11.

Aldehyde	M^+	From lactone **79**		From lactone **80**	
		Yield/%	dr	Yield/%	dr
PhCHO	Mg^{2+}	92	4.8:1	89	3:1
^{n}PrCHO	Li^+	93	25.3:1	96	8:1
^{i}PrCHO	Li^+	85	9.4:1	86	26.2:1
PhCHO	Zr^{4+}	95	1:4.3	91	1:4.7
^{n}PrCHO	Zr^{4+}	97	1:1.2	91	1:1.7
^{i}PrCHO	Zr^{4+}	91	1:3.1	89	1:5

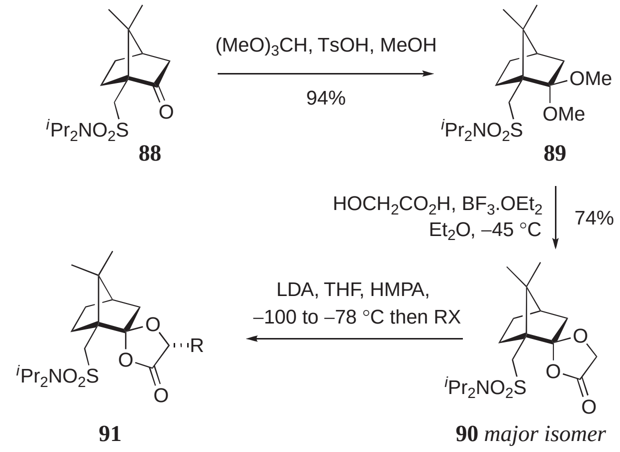
S-hydroxy esters were prepared from **79** and the corresponding *R*-hydroxy esters from lactone **80**. In both cases alkylation proceeded in excellent yield (82–99%) with good to excellent diastereoselectivity (Table 10). The α-hydroxy esters were obtained in good yields (83–95%) by deprotection with HCl–EtOH at reflux with no observed loss of enantiomeric purity.

Enolates of **79** and **80** also undergo aldol condensations with aldehydes to afford α,β-hydroxy esters **83** after ethanolysis.[54a] The method allows any one of the four possible stereoisomers of **83** to be prepared selectively (Scheme 23).

The absolute stereochemistry at C-2 can be controlled by selecting the appropriate dioxolanone, **79** or **80**, while stereocontrol at C-3 is governed by the choice of enolate counterion. Lithium and magnesium enolates gave the *anti*-diol products **84** and **86** whereas zirconium enolates gave the corresponding *syn*-diol products **85** and **87** (Scheme 24 and Table 11). The reactions were facially selective with regard to the glycolate enolate and showed only poor to moderate selectivity at the newly formed alcohol centre. The compounds were finally deprotected with acidified ethanol in good yield (81–95%). The method was applied to a synthesis of the aminopeptidase B inhibitor bestatin.[54b]

3.4 Camphor Sulfonamide Derivatives. Acetalisation of camphor sulfonamide **88** followed by acetal exchange produced a camphor-derived glycolate derivative **90**.[55] This was obtained as the major isomer in a 12:1 mixture of diastereomers at the acetal centre and required separation by recrystallisation or chromatography (Scheme 25).

The diastereoselectivities for the subsequent alkylation reactions with alkyl halides were excellent (>98%) and the yields



Scheme 25.

Table 12. Alkylation of Camphor Sulfonamide Derivatives

R	Yield of **91**/%		de/%
	Without HMPA	With HMPA	
Me	84	86	>98
$CH_2{=}CHCH_2$	76	83	>98
Et	36	65	>98
$PhCH_2$	60	70	>98

moderate to good ranging from 65–86% when HMPA was used as an additive (Table 12).

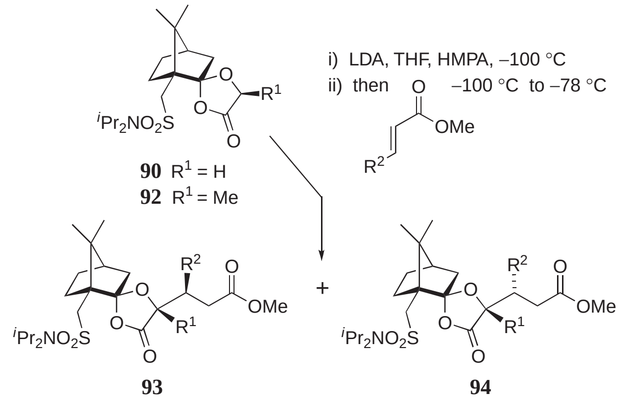
Diastereoselectivity was considerably enhanced by performing both the enolate formation and the addition of the alkylation agent at −100 °C (then allowing the reaction to warm to −78 °C). For example, a de of 93.5% was obtained in the case of the methyl-alkylated product when the procedure was performed at −78 °C, whereas at −100 °C this was raised to >98%. In addition, formation of fully substituted α-hydroxy acids was investigated by acetalisation of the auxiliary with lactic and mandelic acids, followed by subsequent enolate alkylation. These reactions proceeded in good yields (67–84%) and with excellent de (>98%).

Michael additions involving chiral glycolate **90** and the lactate derivative **92** have also been described that provide adducts in excellent yields and with excellent selectivities across a range of substituted acrylate esters.[56] The Michael addition of enolates obtained from **90** and **92** to the esters took place selectively on different faces (*Si* and *Re* respectively) of the double bond. This methodology was applied to a synthesis of (+)-crobarbatic acid (Scheme 26 and Table 13).

4. Six-Membered Ring Containing Chiral Auxiliaries

4.1 Morpholine-3-one-Derived Auxiliaries. Chiral glycolate lactams **95–97** showed variable selectivity during alkylation reactions to yield products based on **98**,[28] although alkylation with methyl iodide failed (Scheme 27 and Table 14).

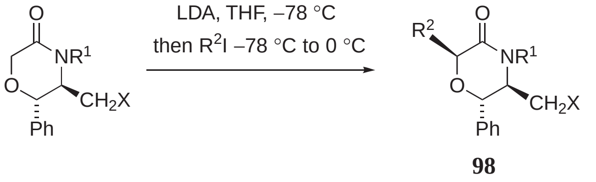
4.2 Diaryl Dioxalones. Chiral glycolates **101** and **102** have been used extensively in *anti*-selective glycolate aldol reactions.[57] They were obtained by Sharpless asymmetric dihydroxylation of the corresponding stilbenes **99** followed by tin-mediated cyclisation of the intermediates **100** (Scheme 28 and Table 15).



Scheme 26.

Table 13.

R^1	R^2	Yield/%	dr of **93**:**94**
Me	H	88	>99:1
Me	Ph	78	>99:1
Me	Pr	88	>99:1
Me	^{i}Pr	84	>99:1
H	H	76	<1:99
H	Me	82	<1:99
H	Ph	77	<1:99



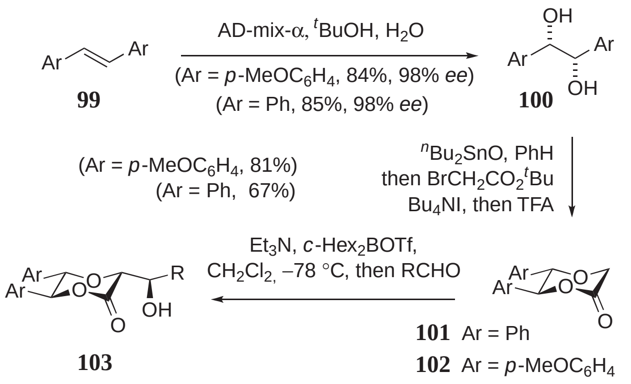
95 R^1 = Me, X = H; **96** R^1 = H, X = OMe; **97** R^1 = Me, X = OMe

Scheme 27.

