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Dispiroketals in Synthesis (Part 10)[1]: Further Reactions of Dispoke Protected Lactate and Glycolate Enolates†

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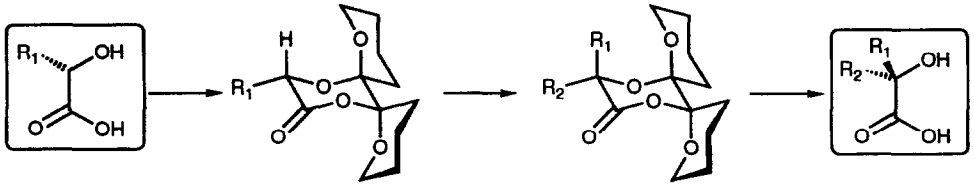
Abstract: α-Hydroxy acids have been reacted with *bis*-dihydropyrans to give dispiroketal adducts (1,8,13,16-tetraoxadispiro[5.0.5.4]-hexadecan-14-ones). The enolates derived from these compounds undergo reaction with electrophiles with generally high levels of diastereoselectivity. Subsequent deprotection of these compounds gives α-hydroxy esters of high enantiomeric excess.

As part of an ongoing total synthetic project we needed to synthesise an enantiopure α,α-disubstituted α-hydroxy acid, which we envisaged could be achieved through the use of a non-racemic equivalent of the enolate of lactic acid.[2] Whilst the excellent method of Seebach[3] presented one solution, the development in these laboratories of Dispoke protection for 1,2 diols suggested an interesting alternative, namely to attempt the formation of a dispiroketal adduct of an α-hydroxy acid.[4] On the basis of previous work with diols it was hoped that such a reaction with a homochiral substrate would give a majority of one diastereomer, with the substituent on the hydroxy acid preferentially adopting an equatorial position (Scheme 1). This tendency would, in conjunction with maximisation of anomeric stabilisation, control the configuration at the spiroketal carbons. Having stored the chiral information as the dispiroketal, the original stereogenic centre could be destroyed by deprotonation to give the enolate which would then undergo a diastereoselective reaction with an electrophile. Finally deprotection would afford the product of a useful overall enantioselective transformation (Scheme 1). Herein we report the success of this general scheme.



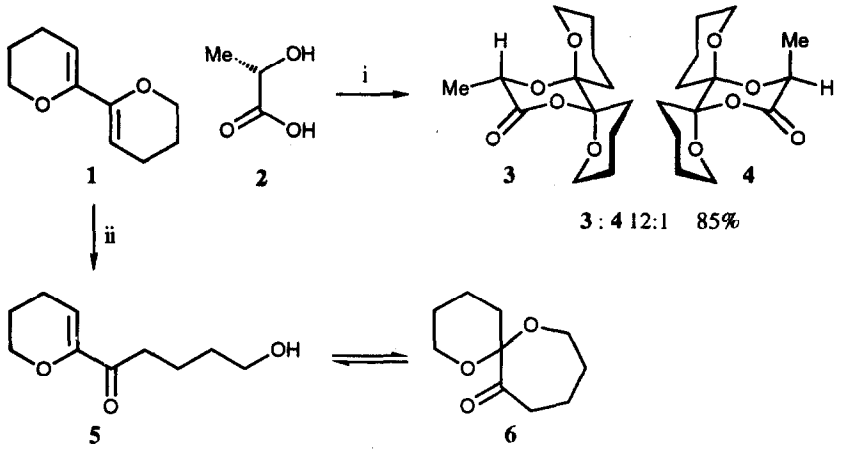
Scheme 1. Overall Enantioselective Transformation *via* a Dispiroketal

† Dedicated to our friend Professor Léon Ghosez on the occasion of his 60th birthday.

DISPIROKETAL ADDUCTS FROM THE CHIRAL POOL

Preparation of the dispiroketal

(*S*)-Lactic acid **2** was protected by acid-catalysed reaction with the *bis*-dihydropyran **1**, giving a mixture of diastereoisomers **3** and **4** (Scheme 2). The absence of water is required to avoid the rapid decompostition of the *bis*-dihydropyran to a mixture of the enone **5** and spiroketone **6**.[5] Optimisation of the reaction conditions for the preparation of the lactic acid derivative revealed that a strong acid such as HCl (used as a 1.0 M solution in ether) was required for efficient conversion. Toluene was found to be a superior solvent over chloroform and tetrahydrofuran (THF). In conjunction with relatively low temperatures (0°C or room temperature) these conditions gave both the best yield and highest ratio of diastereoisomers.



i) 10 mol% HCl (1.0 M in ether), toluene, r.t., 48 hr. ii) H^+, H_2O

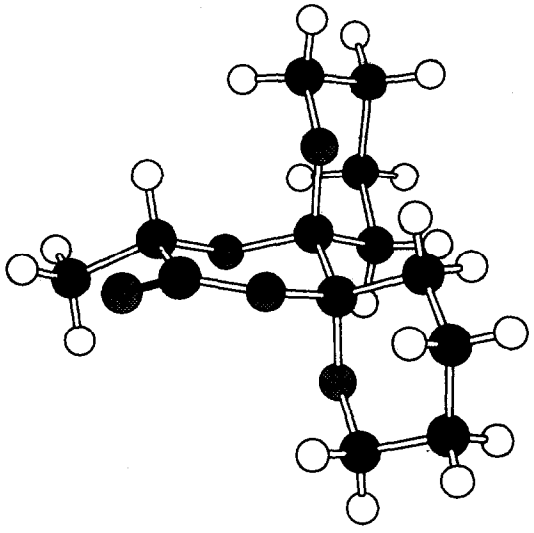
Scheme 2. Preparation of the Dispoke adduct.

The major diastereoisomer **3** can be obtained free from the minor compound **4** by recrystallisation, with a single recrystallisation from 40-60 petrol sufficing to remove all traces by 250 MHz ^1H NMR. The structure of the major compound was determined by X-ray crystallography (Figure 1)[6] and found to be consistent with our expectations, having an all-chair conformation with the substituent equatorial and the maximum anomeric stabilisation. The dioxane ring is somewhat flattened due to the presence of the carbonyl group. No crystal structure of the minor diastereoisomer has yet been obtained, but its structure must represent a thermodynamically less stable compromise between an all chair conformation having an unfavourable 1,3 diaxial interaction between the substituent and a carbon-oxygen bond, and a structure possessing a twist boat conformation for the dioxane ring which relieves this steric interaction at the expense of eclipsing strain and reduced anomeric stabilisation.

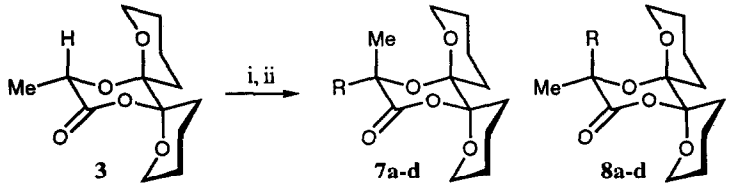
Reactions of the enolate derived from 3

Deprotonation of **3** occurred readily on treatment with lithium diisopropylamide (LDA) in THF at -78°C.

Figure 1. X-ray structure of 3



The enolate thus generated reacted (Scheme 3) in a highly stereoselective manner with allyl and benzyl bromide (entries 1-4, Table 1), and in a less selective manner with n-alkyl iodides (entries 5, 6, 8 and 9). N,N'-Dimethylpropyleneurea (DMPU)[7] was added to the lithium enolates to give greater reactivity. In the cases where moderate selectivity was observed this could be improved by the use of potassium hexamethyldisilazide (KHMDS) instead of LDA (entries 7 and 10). As has been previously reported[3b] the deprotonation of the diisopropylamine generated during enolate formation by an equivalent of n-butyllithium gives increased yields.



7a, 8a R = benzyl
7b, 8b R = allyl
7c, 8c R = ethyl
7d, 8d R = n-propyl

i) Base, THF, -78°C. ii) R-X

Scheme 3. Alkylation of 3.