Table 14. Alkylation of Morpholine-3-one-Derived Auxiliaries

Glycolate	R^2I	Yield of **98**/%	dr
95	^{n}BuI	85	54:46
96	MeI	0	—
96	^{n}BuI	99	>98:2
96	EtI	84	95:5
97	MeI	95	55:45

Selectivities in aldol reactions varied from poor to fairly high for the *anti*-diol products obtained from the cyclic glycolate equivalents **101** and **102**. The minor diastereomers obtained were assigned as the corresponding axial *anti*-diol products arising from electrophilic attack on the opposite face of the cyclic enolate. In some cases, *syn*-diastereoisomers were also observed. The *p*-methoxyphenyl derivative was introduced to allow milder deprotection under oxidative conditions (the phenyl auxiliary requires high-pressure hydrogenation at 100–200 psi) but shows lower diastereoselectivities in most



Scheme 28. Selective glycolate aldol reactions using chiral gylcolates **101** and **102**.

Table 15. Aldehyde Substrate Scope

Glycolate	Aldehyde	Yield/%	dr
101	EtCHO	92	>20:1
101	^{n}C$_5$H$_{11}$CHO	92	10:1
101	^{i}BuCHO	91	8:1
101	PhCHO	81	6:1
101	1-Naphthyl-CHO	71	4:1
101	PhCH=CHCHO	77	6:1
101	PhC≡CCHO	79	7:1
101	*S*-Glyceraldehyde acetoniden	62	16:1
101	*S*-Glyceraldehyde acetonide	70	6:1
102	EtCHO	82	11:1
102	^{i}PrCHO	91	11:1
102	^{i}BuCHO	83	12:1
102	*c*-HexCHO	78	7:1
102	PhCHO	81	2:1
102	PhCH=CHCHO	87	4:1
102	PhCH=CMeCHO	93	4:1
102	PhC≡CCHO	94	5:1

cases. The auxiliary can be removed by basic hydrolysis followed by CAN-mediated oxidative deprotection. Both these *anti*-selective aldol reactions and *syn*-selective reactions of a Masamune norephedrine ester auxiliary were applied to a total synthesis of the Hsp90 inhibitor (+)-geldanamycin (Fig. 5).[58]

Chiral α-hydroxy-β-keto esters were produced in yields over 90% by an asymmetric Ti-mediated crossed-Claisen condensation of a six-membered ring derivative derived from atrolactic acid (Scheme 29). After further elaboration, these esters were incorporated into the synthesis of the natural angiogenesis inhibitor (−)-azaspirene and the optically active compound altanaric acid (Fig. 5).[59]

4.3 Dispiroketal-Based Systems. Our own work on the use of dispiroketals[60] as an easily decorated, well-defined skeletal motif in synthesis applications has been reviewed.[61] The low molecular weight of dispiroketals, their propensity for divergent substitution patterns, their facile preparation and the excellent stereocontrol that these systems can achieve as a result of the multiple anomeric effects associated with the two spiroketal centres offer significant benefits as chiral auxiliaries.

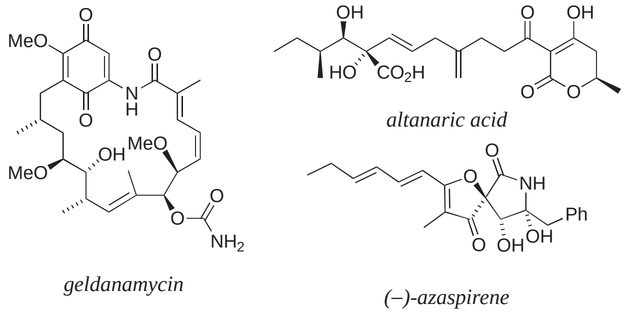
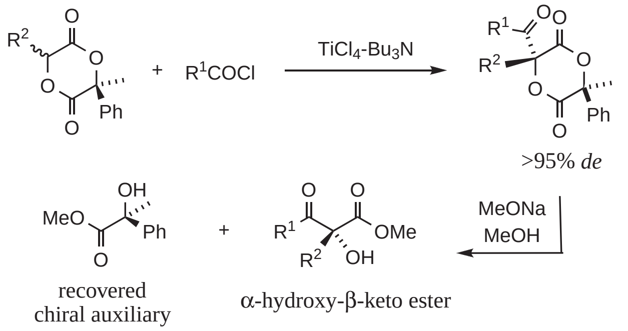
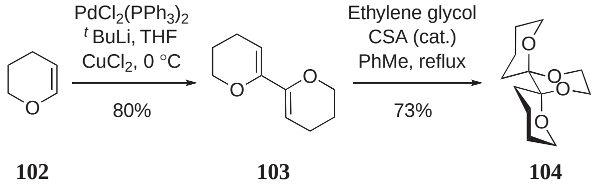


Fig. 5. A selection of applications of diaryl dioxalone chiral auxiliaries to the synthesis of complex natural products.



Scheme 29.



Scheme 30. Dispiroketal synthesis.

The bis-dihydropyran **103** can be accessed in good yield by oxidative homocoupling of dihydropyran. This compound was initially developed as a selective protecting group for vicinal 1,2-diequatorial diols. Owing to favourable operating anomeric effects, single dispiroketal products such as **104** can be expected in the reaction of equatorial diols (Scheme 30).

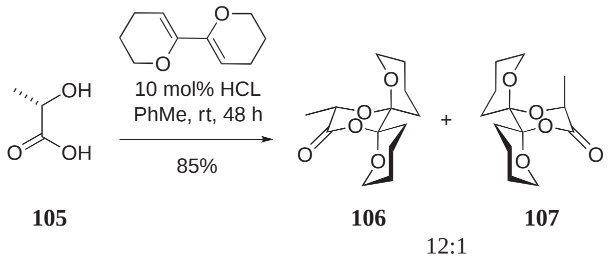
We then extended the work to the preparation of enantiopure α,α-disubstituted-α,β-hydroxy acids. Foreseeing the use of dispiroketals as non-racemic equivalent of lactic acid, we anticipated that the reaction of the bis-dihydropyran **103** with a homochiral substrate would yield one major diastereoisomer, with the substituent on the hydroxy acid preferentially occupying an equatorial position. Having stored the chiral information in the dispiroketal, the original stereocentre could then be lost on deprotonation in forming an enolate, to be reclaimed by diastereoselective reaction with an electrophile, similar to the concepts established by Seebach.[16,17]

Reaction of (*S*)-lactic acid **105** with the bis-dihydropyran **103** furnished dispiroketal products **106** and **107** as a 12:1 mixture. The alkyl group preferentially occupied the equatorial position and the structure of the major diastereoisomer was confirmed by X-ray crystallography (Scheme 31). The protected derivatives were recrystallised to diastereomeric purity,

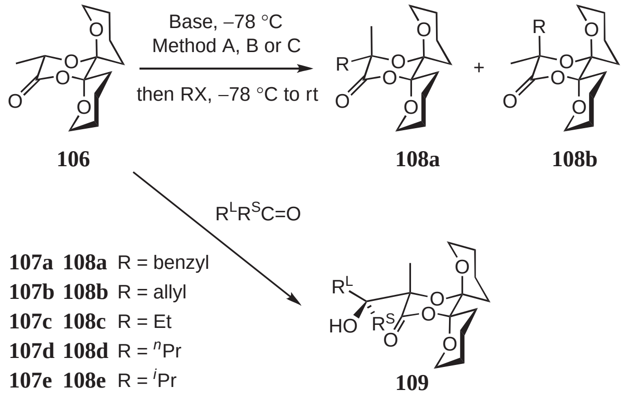
Table 16. Asymmetric Alkylation of Dispiroketal-Protected *S*-Lactic Acid

Entry	Product	Electrophile	Method[a)]	Yield/%	dr
1	**107a**	BnBr	A	72	>98:2
			B	86	>98:2
2	**107b**	$CH{=}CH_2CHBr$	A	95	96:4
	107b	$CH{=}CH_2CHBr$	B	94	96:4
3	**107c**	EtI	A	83	81:19
	107c	EtI	B	84	82:18
	107c	RtI	C	85	89:11
4	**107d**	^{n}PrI	A	73	77:23
	107d	^{n}PrI	B	79	83:17
	107d	^{n}PrI	C	67	92:8
5	**107e**	^{i}PrI	B	47	83:17
6	**109a**	Benzaldehyde		96	—
7	**109b**	Acrolein		94	—
8	**109c**	Acetaldehyde		93	93:4
9	**109d**	Cyclopentanone		35	—
10	**109e**	Acetophenone		29	—

a) Method A: LDA, THF/DMPU; Method B: LDA, ^{n}BuLi, THF/DMPU; Method C: KHMDS, THF/PhMe.



Scheme 31. Formation of dispiroketal-protected *S*-lactic acid.



Scheme 32. Alkylation of dispiroketal-protected glycolate **106**.

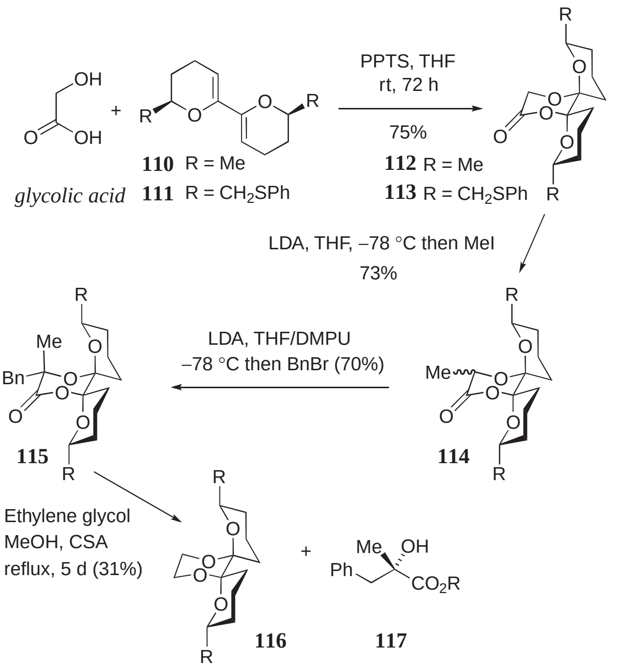
deprotonated and alkylated under the directing influence of the acetal chirality moiety.

Reactions of lactate derivative **106** (R = Me) with alkyl halides (Entries 1–5) and aldehydes (Entries 6–8) proceeded in good to excellent yield and with high diastereoselectivity to afford products **108a** and **108b** respectively. Reaction with ketones (Entries 9 and 10) led to aldol products **109** diastereoselectively, albeit in low yield (Scheme 32 and Table 16).

The above reactions paved the way for the next important development. Since the availability of enantiopure hydroxy acids as starting materials to embed the initial chirality in the dispiroketal is often problematic, our next step was to exploit a chiral bis-dihydropyran to effect the desymmetrisation of glycolic acid itself.

Treatment of glycolic acid with the bis-dihydropyran enol ether **110** or **111** gave desymmetrised glycolic acids **112** and **113**, wherein the alkyl groups on the spiroketal rings preferentially occupy equatorial positions (Scheme 33).[61,62] Alkylation and aldol reactions conducted on these glycolate dispiroketal derivatives showed good selectivities and allowed two new carbon–carbon bonds to be formed asymmetrically, with complete control of stereochemistry in the achiral substrate (glycolic acid). The auxiliary can be readily recycled via the dispiroketal **116**.

One of the most interesting applications of these chiral dispiroketal glycolate derivatives was during the total synthesis of okadaic acid **123**, which contains a dialkylated α-hydroxy acid moiety.[1] In this work, glycolic acid was reacted with the enantiopure phenyl-substituted bis-dihydropyran **118** to give the enantiopure dispiroketal product as a single compound **119** in 89% yield. This was then dialkylated, firstly via enolate quenching with methyl iodide and subsequently with allyl bromide to give **120** as the only isolable isomer in 74% overall yield. Compound **120** was readily elaborated to the sulfone-coupling fragment **121** that was then used to complete the synthesis of okadaic acid. The side chain phenyl groups in the dispiroketal were chosen deliberately to assist final global deprotection under reductive conditions using calcium metal in ammonia at −33 °C, following prior removal of the silicon



Scheme 33. Reactions of the symmetrical glycolate acid protected as its dispiroketal derivative.

protecting groups in the fully protected compound **122** (Scheme 34).