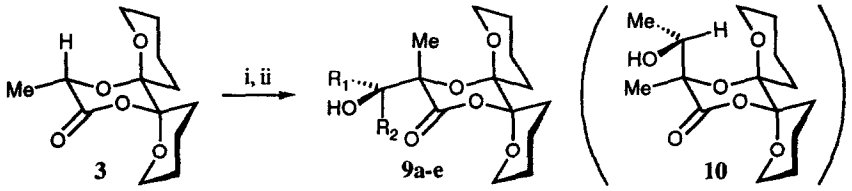
When the lithium enolate of **3** was reacted with carbonyl compounds, excellent diastereoselctivity was observed. In most cases, only one of the four possible diastereoisomers was produced (Scheme 4). Even in the reaction with acetaldehyde (Table 2, entry 3), which we would predict to give the lowest level of stereoselectivity, an impressive 93:4 ratio (based on material isolated) of two separable diastereoisomeric products was obtained. In the reactions with aldehydes high yields were consistently obtained, but reactions with ketones gave lower yields with significant quantities of starting material being recovered, although the

Entry	R-X	Base	Product(s)	Ratio 7:8	Yield (%)[a]
1	benzyl bromide	LDA	**7a**[b]	>98:2[b]	72
2	benzyl bromide	LDA[c]	**7a**[b]	>98:2[b]	86
3	allyl bromide	LDA	**7b; 8b**	96:4[d]	95 (71[e])
4	allyl bromide	LDA[c]	**7b; 8b**	96:4[d]	94
5	ethyl iodide	LDA	**7c; 8c**	81:19[d]	83
6	ethyl iodide	LDA[c]	**7c; 8c**	82:18[d]	84 (67, 15[f])
7	ethyl iodide	KHMDS	**7c; 8c**	89:11[d]	75
8	n-propyl iodide	LDA	**7d; 8d**	77:23[d]	73
9	n-propyl iodide	LDA[c]	**7d; 8d**	83:17[d]	79 (60, 13[f])
10	n-propyl iodide	KHMDS	**7d; 8d**	92:8[d]	67

a) Yield refers to the mixture of diastereoisomers isolated by flash chromatography. Yields in parentheses refer to yields of single diastereoisomers obtained by further purification techniques. (yield of 7, %, yield of 8, %). b) The minor diastereoisomer 8a could not be detected by 400 MHz ^{1}H or 62.5 MHz ^{13}C NMR. c) 1.1 eq. n-BuLi solution added after enolate formation. d) Determined by capillary GC. e) Recrystallised from MeOH. f) Preparative HPLC separation.

Table 1. Alkylation results.

excellent selectivities were still maintained. Ketones are less reactive than aldehydes, which allows enolisation of the ketone to become a significant competing process. This results in the quenching of the lactate enolate and the generation of products of self-condensation of the ketone component. Secondly, the desired compounds produced are susceptible to retro-aldol cleavage. The presence of two R groups at the newly-formed carbinol carbon increases the propensity for retro-aldol cleavage to occur, in order to relieve steric compression. Thus in all the reactions with carbonyl compounds and particularly ketones the reaction is quenched at -78°C before product isolation.



9a	R_1 = Ph	R_2 = H
9b	CH_2CH	H
9c	CH_3	H
9d	$R_1 = R_2$	$(CH_2)_4$
9e	Ph	Me

i) LDA, THF, -78°C. ii) R_1R_2CO

Scheme 4. Reaction with carbonyl compounds.

Entry	Electrophile	Product	Yield (%)[a]
1	benzaldehyde	**9a**[b]	96
2	acrolein	**9b**[b]	94
3	acetaldehyde	**9c**[c]	93
4	cyclopentanone	**9d**[b]	35 (46)
5	acetophenone	**9e**[b]	29 (56)

a) Yield of recovered starting material in parentheses. This was typically a 1:1 mixture of **3** and its C15 epimer, as a result of non-selective quenching of the enolate. b) Single diastereoisomers by 400 MHz ^{1}H and 100 or 62.5 MHz ^{13}C NMR. c) Compound **10** was also isolated in 4% yield.

Table 2. Results of reactions with carbonyl compounds.

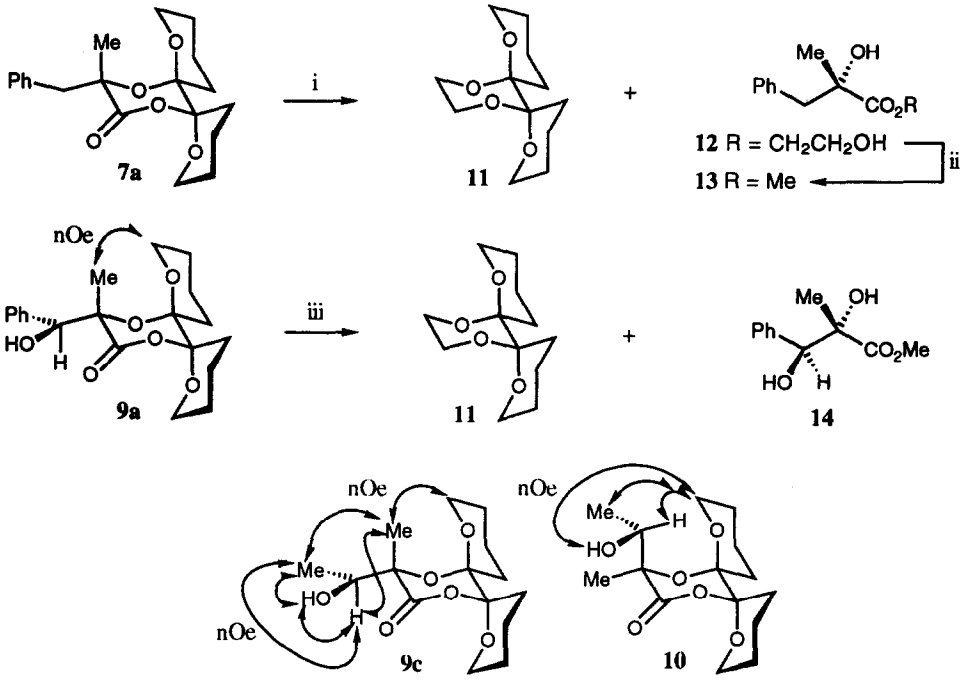
Structure elucidation

As mentioned earlier (fig.1), the structure of **3** has been determined by X-ray crystallography. The structures of a number of products derived from **3** have been determined by a combination of NMR experiments and their conversion to known compounds. For example, compound **7a** was confirmed as having the structure shown, with the 15*S* configuration, by treatment of **7a** with excess ethylene glycol and *dl*-camphorsulfonic acid (CSA) to give the dispiroketal adduct of ethylene glycol **11** and the ethylene glycol monoester **12**, which was then transesterified with methanolic sodium carbonate to give methyl 2-hydroxy-2-methyl-3-phenylpropanoate **13** (Scheme 5) in 80% overall yield. Although to the best of our knowledge this compound has not been reported in enantiopure form before, Yamada *et al.* prepared the optically active compound (*ee.* 60%) by nitrous acid deamination of (*R*) methyl 3-phenyl-2-amino-2-methylpropionate and converted the product to known compounds, allowing them to assign its absolute configuration.[8] The reported rotation of this compound indicated that our compound was of the *S* configuration, hence compound **7a** must have the structure shown. As a result this methodology gives substitution of the α proton of lactic acid with inversion. Additionally, **13** was shown by chiral GC to have an enantiomeric excess of 97.6%, indicating that the enantiomeric purity of these compounds remains high both during the preparation of the initial lactic acid adduct **3** and the deprotection step.

Compound **9a** displayed a strong nOe (500 MHz NOESY spectrum) between the methyl group and the axial proton on C2 of the tetrahydropyran ring. Thus the α chiral centre is formed in the same sense as in the reaction between **3** and benzyl bromide. Deprotection of **9a** was achieved more conveniently by treatment with a small excess of ethylene glycol in methanol with catalytic CSA, thereby providing the methyl ester **14** directly in approximately quantitative yield with concomitant formation of **11**. Comparison of the ^{13}C NMR data with literature data[9] showed that the *erythro* compound had been obtained. Since the configuration of the α chiral centre was known we can conclude that compound **14** was the *S,S* enantiomer and that **9a** had the structure depicted.

The structures of **9c** and **10** were inferred from 500 MHz NOESY experiments. The major diastereoisomer displayed nOe signals which were consistent with the structure shown, although the results were ambiguous due to the coincidence of signals in the proton NMR spectrum. However, it is unlikely that

the chiral centres are formed in a different sense to the benzaldehyde case. The minor diastereoisomer had a more resolved proton NMR spectrum and gave nOe signals from the hydroxyl proton, H1' and the C2' methyl group to one of the tetrahydropyran rings (axial proton on C2) and no signals between the methyl group and either tetrahydropyran ring. This suggests that the minor diastereoisomer **10** has an equatorial methyl group, and the structure is tentatively assigned as that shown with the configuration of the carbinol carbon arising as a result of an appropriate six-membered transition state (*vide infra*).



i) Ethylene glycol, H^+, Δ. ii) MeOH, Na_2CO_3, 80% (two steps). iii) ethylene glycol/MeOH, H^+, Δ, 100%.

Scheme 5. Deprotection reactions and structure elucidation.

Rationalisation of the observed selectivities

The preference in the alkylation reactions for the products with the new R group equatorial is as expected and is explained by the incoming electrophile approaching from the face of the enolate which does not present a 1,3-interaction with the axially disposed C-O bond of the spiroketal (Figure 2, diagram 1). Steric repulsion alone determines the outcome and the relative energy levels of the competing pathways are shown as **a** and **b** (not to scale). We believe the lower selectivity observed with the less reactive alkyl iodides is due to the operation of a later transition state (TS) than in the case of reaction with allyl and benzyl bromide. If the electrophile attacks from the lower face as shown in Figure 2, diagram 2, the developing pyramidal character at the nucleophilic carbon pushes the methyl group towards an axial orientation, with an unfavourable 1,3 diaxial interaction with the spiroketal C-O bond. This raises the energy of this transition

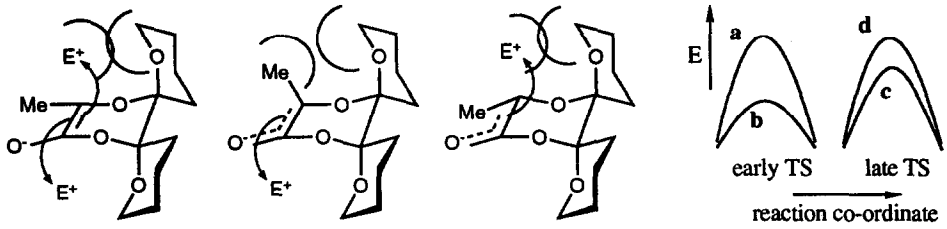


diagram 1. diagram 2. diagram 3

Figure 2.

state (shown as **c**), but the energy of the TS for reaction from the upper face (**Figure 2, diagram 3**) is relatively unaffected (shown as **d**), because the methyl group does not experience a 1,3 interaction as it is displaced downwards. The difference in the energy of the transition states of these two competing pathways is thus smaller, hence the reaction less selective.

The large preference for one diastereoisomer in the aldol reactions can be rationalised by consideration of the two chair-like six-membered transition states shown below (figure 3). In both, the larger substituent of the carbonyl component (shown here for an aldehyde) is directed pseudoequatorially. The smaller substituent, in this case hydrogen, is axial and placed over the dioxane ring. In the TS on the left (which leads to the major diastereoisomer **9**) models suggest that this hydrogen atom does not suffer major steric interaction with the tetrahydropyran ring. In the alternative TS the hydrogen atom and the R group of the aldehyde are in close proximity to the adjacent tetrahydropyran ring, causing severe steric repulsion. Hence this transition state only gives rise to measurable quantities of product when R is small, as in the case of acetaldehyde (giving rise to compound **10**).

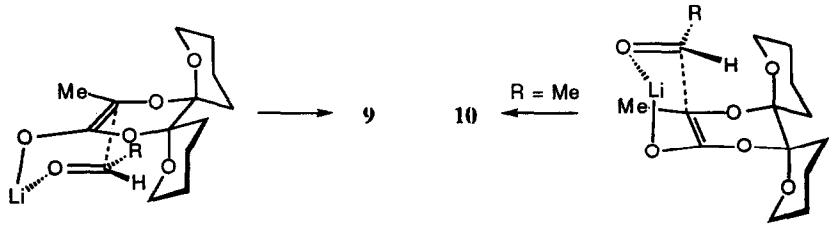
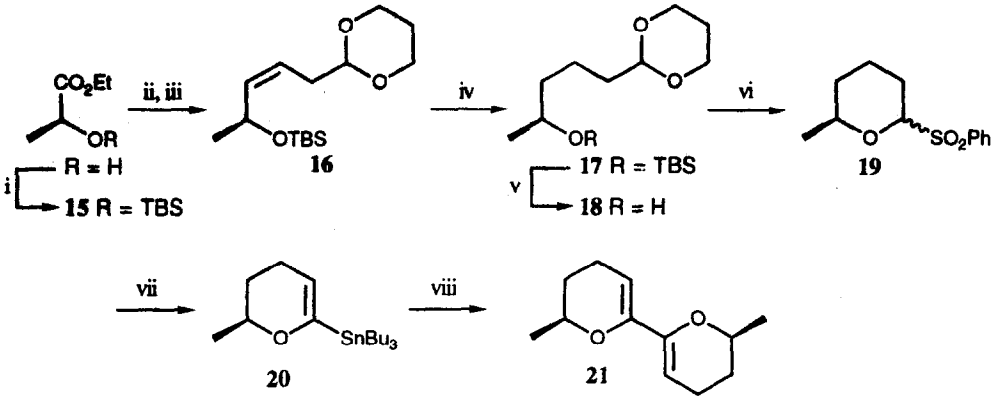


Figure 3. Aldol reaction transition states.

A NON-RACEMIC EQUIVALENT OF A GLYCOLIC ACID ENOLATE

Methods which rely on the hydroxy acid itself to introduce chirality are inherently limited to the preparation of those disubstituted hydroxy acids in which one of the α substituents is found in a corresponding chiral pool compound. It would be beneficial to have a means of utilising this methodology but applied instead to a non-racemic glycolic acid enolate, thereby allowing access to α,α disubstituted hydroxy acid derivatives where neither substituent falls into the limited class outlined above. This has been achieved by the synthesis of the methyl disubstituted *bis*-dihydropyran **21**[10] (Scheme 6). (*S*)-Ethyl lactate

was first protected as its *tert*-butyldimethylsilyl ether **15** before reduction with DIBAL-H in dichloromethane (DCM) and Wittig reaction with 2-(1,3-dioxan-2-yl)ethyltriphenylphosphorane to give compound **16**. Hydrogenation to **17** and silyl ether cleavage with tetrabutylammonium fluoride (TBAF) gave the alcohol **18**, the enantiomeric excess of which was checked by preparation of both *R* and *S* Mosher's esters[11] and determined to be greater than 98% by ^{19}F and ^{1}H NMR. One-pot dioxane cleavage and anomeric sulfone preparation was effected by treatment of **18** with an excess of freshly-prepared phenylsulfinic acid,[12] providing **19** as a mixture of anomers. Due to the slight instability of these compounds the anomers were not separated but rapidly purified by flash chromatography on Florisil® and immediately deprotonated with n-butyllithium before quenching the anion with tri-n-butyltin chloride. Refluxing the product with Hünig's base (N,N-diisopropylethylamine) eliminated phenylsulfinic acid to give the vinyl stannane **20** in good yield. Transmetallation of the stannane with n-BuLi to give the vinyl lithium species and palladium catalysed homocoupling using copper (II) chloride as the oxidant afforded the dimethyl *bis*-dihydropyran **21**.