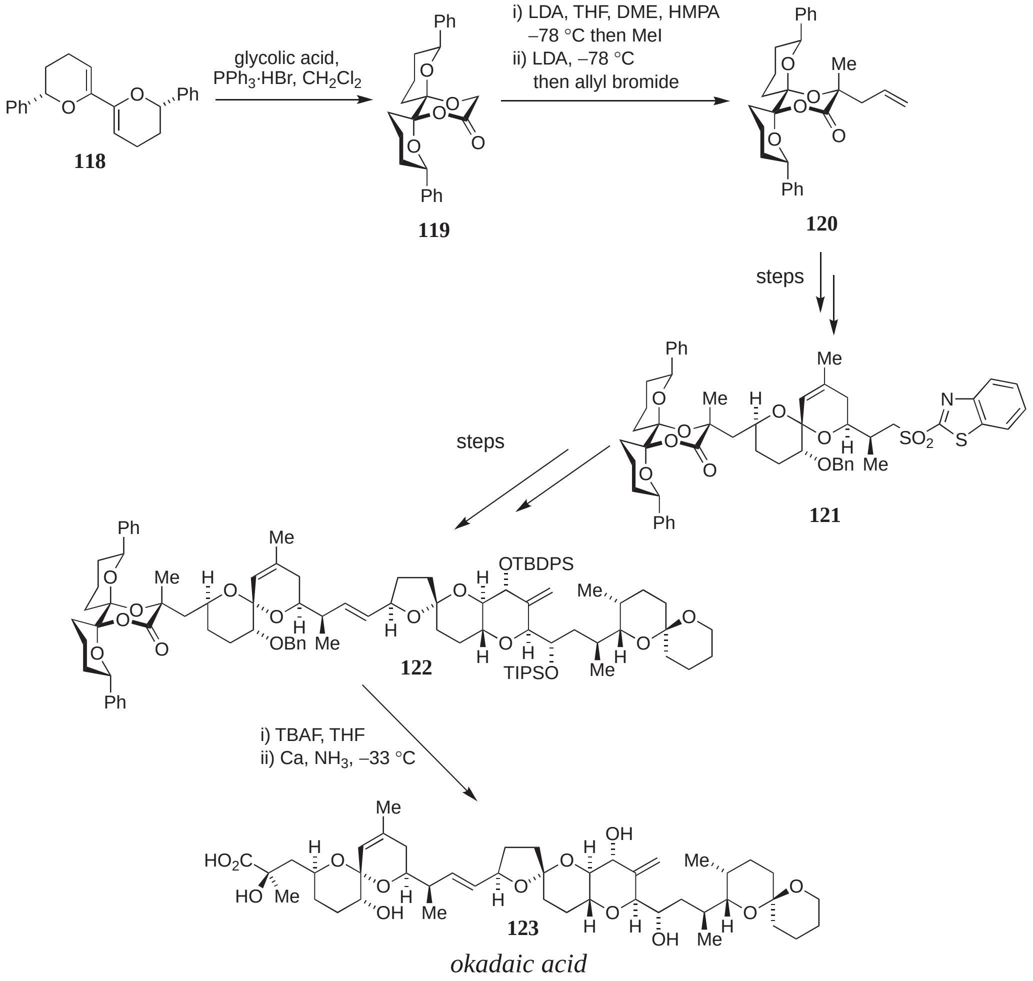
However, since the chiral starting materials for these substituted bis-dihydroxypyrans required some five or six synthesis steps and that deprotection could sometimes be problematic, we sought alternative strategies based on the concepts 1,2-diacetals.

4.4 Butane Diacetal Glycolic Acid. Chiral butane-1,2-diacetal derivatives of glycolic acid **124** and **125** were considered to be attractive auxiliaries owing to the ease of preparation of both enantiomers and their low molecular weight (190 Daltons) (Fig. 6). Moreover, these compounds and their products are often crystalline, or at least solids, and display NMR signals that enable the rapid determination of reaction selectivity in the use of asymmetric transformations.

A number of chiral butane-1,2-diacetal (BDA)-based building blocks for 1,2-diol synthesis have been developed in our

(*S*,*S*)–**124** (*R*,*R*)–**125**

Fig. 6. Chiral butane 1,2-diacetal derivatives of glycolic acid.[72]



Scheme 34. An application of chiral dispiroketal glycolates to the synthesis of okadaic acid **123**.

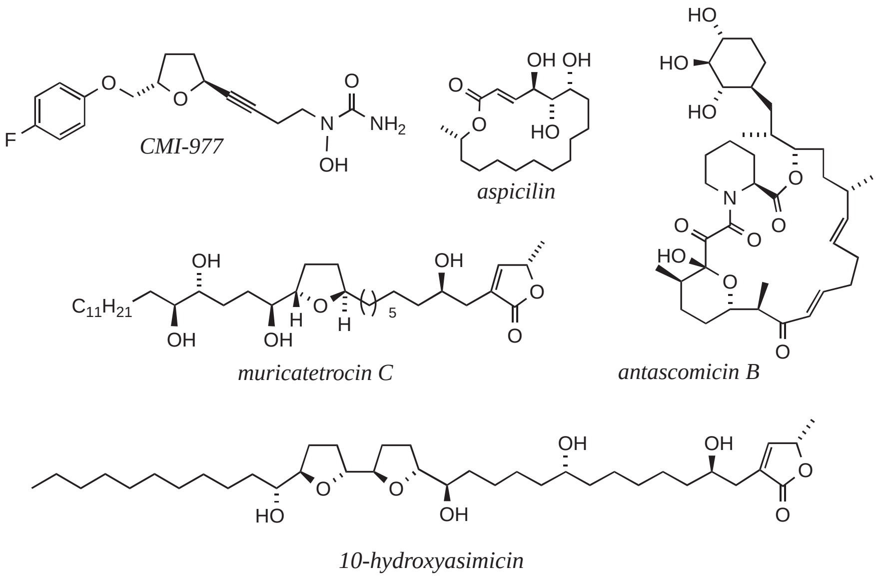
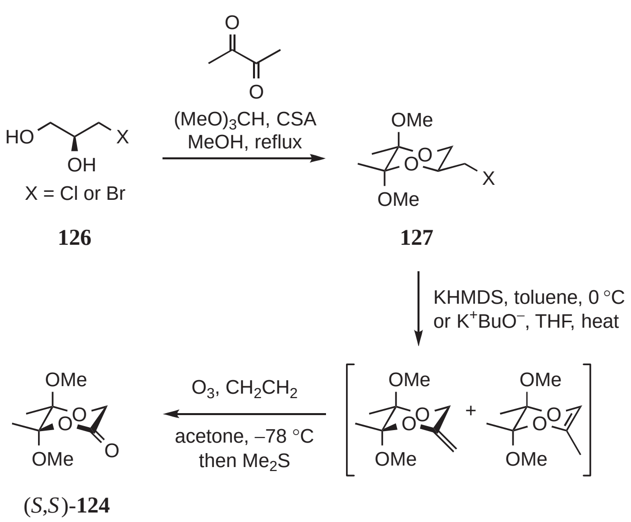


Fig. 7. Applications of BDA-protected building blocks in synthesis.

group,[63] and we have reported the synthesis of the corresponding BDA derivatives using butanedione itself.[64] We have exemplified their use in the synthesis of several biologically active natural products, including the potent 5-lipoxygenase inhibitor CM1-977,[65] the macrolactone (+)-aspicilin,[66] the annonaceous acetogenin muricatrocin C,[67] antascomicin,[68] and 10-hydroxyasimicin (Fig. 7).[69] We have also introduced BDA-protected glyceraldehydes[70] and glycine[71] scaffolds.