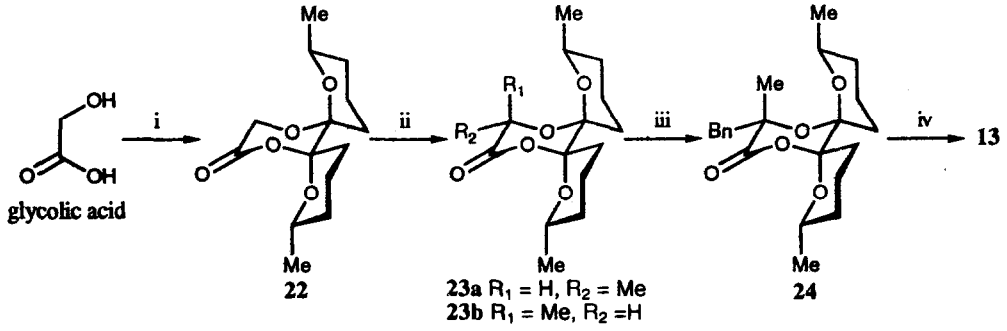


i) TBSCl, imidazole, 98%. ii) DIBAL-H, DCM, -78°C. iii) 2-(1,3-dioxan-2-yl)ethyltriphenylphosphorane, 79% over two steps. iv) H_2/PtO_2, EtOAc, 98.5%. v) TBAF, THF, 94%. vi) $PhSO_2H$, $CaCl_2$, DCM, 89%. vii) n-BuLi, THF, -78°C; Bu_3SnCl, -20°C; aqueous work-up; $^{i}Pr_2EtN$, $CHCl_3$, Δ, 75%. viii) n-BuLi, THF, -78°C; 6 mol% $PdCl_2(MeCN)_2$, $CuCl_2$, -78 to 0°C; NH_4Cl/NH_3, 60%.

Scheme 6. Preparation of dimethyl *bis*-dihydropyran 21

On reaction of **21** with glycolic acid (Scheme 7) the methyl groups control the structure formed by adopting equatorial positions and compound **22** was isolated as a single diastereoisomer. For the purpose of correlation of the products, our initial investigation looked at the preparation of a compound also available to us *via* the lactic acid-based route above, hence compound **22** was treated with LDA in THF followed by methyl iodide. This gave a mixture of **23a** and **23b** in an interesting 10:1 ratio. By this process, we had obtained an equivalent of **3**, by a route not directly using a chiral-pool derived hydroxy acid. The mixture of **23a** and **23b** was deprotonated with LDA, giving a single enolate which was then allowed to react with

benzyl bromide under conditions developed for the lactic acid derived compound, to give **24** as a single diastereoisomer. Deprotection of this compound gave **13** identical to the compound prepared *via* **3**, in an unoptimised yield of 31%. Although the *bis*-dihydropyran is >98% *ee*., the enantiomeric excess of **13** was measured to be 96.0% by chiral GC, slightly lower than that of **13** derived from lactic acid. The lower *ee* and poor yield are probably a consequence of the longer time required for completion of this reaction due to the robust nature of the dispiroketal.



i) PPTS, THF, 75%. ii) LDA, THF, -78°C; MeI, 73%. iii) LDA, THF/DMPU, -78°C; BnBr, 70%. iv) CSA, MeOH, ethylene glycol, Δ, 31%.

Scheme 7. Enantioselective dialkylation of glycolic acid.

Summary and Conclusions

In this paper we have developed a new α-hydroxy acid protecting group using dispiroketals. These compounds may be readily alkylated and deprotected to substituted products with control of the α-chiral centres. The new method compares favourably with and is complementary to existing literature procedures and additionally allows synthesis of compounds of high enantiomeric purity from achiral glycolic acid itself. The method therefore creates new opportunities for asymmetric synthesis.

EXPERIMENTAL SECTION

Proton and carbon nmr spectra were recorded on Bruker AC200, AC250, WM250, AC400 and DRX500 machines. Chemical shifts are quoted in ppm relative to residual protic solvent ($C\underline{H}Cl_3$, δ_H=7.26) or deuteriochloroform ($\underline{C}DCl_3$, t, δ_C=77.0). ^{13}C NMR assignments were confirmed by DEPT or APT spectra. Infra-red spectra were recorded on Perkin-Elmer 1600 series FTIR machine. Mass spectra were recorded in the University Chemistry Department or by the SERC mass spectroscopy service at Swansea. Microanalyses were performed by the University Chemistry Department microanalytical service. Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Optical rotations were

measured with an Optical Activity AA-1000 polarimeter using acid- and ethanol-free chloroform as solvent. Analytical GC was carried out on a 10m polyphenylmethylsiloxane column or for chiral GC on a 25m LipodexE® fused silica column[13] (carrier gas He, 70 kPa) with a Perkin-Elmer Sigma 3 GC and Perkin-Elmer LCI-100 integrator. Flash column chromatography was carried out on Merck Kieselgel 60 (230-400 mesh). Solvents and reagents were purified by standard procedures where necessary or used as purchased. Analytical thin layer chromatography was performed using precoated glass-backed plates (Merck Kieselgel 60 F_{254}) and visualised by acidic ammonium molybdate (IV).

(6*R*,7*R*,15*S*)-15-methyl-1,8,13,16-tetraoxadispiro[5.0.5.4]-hexadecan-14-one, 3.

A mixture of *bis*-dihydropyran **1** (3.41g, 2.1 mmol) and lactic acid **2**[14] (1.85g, 1 eq.) were dried *in vacuo* for 1 hour to remove traces of water. The mixture was placed under argon, and toluene (25ml) and a 1.0 M solution of HCl in ether (2.0 ml, 10 mol%) were added. The mixture was stirred at room temperature for 48 hrs during which time the mixture became dark, then the solvent was evaporated *in vacuo* and the residue purified by flash chromatography (20% ether/petrol). This gave a mixture of **3** and **4** in a combined yield of 85% and 12:1 ratio by ^{1}H nmr. A single recrystallisation from 40-60 petrol (15ml/g) gave diastereoisomerically pure **3**. MPt. 84-86°C with prior softening (40-60 petrol). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.31 (1H, q, J=7.0 Hz, H15), 4.00-3.54 (4H, m, 2×H2, 2×H9), 2.01-1.41 (15H, m, inc. 3H, d, J=7.0 Hz, Me; 6×CH_2); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.6 (C=O), 103.3, 95.4 (C6, C7), 65.8 (C15), 62.7, 62.3 (C2, C9), 28.4, 27.9 (2×CH_2), 24.6 (CH_3), 24.4, 18.2, 18.0, 17.2 (4×CH_2); IR (Nujol mull) 1740 cm^{-1} (C=O); MS (EI) m/z 257.1 (MH^+), 168.1, 156.1, 128.1, 111.1. Analysis calculated for $C_{13}H_{20}O_5$: C 60.92, H 7.86. Found C 61.13, H 8.02. $[\alpha]_D^{25}$ -124 (c=0.96, $CHCl_3$).

General procedure for enolate alkylations. A solution of LDA in THF (2.5 ml) was prepared under argon from diisopropylamine (1.1 eq.) and n-BuLi solution (1.6 M solution in hexanes, 1.1 eq). After stirring for 20 minutes and cooling to -78°C, a solution of **3** in THF (1.5 ml) was added *via* cannula, the flask being rinsed with THF (2×0.5 ml). Where deprotonation of the diisopropylamine generated by this procedure was required, a second portion of n-BuLi solution (1.1 eq.) was added after 30 minutes had elapsed. DMPU (0.5 ml) was added and the mixture allowed to stir for 30 minutes, then the appropriate electrophile (2 eq.) was introduced. The reactions were monitored by tlc until no further change was observed then the mixture was allowed to warm to room temperature and quenched with 80% saturated ammonium chloride solution. The mixture was extracted with ether (×3), the combined organic phases dried ($MgSO_4$), evaporated *in vacuo* and the residue purified by flash chromatography on silica to give the desired compound.