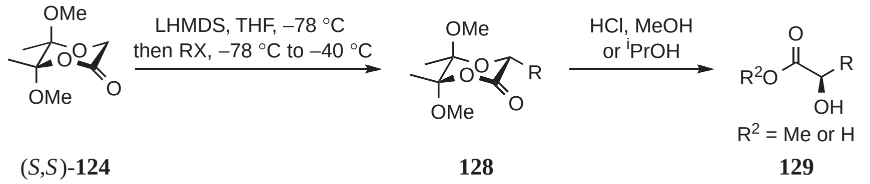
These materials were typically prepared on a 30–50 g scale from commercially available 3-halopropoane-1,2-diols **126** and obtained in high ee by the Jacobsen protocol for the hydrolytic kinetic resolution of epoxides.[72] Depending on the required chirality, the resulting butane 1,2-diacetal protected product reacted with the halopropane diol to give a single product **127** (whereby the pre-existing stereogenic centre adopts the favoured equatorial position) while embedding a further chiral memory into the molecule using the stereogenic centres of the acetal which are again favoured under thermal and anomerically stabilising conditions (Scheme 35). After elimination and ozonolysis, the appropriate butane-1,2-diacetal of glycolic acid was obtained in a good overall yield. Recrystallisation enriched the ee's to greater than 99%. Direct acetal protection of chiral α-hydroxy acetals such as lactic acid or mandelic acid was also possible to give substituted chiral derivatives. Similarly, alternative acetal groups to methoxy were developed such as benzyloxy or allyloxy, to allow useful variation to potential end-game deprotection strategies.[72]



Scheme 35.

The chiral acetals (*S*,*S*)-**124** and (*R*,*R*)-**125** can also be prepared on scale from ascorbic acid or D-mannitol,[70b] albeit via a longer sequence of reactions and have been used in various alkylation reactions. For example, (*S*,*S*)-**124** following deprotonation with LHMDS and subsequent alkylation with a number of different halides, excellent yields and diastereoselectivities were possible (Scheme 36 and Table 17).[72]

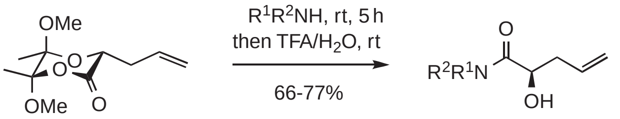
Selected products were also deprotected under mild conditions to the corresponding α-hydroxy acids or α-hydroxy esters. In further work, it was found that the lactone ring could be unravelled by reaction with an excess of amine to yield



Scheme 36.

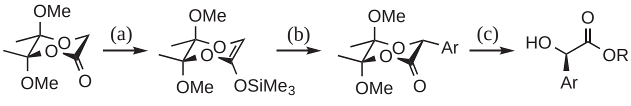
Table 17. Alkylation Reactions of Lactone **124**

RX	Yield of **128**/%	dr	Yield of **129**/%
MeI	93	9:1	—
EtI	61	15:1	—
^{n}BuI	57	21:1	—
$BrCH_2CN$	85	10:1	—
$MeO(CH_2)_2OCH_2Cl$	64	10:1	—
^{t}BuOCOCH$_2$Br	92	18:1	77
$CH_2{=}CHCH_2Br$	89	60:1	—
$PhCH_2Br$	96	>99:1	100
(2-Napthyl)CH$_2$Br	84	>99:1	95
$ICH_2CH_2CH_2I$	62	>24:1	90



130

Scheme 37.



(*S*,*S*)–**124** **131** **132** **133**

(a) LDA, Me$_3$SiCl, THF, −78 °C;
(b) ArBr, 5% Pd(dba)2, 10%, P(*t*Bu)3, additive, DMF
(c) TMSCl, MeOH

Scheme 38.

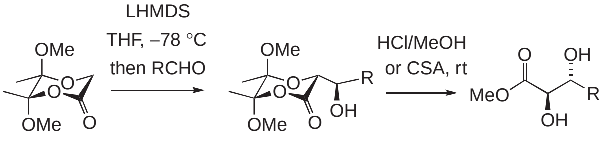
Table 18. Chiral α-Hydroxy Compounds Prepared Using a Palladium-Catalysed Process

ArBr	Zinc additive$^{a)}$ (equiv)	T/°C	Yield/%	dr
PhBr	A (0.25)	rt	73	>50:1
2-Napthyl-Br	B (0.5)	80	58	>50:1
1-Napthyl-Br	B (1.0)	80	72	>50:1
p-MeO$_2$CC$_6$H$_4$Br	A (0.5)	rt	95	>50:1
m-O$_2$NC$_6$H$_4$Br	B (0.5)	rt	89	>50:1
m-MeCOC$_6$H$_4$Br	B (1)	80	76	25:1
p-MeOC$_6$H$_4$Br	B (0.5)	80	57	>50:1
o-ClC$_6$H$_4$Br	B (1)	80	78	20:1

a) Zinc additives: A = Zn(O^{t}Bu); B = ZnF$_2$.

the corresponding α-hydroxyamides **130** after acidic work up (Scheme 37).[72]

The silyl enol ether derived from the BDA unit (*S*,*S*)-**124** was reported by Hartwig to react with aryl bromides in a palladium-catalysed process that gave 2-aryl-2-hydroxy acid derivatives with excellent diastereoselectivity (Scheme 38 and Table 18).[73] The aryl derivatives were deprotected without epimerization using dilute acid under standard conditions.

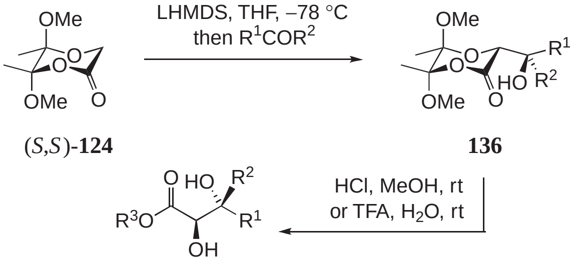


(*S*,*S*)-**124** **134** **135**

Scheme 39.

Table 19. Lithium Enolate Aldol Reactions of (*S*,*S*)-**124**

Aldehyde	Yield of **134**/%	de of **134**/%	Yield of **135**/%
MeCHO	86	92	75
EtCHO	86	>95	86
^{t}BuCHO	89	>95	89
MeCH=CHCHO	92	95	93
PhCH=CHCHO	90	>95	—
p-MeOC$_6$H$_4$CHO	96	>95	—
p-NO$_2$C$_6$H$_4$CHO	70	94	—



(*S*,*S*)-**124** **136**

R^3 = Me or H **137**

Scheme 40.

The reaction of (*S*,*S*)-**124** with aldehydes proceeded with even greater diastereoselectivity (92–95%) than the alkylations described above, with only one of the four possible diastereomeric products observed in many cases.[74,75] Deprotection with methanolic acid or CSA then furnished the *anti*-2,3-dihydroxy esters **135** (Scheme 39 and Table 19).

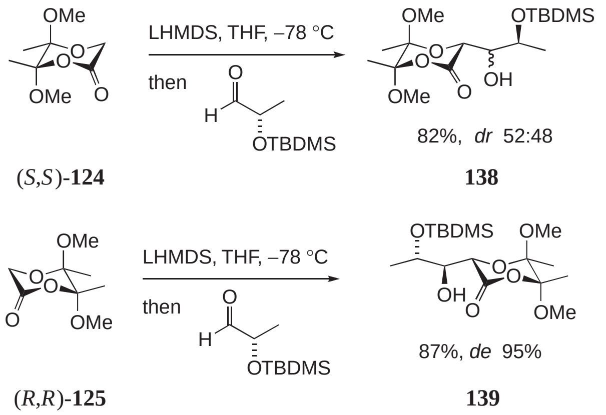
Reactions with selected ketones were also successful and proceeded with high diastereoselectivity and yields in most cases (Scheme 40 and Table 20).[76]

BDA glycolate (*S*,*S*)-**124** performed well in matched and mismatched aldol reactions with a chiral lactate-derived aldehyde (Scheme 41).[74] Both enantiomers reacted in a highly diastereoselective manner with less sterically demanding aldehydes.

Given that the stereochemical outcome of aldol reactions using desymmetrized BDA glycolates was highly stereoselective, we next examined a complementary process to afford the alternative C-3 hydroxylic stereogenic centre. This was achieved in a two-step process. Reaction of the enolate of (*S*,*S*)-**124** with an acyl chloride gave an enolised β-keto product **140** in either 73% yield for the *tert*-butyl derivative or 68% yield where the R-group is cyclohexyl.[74] Compound **140** was then reduced with tetra-*N*-butylammonium borohydride to the corresponding hydroxy derivative **141** with high stereoselectivity (14:1 and 15:1 for the *tert*-butyl and cyclohexyl de-

Table 20. Reactions of BDA Glycolate (*S*,*S*)-**124** with Ketones

Ketone	Yield of **136**/%	de of **136**/%	Yield of **137**/%
^{t}BuCOMe	32	95	38
^{t}BuCOCH$_2$Cl	89	95	95
PhCOCF$_3$	92	17	—
PhCOMe	79	91	84
PhCOCH$_2$OMe	96	90	91
PhCOEt	76	76	—
PhCOCH$_2$Br	92	90	92
(3-Pyridyl)COMe	93	85	95
(2-Furanyl)COMe	70	80	—
PhCOCH=CHPh	90	82	—



(*S*,*S*)-**124** **138**

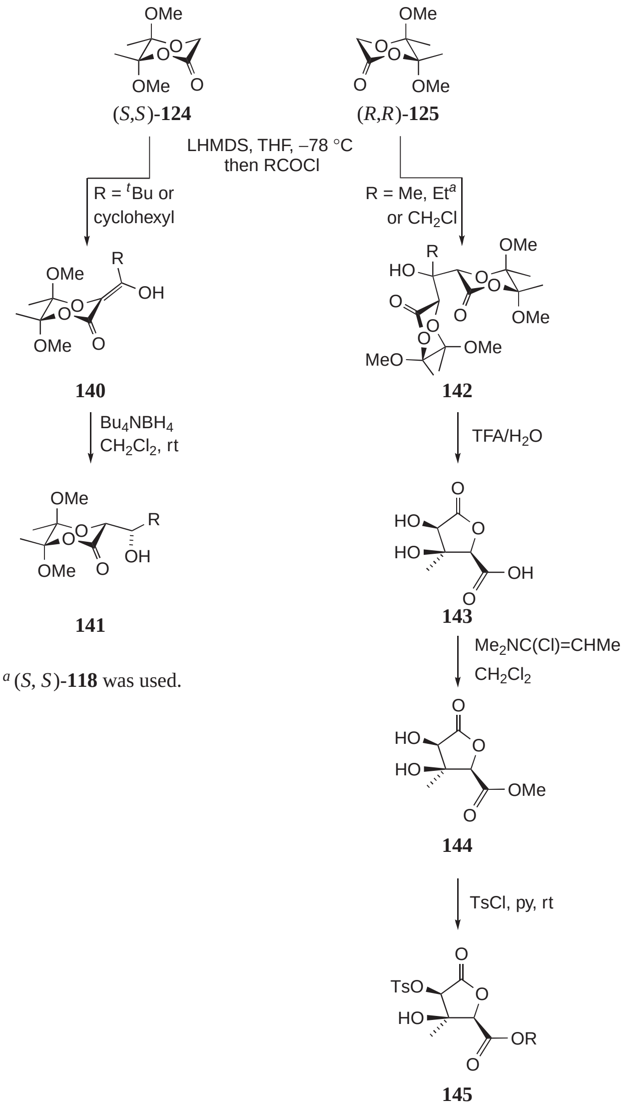
(*R*,*R*)-**125** **139**

Scheme 41.

rivates respectively).[74] The stereochemistry obtained was shown to be complementary to the products obtained from direct aldol reaction. When the enolates of (*S*,*S*)-**124** or the opposite enantiomer **125** were reacted with less hindered acyl chlorides dimeric adducts **142** were obtained as white crystalline solids, after simple trituration of the crude reaction product. These unusual bis-BDA derivatives resulted from the addition of two equivalents of the glycolate enolate to the acid chloride. Alcohol **142** contains two diastereotopic butane-diacetal-protected lactones that were differentiated by acidic methanolysis to lactone **144**. The chiral centre at the tertiary alcohol favoured the *syn*-diol lactone **144** (R = Me) in a 13:1 ratio. Acidic hydrolysis gave the corresponding acid **143** as a more favourable 25:1 ratio of diastereoisomers. Spectroscopic data was insufficient to determine the stereochemistry of these products but conversion to the tosylate derivative **145** enabled the absolute and relative stereochemistry to be determined by X-ray diffraction techniques (Scheme 42).

The enolate of (*S*,*S*)-**124** was also shown to undergo Michael addition reactions with a range of acceptors, again in high yield and with high diastereoselectivity in most cases; the example in Scheme 43 typifies the procedure.[77,78a] Notably, Michael addition to cyclopent-2-enone was favoured over deprotonation (Table 21).

The yield of the Michael addition to cyclohexenone (30%) was improved substantially to 89% by using the fluoride-catalysed Michael addition of silyl ketene acetal **148** to afford adduct **149** (Scheme 44).[77] These reactions were the first reported examples of TBAT-catalysed Michael addition of silyl ketene acetals.



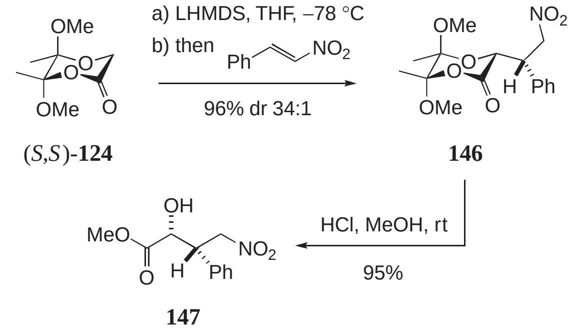
(*S*,*S*)-**124** (*R*,*R*)-**125**

140 **142**

141 **143** **144** **145**

^{a} (*S*, *S*)-**118** was used.

Scheme 42.



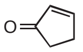
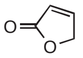
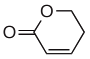
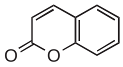
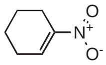
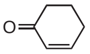
(*S*,*S*)-**124** **146**

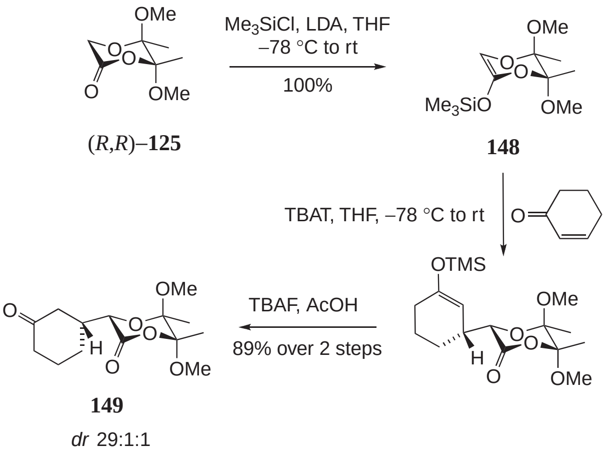
147

Scheme 43.