(6*R*,7*R*,15*S*)-15-benzyl-15-methyl-1,8,13,16-tetraoxadispiro[5.0.5.4]-hexadecan-14-one, 7a.

By the general procedure described above using **3** (121 mg, 0.47 mmol) and benzyl bromide (124 µl, 2.2 eq.), **7a** was obtained (141 mg, 86%) after flash chromatography (15% ether/petrol) as a colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25-7.15 (5H, m, Ar*H*), 3.79-3.69 (1H, m), 3.63-3.56 (2H, m), 3.44-3.37 (1H,

m, 2×H2, 2×H9), 3.23 (1H, d, J=13.2 Hz, PhCH_2), 2.85 (1H, d, J=13.2 Hz, PhCH_2), 1.99-1.43 (15H, m, inc. 1.46, 3H, s, Me; 6×CH_2); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 172.8 (C=O), 136.1 (*ipso*-C), 131.2, 127.6 (*ortho*/*meta*-C), 126.5 (*para*-C), 103.7, 95.7 (C6, C7), 76.0 (C15), 62.0, 61.8 (C2, C9), 46.6 (PhCH_2), 29.1, 28.6 (2×CH_2), 26.3 (Me), 25.0, 24.3, 18.2, 17.5 (4×CH_2); IR (thin film) 2949, 1746, 1454, 1368, 1273, 1214 cm^{-1}; MS (EI) m/z 347.2 (MH^+), 255.2, 185.1, 167.1, 146.1, 118.1. Analysis calculated for $C_{20}H_{26}O_5$: C 69.35, H 7.56. Found C 69.34, H 7.45. $[\alpha]_D^{25}$ -89.7 (c=1.0, $CHCl_3$).

(6*R*,7*R*,15*S*)-15-(2-propenyl)-15-methyl-1,8,13,16-tetraoxadispiro[5.0.5.4]-hexadecan-14-one, 7b. By the general procedure using **3** (152 mg, 0.59 mmol) and allyl bromide (103 µl, 2.0 eq.), **7b** was obtained (166 mg, 94%) after flash chromatography (15% ether/petrol) as a 96:4 mixture of diastereoisomers by GC (170°C). Recrystallisation from methanol gave the pure major diastereoisomer, MPt. 74.5-76.5°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.91-5.80 (1H, m, H2'), 5.05 (1H, s, H3'-*cis* to H2'), 5.02 (1H, d, J=5.5 Hz, H3'-*trans* to H2'), 3.89-3.76 (2H, m), 3.74-3.69 (1H, m), 3.65-3.60 (1H, m, 2×H2, 2×H9), 2.55 (1H, dd, J=13.6, 7.3 Hz), 2.43 (1H, dd, J=13.6, 7.3 Hz, 2×H1'), 1.99-1.87 (2H, m), 1.80-1.70 (2H, m), 1.67-1.42 (11H, m, inc. 1.46, 3H, s, Me; 6×CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.5 (C=O), 132.9 (C2'), 118.1 (C3'), 103.8, 95.7 (C6, C7), 75.7 (C15), 62.1, 61.9 (C2, C9), 45.6 (C1'), 29.0, 28.7 (2×CH_2), 26.1 (Me), 25.0, 24.4, 18.2, 17.5 (4×CH_2); IR (thin film) 2950, 2884, 1747, 1640, 1214, 1076 cm^{-1}; MS (CI) m/z 297.2 (MH^+), 255.1, 168.1, 111.1. Analysis calculated for $C_{16}H_{24}O_5$: C 64.85, H 8.16. Found C 64.94, H 8.39. $[\alpha]_D^{25}$ -75.6 (c=1.02, $CHCl_3$).

(6*R*,7*R*,15*S*)-15-ethyl-15-methyl-1,8,13,16-tetraoxadispiro[5.0.5.4]-hexadecan-14-one, 7c and (6*R*,7*R*,15*R*)-15-ethyl-15-methyl-1,8,13,16-tetraoxadispiro[5.0.5.4]-hexadecan-14-one, 8c

By the general procedure using **3** (129 mg, 0.50 mmol) and ethyl iodide (81 µl, 2.0 eq.), a mixture of **7c** and **8c** were obtained in a ratio of 82:18 by GC of the crude product (160°C). Flash chromatography (10% ether/petrol) followed by HPLC separation gave **7c** (96 mg, 67%) and **8c** (22.2 mg, 15.5%).

Major diastereoisomer **7c**: MPt. 79-81°C without recrystallisation. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.92-3.77 (2H, m), 3.75-3.69 (1H, m), 3.67-3.61 (1H, m, 2×H2, 2×H9), 2.01-1.47 (17H, m, inc. 1.51, 3H, s, Me, 7×CH_2), 0.92 (3H, t, J=7.5 Hz, Me2'); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 173.1 (C=O), 103.8, 95.5 (C6, C7), 76.2 (C15), 62.1, 61.9 (C2, C9), 34.5, 29.1, 28.7 (3×CH_2), 26.1 (Me), 25.1, 24.4, 18.3, 17.5 (4×CH_2), 8.1 (C2'); IR (thin film) 2950, 1746, 1456, 1368, 1272, 1168, 1076, 980 cm^{-1}; MS (EI) m/z 285.2 (MH^+), 255.1, 226.1, 184.1, 168.1, 111.1, 98.1. Analysis calculated for $C_{15}H_{24}O_5$: C 63.36, H 8.50. Found C 63.43, H 8.73. $[\alpha]_D^{30}$ -87.3 (c=1.0, $CHCl_3$).

Minor diastereoisomer **8c**: MPt. 81-86°C without recrystallisation. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.97-3.87 (1H, m), 3.82-3.64 (3H, m, 2×H2, 2×H9), 2.03-1.91 (3H, m), 1.88-1.73 (3H, m), 1.71-1.47 (8H, m, 7×CH_2), 1.43 (3H, s, Me), 1.05 (3H, t, J=7.5 Hz, Me2'); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 173.8 (C=O), 103.3, 95.7 (C6, C7), 75.2 (C15), 62.3, 62.1 (C2, C9), 31.7, 29.3, 28.7, 25.2, 24.45 (5×CH_2), 24.38 (Me), 18.4, 17.5 (2×CH_2), 6.9 (C2'); IR (thin film) 2961, 1736, 1442, 1367, 1276, 1159, 1101, 1031, 978 cm^{-1};

MS (EI) m/z 285.0 (MH^+), 185.0, 168.0, 127.0, 111.0. Accurate mass calc. for $C_{15}H_{25}O_5$ (MH^+): 285.1702. Found 285.1716. $[\alpha]_D^{30}$ -62.7 (c=1.0, $CHCl_3$).

Preparation of 7c/8c using KHMDS as base.

To a solution of **3** (132 mg, 0.52 mmol) in THF (5 ml) under argon at -78°C was added a 0.5 M solution of KHMDS in toluene (1.34 ml, 1.3 eq.). After 20 minutes, ethyl iodide (82 µl, 2.0 eq.) was added and the reaction stirred at -78°C for 2 hours, then allowed to warm to room temperature over 2 hours. The mixture was poured into 80% saturated ammonium chloride solution, which was then extracted with ether (×4). The organic extracts were dried and evaporated *in vacuo* and the residue purified by flash chromatography (10% ether/petrol) to give a mixture of **7c** and **8c** (110 mg, 75%). Spectral data as given above. Ratio of **7c**:**8c** determined by GC to be 89:11.

(6*R*,7*R*,15*S*)-15-propyl-15-methyl-1,8,13,16-tetraoxadispiro[5.0.5.4]-hexadecan-14-one, 7d and (6*R*,7*R*,15*R*)-15-propyl-15-methyl-1,8,13,16-tetraoxadispiro[5.0.5.4]-hexadecan-14-one, 8d.