In sequential Michael–aldol reactions, BDA glycolate (*R*,*R*)-**125** was deprotonated with LHMDS and treated with a Michael acceptor (5,6-dihydro-2*H*-pyran-2-one or coumarin). A second electrophile, either benzaldehyde or anisaldehyde,

Table 21. Asymmetric Michael Addition Reactions

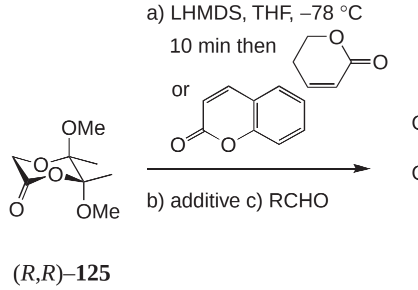
Electrophile	Yield of **147**/%	dr of **147**/%
	61	14:1
	35	10:1
	63	22:1
	90	65:1
PhCH=CHNO$_2$	96	34:1
PhCH=CMeNO$_2$	85	1.4:1
	98	16:1
	30	13:1



Scheme 44.

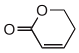
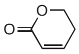
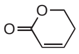
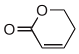
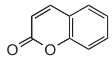
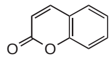
was then added and the three-component coupled products **150** were obtained as a mixture of two diastereoisomers in a process that led to the formation of two new C–C bonds and three new stereogenic centres (Scheme 45 and Table 22). Improved selectivity was achieved with the additive trimethyl borate at the intermediate Michael reaction stage.

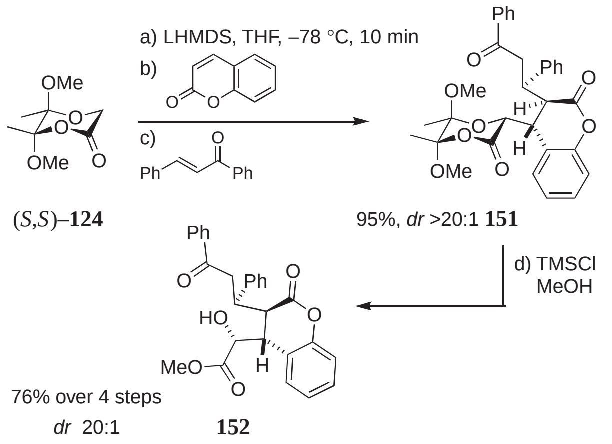
The consecutive Michael–Michael reaction of the enolate of (*S*,*S*)-**124** with the same acceptors, followed by addition of either *trans*-β-nitrostyrene, 1-nitro-1-cyclohexene or *trans*-chalcone led to the corresponding addition products **151** in a sequence that established two new C–C bonds and up to five stereogenic centres in a single step. The reaction involving coumarin and *trans*-chalcone in Scheme 46 typifies the results. Trimethylsilyl chloride in methanol was used to deprotect **151** to **152** in 76% overall yield and with a diastereomeric ratio of 20:1.



Scheme 45.

Table 22. Sequential Michael–Aldol Reactions

Michael acceptor	R	Addititve	dr of **150**/%	Yield of **150**/%
	Ph	—	2.8:1	74
	Ph	B(OMe)$_3$	4.0:1	72
	*p*-MeO-C$_6$H$_4$	—	2.5:1	66
	*p*-MeO-C$_6$H$_4$	B(OMe)$_3$	5.2:1	63
	*p*-MeO-C$_6$H$_4$	—	3.2:1	73
	*p*-MeO-C$_6$H$_4$	B(OMe)$_3$	3.3:1	64

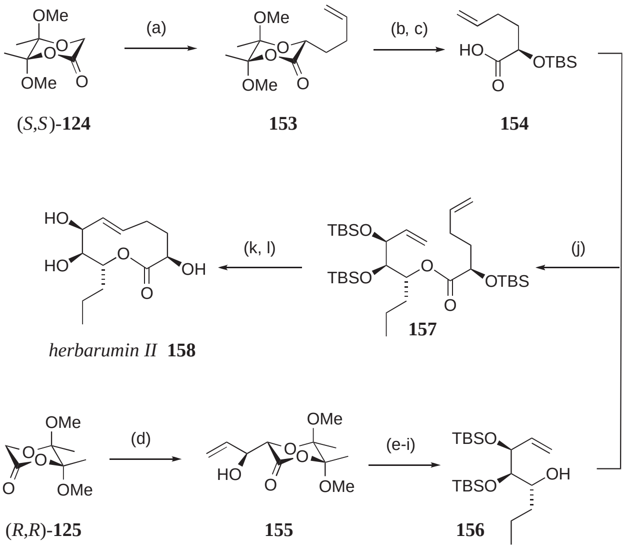


Scheme 46.

A number of natural products have been synthesised using these new butane diacetal glycolic acid building blocks. In the first of these, a short synthesis of the phytotoxic agent herbarumin II **158** was achieved using both enantiomeric forms of the butane diacetal glycolic acid **124** and **125** to deliver the required stereogenic centers.[79] For example, (*S*,*S*)-**124** after stereo-controlled alkylation of the corresponding lithium enolate with iodobut-3-ene gave **153** which was readily transformed to the first coupling partner **154**. While (*R*,*R*)-**125** underwent the aldol reaction with acrolein in better than 96% de to give **155** which was then converted to the second coupling unit **156** by a series of straightforward steps. Coupling of the two units, followed by metathesis and global deprotection, afforded herbarumin II **158** (Scheme 47).

In a similar fashion the two glycolate BDA-protected enantiomers (*S*,*S*)-**124** and (*S*,*S*)-**125** were used very effectively to prepare a ceramide sphingolipid isolated as a pheromone from the hair crab pheromone *Eramacrus isembecki*.[78b]

Here, (*S*,*S*)-**124** was firstly stereoselectivity alkylated with allyl bromide then the side chain was homologated by standard transformations and finally deprotected to the hydroxy acid **160** as one of the key fragments of the natural product (Scheme 48). The second, more elaborate fragment **165** was derived from the (*R*,*R*) building block via a series of reactions commencing with the aldol coupling to the amino aldehyde shown. Finally, coupling of **165** and **160** followed by TBAF deprotection gave the hair crab pheromone (Scheme 49).



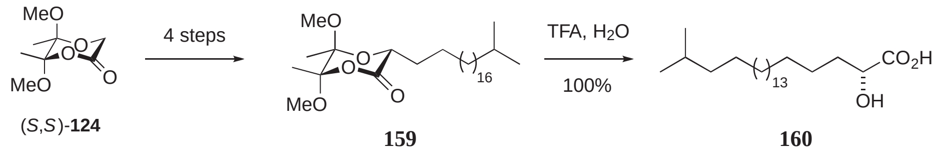
(a) LHMDS, THF, −78 °C, 20 min, 4-iodo-1-butene, −78 °C to −20 °C, 20 h (56%); (b) TFA/H_2O (87%); (c) TBSCl, imidazole, DMF (80%); (d) LHMDS, THF, −78 °C, 20 min, acrolein, −78 °C, 1 h (86%); (e) HCl, MeOH, rt, 1 h (72%); (f) TBSCl, imidazole, DMF, rt,1.5 h (96%); (g) DIBAL, CH_2Cl_2, −30 °C, (90%); (h) PCC, CH_2Cl_2, rt, 1.5 h; (i) ^{n}PrMgCl, toluene, −78 °C, 2 h, dr >12:1, 68% over 2 steps; (j) NEt_3, 2,4,6-trichlorobenzoyl chloride, DMAP, rt, 16 h (78%); (k) Grubbs II catalyst, CH_2Cl_2, reflux, 8 h (85%); (l) TBAF, THF, rt, 1.5 h (quant.)

Scheme 47.

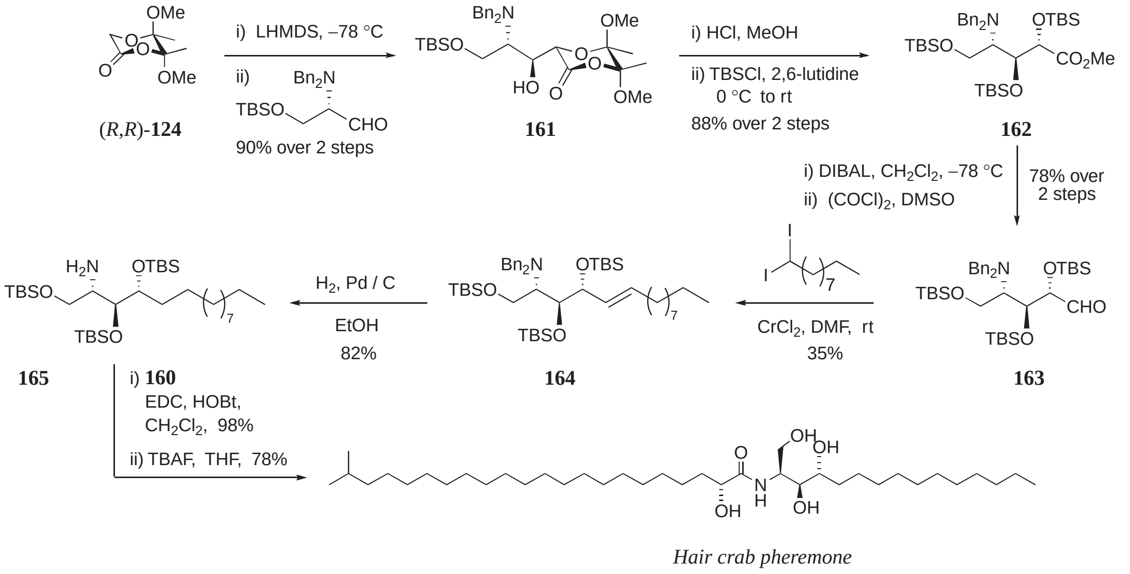
Finally, an application of the BDA glycolate dervative (*R*,*R*)-**125** to the construction of a key component for the synthesis of rapamycin **174** has recently been reported.[80] In this work, the building block undergoes a highly stereoselective aldol reaction with chiral aldehyde **166** in a chirality matched coupling to give **167** as the only detectable product (Scheme 50). The BDA protecting group was efficiently removed in 80% yield by deprotection with camphorsulfonic acid in methanol. Following a number of additional steps and coupling reactions, a new synthesis of rapamycin **174** was completed. This synthesis provides further illustration of the power these small molecular weight butane-2,3-diacetal glycolic acid derivatives possess as chiral α-hydroxy acid auxiliaries in synthesis.

5. Conclusion

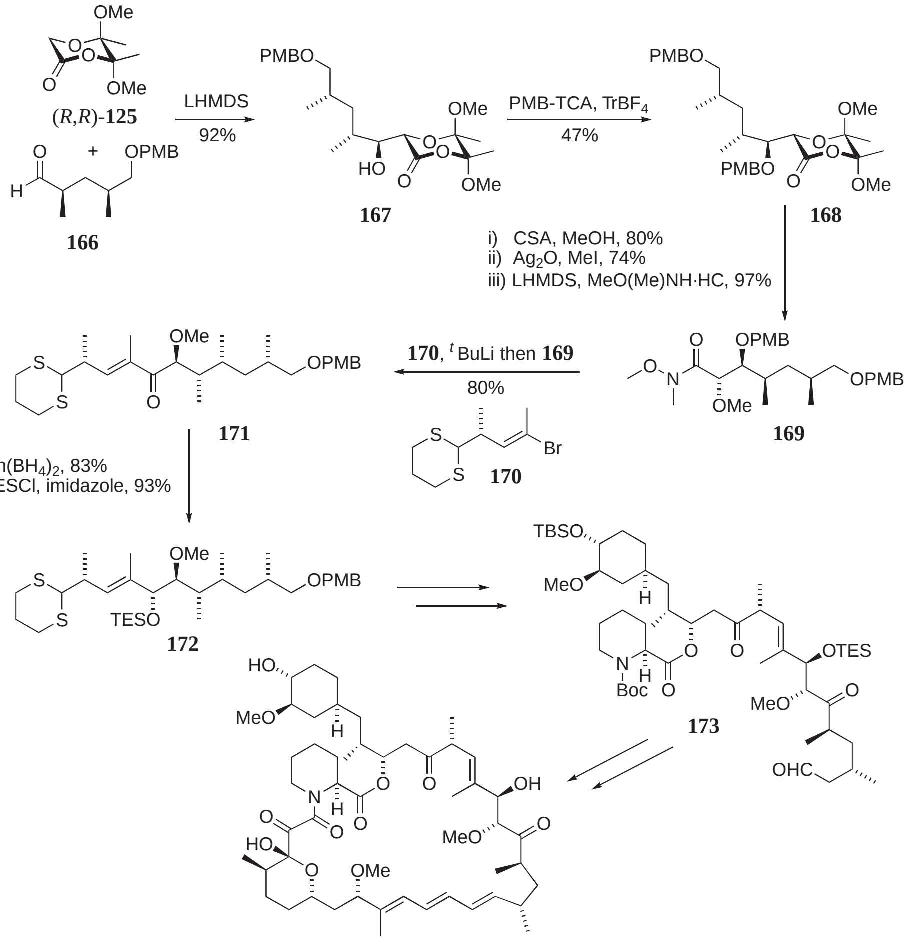
This short review has highlighted the use of enolates in stereoselective bond construction from various chiral auxiliaries derived from α-hydroxycarbonyl compounds. These methods are of considerable importance in complex molecule synthesis, particularly for natural products. While no method suits all applications, those that deliver the product with high yield and stereoselectivity in the required enantiomeric series are clearly favoured. However, considerations such as availability,



Scheme 48.



Scheme 49.



(–)-rapamycin **174**

Scheme 50.

low molecular weight and product crystallinity, together with their ease of deprotection under a variety of conditions adds value to the use of the auxiliary. The area continues to evolve to meet the demands of modern day organic synthesis.

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