By the general procedure using **3** (147 mg, 0.57 mmol) and n-propyl iodide (112 µl, 2.0 eq.), a mixture of **7d and 8d** were obtained in a ratio of 83:17 by GC of the crude product (170°C). Flash chromatography (10% ether/petrol) followed by HPLC separation gave **7d** (90 mg, 60%) and **8d** (18 mg, 13%).

Major diastereoisomer: MPt. 59-61°C (pentane). ^1H NMR ($CDCl_3$, 400 MHz) δ 3.92-3.80 (2H, m), 3.76-3.72 (1H, m), 3.67-3.63 (1H, m, 2×H2, 2×H9), 2.03-1.90 (2H, m), 1.85-1.47 (16H, m, inc. 1.51, 3H, s, Me), 1.39-1.26 (1H, m, 8×CH_2), 0.88 (3H, t, J=7.4 Hz, Me3'); ^{13}C NMR ($CDCl_3$, 250 MHz) δ 173.3 (C=O), 103.9, 95.6 (C6, C7), 76.1 (C15), 62.2, 62.0 (C2, C9), 43.9 (C1'), 29.2, 28.8 (2×CH_2), 26.8 (Me), 25.2, 24.5, 18.4, 17.6, 17.0 (5×CH_2), 14.4 (C3'); IR (thin film) 2954, 1746, 1443, 1355, 1273, 1196, 1076 cm^{-1}; MS (EI) m/z 299.2 (MH^+), 255.1, 198.1, 185.1, 168.1, 111.1, 98.1. Analysis calculated for $C_{16}H_{26}O_5$: C 64.41, H 8.78. Found C 64.38, H 8.90. $[\alpha]_D^{26}$ -76.9 (c=1.0, $CHCl_3$).

Minor diastereoisomer: MPt. 71.5-78°C without recrystallisation. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.95-3.86 (1H, m), 3.81-3.77 (1H, m), 3.71-3.64 (2H, m, 2×H2, 2×H9), 2.02-1.89 (3H, m), 1.83-1.48 (13H, m, 8×CH_2), 1.44 (3H, s, Me), 0.95 (3H, t, J=7.3 Hz, Me3'); IR (thin film) 2940, 1738, 1444, 1367, 1276, 1200, 1030 cm^{-1}; MS (EI) m/z 299.2 (MH^+), 198.1, 185.1, 168.1, 111.1, 98.1. Accurate mass calculated for $C_{16}H_{27}O_5$ (MH^+): 299.1858. Found 299.1855. $[\alpha]_D^{25}$ -67.5 (c=1.0, $CHCl_3$).

Preparation of 7d/8d using KHMDS as base.

To a solution of **3** (156 mg, 0.61 mmol) in THF (2.5 ml) under argon at -78°C was added a 0.5 M solution of KHMDS in toluene (1.58 ml, 1.3 eq.). After 45 minutes, n-propyl iodide (119 µl, 2.0 eq.) was added and the reaction stirred at -78°C for 2 hours, then allowed to warm slowly to room temperature. The mixture was poured into 80% saturated ammonium chloride solution, which was then extracted with ether (×3). The organic extracts were dried and evaporated *in vacuo* and the residue purified by flash chromatography (10% ether/hexane) to give a mixture of **7d** and **8d** (121 mg, 67%). Spectral data as given above. Ratio of **7d**:**8d** determined by GC to be 92:8.

General procedure for aldol reactions. The enolate of **3** was prepared in the same way as for the alkylation reactions above. A second equivalent of n-BuLi solution was added in all cases except that of benzaldehyde. After addition of the electrophile the reaction was followed by tlc, and when it was judged to be complete the reaction was quenched at -78°C by the addition of saturated ammonium chloride solution. The mixture was then allowed to warm to room temperature, water added to dissolve precipitated salts and extraction carried out as for the alkylation reactions.

[6*R*,7*R*,15*S*,(*S*)]-15-[(hydroxy)phenylmethyl]-15-methyl-1,8,13,16-tetraoxadispiro[5.0.5.4]-hexadecan-14-one, 9a.

By the general procedure, without a second equivalent of n-BuLi solution, using **3** (256 mg, 1 mmol) and benzaldehyde (freshly distilled, 152 µl, 1.5 eq.), compound **9a** was obtained (349 mg, 96%) after flash chromatography (two columns, 50% ether/petrol and 33% ether/petrol) as a white foam. MPt. 46-49°C (pentane). ^{1}H NMR ($CDCl_3$, 400 MHz) 7.38-7.25 (5H, m, ArH), 4.84 (1H, s, PhC*H*), 4.37 (1H, br. s, OH), 4.06-3.95 (1H, m, H9-*ax*,), 3.85-3.75 (2H, m, H2-*ax*, H9-*eq*), 3.71-3.65 (1H, m, H2-*eq*), 2.07-1.90 (3H, m), 1.79-1.49 (9H, m, 6×CH_2), 1.40 (3H, s, Me); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 169.2 (C=O), 137.6 (*ipso*-C), 128.5, 126.9 (*ortho*/*meta*-C), 127.6 (*para*-C), 103.6, 95.6 (C6, C7), 79.4, 79.1 (PhC, C15), 62.5, 62.0 (C2, C9), 28.5, 28.4, 24.4, 23.8 (4×CH_2), 23.0 (Me), 17.8, 17.0 (2×CH_2); IR (thin film) 3465, 2951, 1750, 1453, 1369, 1213, 1073 cm^{-1}; MS (EI) m/z 363.2 (MH^+), 256.1, 185.1, 168.1, 111.1, 98.1. Analysis calculated for $C_{20}H_{26}O_6$: C 66.28, H 7.23. Found C 66.17, H 7.24. $[\alpha]_D^{28}$ -59.5 (c=1.0, $CHCl_3$).

[6*R*,7*R*,15*S*,(*S*)]-15-(1-hydroxy-2-propenyl)-15-methyl-1,8,13,16-tetraoxadispiro[5.0.5.4]-hexadecan-14-one, 9b.

By the standard procedure using **3** (125 mg, 0.49 mmol) and acrolein (82 µl, 2.5 eq.), compound **9b** was obtained (145 mg, 94%) after flash chromatography (25% ether/petrol). MPt. 83-85°C (ether/pentane). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.97 (1H, ddd, J=17.2, 10.3, 7.6 Hz, H2'), 5.33 (1H, ddd, 17.2, 1.6, 1.1 Hz, H3'-*trans* to H2'), 5.27 (1H, dd, 10.2, 1.5 Hz, H3'-*cis* to H2'), 4.15 (1H, s, OH), 4.10 (1H, d, J=7.6 Hz, H1'), 4.03-3.93 (1H, m), 3.87-3.68 (3H, m 2×H2, 2×H9), 2.05-1.50 (12H, m, 6×CH_2), 1.46 (3H, s, Me); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 169.4 (C=O), 134.7 (C2'), 119.2 (C3'), 103.8, 95.9 (C6, C7), 80.0 (C1'), 79.9 (C15), 62.9, 62.4 (2×CH_2O), 28.8, 28.7, 24.8, 24.2 (4×CH_2), 23.8 (Me), 18.2, 17.3 (2×CH_2); IR (thin film) 3472, 2951, 1748, 1443, 1371, 1241, 1073, 1002 cm^{-1}; MS (EI) m/z 313.2 (MH^+), 255.1, 201.1, 185.1, 168.1, 111.1. Microanalysis calculated for $C_{16}H_{24}O_6$: C 61.51, H 7.74. Found C 61.47, H 7.81. $[\alpha]_D^{28}$ -62.5 ($CHCl_3$).

[6*R*,7*R*,15*S*,(*S*)]-15-(1-hydroxyethyl)-15-methyl-1,8,13,16-tetraoxadispiro[5.0.5.4]-hexadecan-14-one, 9c and [6*R*,7*R*,15*R*,(*R*)]-15-(1-hydroxyethyl)-15-methyl-1,8,13,16-tetraoxadispiro[5.0.5.4]-hexadecan-14-one, 10.

The standard procedure using **3** (334 mg, 1.30 mmol) and acetaldehyde (approx. 4 eq.) gave, in order of elution, **10** (16 mg, 4%) and **9c** (364 mg, 93%) following flash chromatography (20% ether/petrol).

9c: MPt. 110-113°C (decomp.); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.97-3.92 (1H, m, H2-*ax* or H9-*ax*), 3.90 (1H, s, OH), 3.85-3.80 (2H, m, H1', H2-*ax* or H9-*ax*), 3.75-3.73 (1H, m), 3.70-3.68 (1H, m, H2-*eq*, H9-*eq*), 2.02-1.46 (15H, m, inc. 1.46, 3H, s, Me; 6×CH_2), 1.24 (3H, d, J=6.4 Hz, Me2'); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.5 (C=O), 103.7, 95.8 (C6, C7), 80.1 (C15), 74.1 (C1'), 62.8, 62.4 (C2, C9), 28.9, 28.7, 24.8, 24.2 (4×CH_2), 23.3 (Me), 18.2, 17.3 (2×CH_2), 16.5 (Me); IR (thin film) 3485, 2944, 2884, 1742, 1446, 1373, 1208, 1106 cm^{-1}; MS (EI) m/z 301.2 (MH^+), 256.1, 201.1, 185.1, 168.1, 111.1, 101.1. Accurate mass calculated for $C_{15}H_{25}O_6$ (MH^+): 301.1651. Found 301.1642. $[\alpha]_D^{28}$ -88.1 (c=1.0, $CHCl_3$).

10: MPt. 144-146°C without recrystallisation; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.32 (1H, s, OH), 4.10 (1H, q, J=6.3 Hz, H1'), 3.96-3.91 (1H, m), 3.87-3.85 (1H, m, 2×H9), 3.74-3.71 (2H, m, 2×H2), 2.06-1.97 (2H, m), 1.88-1.85 (1H, m), 1.77-1.54 (9H, m, 6×CH_2), 1.51 (3H, s, Me), 1.31 (3H, d, J=6.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.7 (C=O), 104.3, 95.8 (C6, C7), 75.9 (C15), 70.2 (C1'), 62.5, 62.3 (C2, C9), 29.0, 28.8, 24.9, 24.3 (4×CH_2), 18.4 (Me), 18.2, 17.5 (2×CH_2), 15.0 (Me); IR (thin film) 3479, 2953, 2894, 1707, 1445, 1359, 1276, 1157, 1115, 1079, 1028 cm^{-1}; MS (EI) m/z 301.2 (MH^+), 255.1, 185.1, 168.1, 111.1. Accurate mass calculated for $C_{15}H_{25}O_6$ (MH^+): 301.1651. Found 301.1648. $[\alpha]_D^{29}$ -44.5 (c=0.72, $CHCl_3$).

(6*R*,7*R*,15*S*)-15-(1-hydroxycyclopentan-1-yl)-15-methyl-1,8,13,16-tetraoxadispiro[5.0.5.4]-hexadecan-14-one, 9d.

The standard procedure using **3** (302 mg, 1.18 mmol) and cyclopentanone (209 µl, 2 eq.) gave, in order of elution, starting material **3** (139 mg, 46%) and compound **9d** (142 mg, 35%) after flash chromatography (20% ether/hexane).

9d: MPt. 131-133°C (60-80 petrol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.95-3.85 (1H, m), 3.83-3.75 (1H, m), 3.73-3.63 (3H, m, incl. 3.73 1H, s, OH; 2×H2, 2×H9), 1.99-1.87 (4H, m), 1.80-1.47 (15H, m, incl. 1.52, 3H, s, Me; 8×CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3 (C=O), 103.6, 95.6 (C6, C7), 87.0, 81.1 (C15, C1'), 62.6, 62.2 (C2, C9), 36.0, 34.4, 29.1, 28.7, 24.9, 24.5, 24.2, 23.8 (8×CH_2), 23.2 (Me), 18.3, 17.3 (2×CH_2); IR (thin film) 3497, 2950, 1745, 1289, 1213, 1073, 983 cm^{-1}; MS (EI) m/z 341.2 (MH^+), 256.1, 201.1, 185.1, 168.1, 140.1, 122.1, 111.1, 101.1. Analysis calculated for $C_{18}H_{28}O_6$: C 63.51, H 8.29. Found C 63.62, H 8.31. $[\alpha]_D^{29}$ -61.5 (c=1.18, $CHCl_3$).

[6*S*,7*R*,15*S*,(*S*)]-15-(1-hydroxy-1-phenylethyl)-15-methyl-1,8,13,16-tetraoxadispiro[5.0.5.4]-hexadecan-14-one, 9e.

The standard procedure using **3** (306 mg, 1.2 mmol) and acetophenone (279 µl, 2.0 eq.) gave, in order of elution, starting material **3** (170 mg, 56%) and **9e** (130 mg, 29%) after flash chromatography (10% EtOAc/hexane).

9e: MPt. 143-144°C (ether/$CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (2H, dd, J=1.2, 7.7 Hz, *ortho*-H), 7.33-7.24 (3H, m, *meta*/*para*-H), 4.54 (1H, s, OH), 4.07-3.97 (1H, m), 3.80 (1H, dd, J=1.6, 10.4 Hz), 3.68-3.58 (2H, m, 2×H2, 2×H9), 2.06-1.93 (3H, m), 1.74-1.44 (15H, m, incl. 1.67, 3H, s, Me2' and 1.44, 3H, s, Me; 6×CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.1 (C=O), 142.0 (*ipso*-C), 127.6, 126.9 (*ortho*/*meta*-C;

para-C probably coincident at δ 126.9), 104.1, 95.6 (C6, C7), 80.5, 77.9 (C15, C1'), 62.5, 62.0 (C2, C9), 29.2, 28.6 (2×CH_2), 25.8 (Me), 24.7, 24.2 (2×CH_2), 23.2 (Me), 18.1, 17.3 (2×CH_2); IR (thin film) 3477, 2951, 2888, 1753, 1713, 1447, 1363, 1273, 1215, 1102, 1074, 1002 cm^{-1}; MS (EI) m/z 377.2 (MH^+), 359.2, 312.2, 257.1, 183.1, 168.1. Accurate mass calculated for $C_{21}H_{27}O_5$ $(M\text{-}OH)^+$: 359.1858. Found 359.1877. $[\alpha]_D^{29}$ -75.4 (c=1.21, $CHCl_3$).

(2*S*) methyl 2-hydroxy-2-methyl-3-phenylpropanoate 13.

From lactic acid: Compound **7a** (64 mg, 0.18 mmol) and *dl*-camphorsulfonic acid (CSA, 25 mg) were heated at 100°C in neat ethylene glycol (0.5 ml) for 1 hour. The mixture was allowed to cool, diluted with ether (10 ml) and washed with saturated sodium bicarbonate solution (10 ml). The organic phase was dried ($MgSO_4$), evaporated and the residue purified by flash chromatography: elution with 20% ether/petrol removed the ethlyene glycol dispiroketal **11**, then elution with neat ether gave the ethylene glycol ester **12** of the desired acid. This was dissolved in anhydrous methanol (1 ml), sodium carbonate (0.10g) added and the mixture stirred at room temperature for 48 hours. The mixture was then diluted with water (10 ml) and extracted with dichloromethane (3×10 ml), the organic extracts being dried ($MgSO_4$), combined and evaporated *in vacuo*. Purification of the residue by flash chromatography (5% ether/petrol) gave the known compound **13** (29 mg, 80% over 2 steps) as a colourless oil.

^1H NMR ($CDCl_3$, 250 MHz) δ 7.34-7.12 (5H, m, aryl H), 3.74 (3H, s, OMe), 3.07 (1H, d, J=13.5 Hz, H3), 3.0 (1H, br.s, exch. with D_2O, OH), 2.89 (1H, d, J=13.5 Hz, H3), 1.48 (3H, s, Me); IR (thin film) 3516, 2949, 2870, 1737, 1451, 1261, 1209, 1093, 1038, 988 cm^{-1}: MS (EI) m/z 194.1 (M^+), 176.1, 135.1, 92.1. Accurate mass calculated for $C_{11}H_{14}O_3$ (M^+): 194.0943. Observed 194.0951. $[\alpha]_D^{30}$ -113 (c=1.0, $CHCl_3$). The enantiomeric excess of this compound was determined to be 97.6% by chiral GC of its trifluoracetate derivative, prepared by reaction with *N*-methylbis(trifluoracetamide). Retention times (115°C): *ent*-**13** 22.9 min, **13** 23.8 min. A sample of **13** of lower *ee* for comparison was prepared by alkylation of a 4:1 mixture of **3** and **4** with benzyl bromide (resulting in an *ee* of approximately 60%) and deprotection under the usual conditions.

From glycolic acid: Compound **24** (50 mg, 0.13 mmol) and ethylene glycol (approx 22 μl, 3 eq.) were dissolved in anhydrous methanol (5 ml), CSA was added (17 mg) and the mixture heated at reflux for 5 days. A further portion of ethylene glycol (100 μl, excess) was added and heating continued for 5 more days. The mixture was allowed to cool and partitioned between sodium bicarbonate solution and ether, then the aqueous phase was extracted with ether (×3). The organic extracts were dried and evaporated *in vacuo*. The residue was purified by preparative tlc, eluting with 20% ether/petrol to give **13** (8.0 mg, 31%). Spectral characteristics identical to those given above. $[\alpha]_D^{30}$ -109 (c=1.14, $CHCl_3$). Enantiomeric excess determined by chiral GC to be 96.0%.

(2*S*,3*S*) methyl 2,3-dihydroxy-2-methyl-3-phenylpropanoate 14.

Compound **9a** (72 mg, 0.20 mmol) was dissolved in anhydrous methanol (3 ml) together with CSA (10 mg). The solution was heated at reflux for 3 hours, no change being observed by tlc. Ethylene glycol (1.5 eq.) was added as a 10% v/v solution in methanol and the solution refluxed for 5 hours. The reaction was quenched with saturated sodium bicarbonate solution and the mixture extracted with ether (3×10 ml), the combined organic extracts dried ($MgSO_4$) and evaporated *in vacuo*. Flash chromatography (50% ether/petrol) gave the known compound **14** in approximately quantitative yield (42 mg). MPt. 118.5-120°C with prior softening (EtOAc/60-80 petrol); ^1H NMR (200 MHz, $CDCl_3$) δ 7.4-7.2 (5H, m, ArH), 4.74 (1H, s, H3), 3.64 (3H, s, MeO), 3.0 (2H, br. s, 2×OH), 1.56 (3H, s, Me); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 175.0 (C=O), 139.1 (*ipso*-C), 128.3 (*para*-C), 128.1, 126.8 (*ortho/meta*-C), 78.0 (C3), (C2 obscured by solvent), 52.6 (CH_3O), 22.4 (CH_3); literature values[9] for *erthro*-**14** 175.0 (C=O), 77.9 (C3), 22.4 (CH_3); *threo*-**14** 176.2 (C=O), 77.6 (C3), 21.9 (CH_3); IR (thin film) 3476, 1727, 1451, 1252, 1160, 1096 cm^{-1}; MS (EI) m/z 193.1 (MH^+), 161.1, 151.1, 133.1, 107.0, 104.0, 89.0, 79.1. Accurate mass calc. for $C_{11}H_{13}O_3$ $(M-OH)^+$: 193.0865. Found 198.0865. $[\alpha]_D^{29}$ +27.2 (c=0.43, $CHCl_3$).

(2*Z*,4*S*)-4-(*tert*-butyldimethylsilyloxy)-1-(1,3-dioxan-2-yl)pent-2-ene 16.

To a solution of (*S*)-ethyl lactate (6.52g, 55.2 mmol) in distilled DMF (40 ml) was added imidazole (4.13g, 60.7 mmol) and TBDMS-Cl (8.99g, 59.6 mmol). The mixture was stired under argon for 48 hours at room temperature then poured into ice-water. This was then extracted with ether (×2), the combined organic extracts being washed with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography (ether/petrol 1:2) gave **15** as an oil (12.51g, 98%).

A solution of **15** (12.02g, 51.8 mmol) in DCM (150 ml) was cooled to -78°C under argon. A 1.0 M solution of DIBAL-H (54.4 ml, 54.4 mmol) in DCM was added slowly, the resulting solution being stirred at -78°C for 1 hour. Water (10 ml) was added and the mixture allowed to warm to r.t. before the addition of anhydrous magnesium sulfate. After stirring for 10 minutes to coaggulate the salts present, the suspension was filtered through celite, the filtered solids being well washed with ethyl acetate. The filtrate was dried ($MgSO_4$) and evaporated to give an oil (9.74g) which was used immediately in the Wittig reaction.

A solution of 2-(1,3-dioxan-2-yl)ethyltriphenylphosphonium bromide (17.28g, 48.4 mmol) in THF (200 ml) was cooled to 0°C under argon. To it was added KHMDS (9.74g, 48.8 mmol) portionwise, then the solution was stirred for 2 hours while warming to room temperature. The crude aldehyde from the DIBAL-H reduction was added to the solution of the ylid as a solution in THF (15 ml), the reaction mixture then being allowed to stir at room temperature for 36 hours. Ether was then added, the solids removed by filtration through Florisil®, the filtrate dried ($MgSO_4$) and evaporated to give a white solid. Treatment of this residue with 10% ether/petrol allowed the removal of further triphenylphosphine oxide by filtration. Then the filtrate was evaporated and the residue purified by flash chromatography (10% ether/petrol) to give **16** as an oil (11.70g, 79% from **15**). ^1H NMR ($CDCl_3$, 400 MHz) δ 5.55-5.50 (1H, m, H3), 5.31 (1H, dt, J=11.1, 7.4 Hz, H2), 4.57 (1H, qn, J=5.1 Hz, H4), 4.50 (1H, t, J=5.2 Hz, H2'), 4.09 (2H, dd, J=10.9, 5.0 Hz, H4'-*eq*, H6'-*eq*), 3.74 (2H, td, 12.3, 3.3 Hz, H4'-*ax*, H6'-*ax*), 2.34 (2H, ddd, J=7.0, 5.4, 1.4 Hz, H1), 2.07 (1H, qt, J=12.8, 5.0 Hz, H5'-*ax*), 1.33 (1H, dm, J=13.5 Hz, H5'-*eq*), 1.17 (3H, d, J=6.3 Hz, Me), 0.86 (9H, s, Me_3C), 0.03 (3H, s, MeSi), 0.02 (3H, s, MeSi); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.8, 121.1 (C2, C3),

101.6 (C2'), 66.9 (C4', C6'), 65.2 (C4), 33.8 (C1), 25.9 (Me_3), 25.7 (C5'), 24.6 (C5), 18.2 (Me_3CSi), -4.5, -4.7 (2×MeSi); IR (thin film) 2956, 2854, 1660, 1472, 1378, 1251, 1144, 1083; MS (EI) m/z 285.2 $(M-H)^+$, 271.1, 229.1, 171.1, 166.1, 153.1. Accurate mass calculated for $C_{15}H_{29}O_3Si$ $(M-H)^+$: 285.1886. Found 285.1890. $[\alpha]_D^{29}$ +31.06 (c=2.07, $CHCl_3$).

(4*S*)-4-(*tert*-butyldimethylsilyloxy)-1-(1,3-dioxan-2-yl)pentane 17.

To a solution of alkene **16** (7.09g, 24.8 mmol) in ethyl acetate (100 ml) under argon was added platinum (IV) oxide (200 mg, 0.88 mmol). Argon was exchanged for hydrogen and the reaction mixture stirred vigorously at ambient temperature and pressure for 3 hours. The suspension was filtered through celite, the filtrate evaporated and the residue purified by flash chromatography (20% ether/petrol) to give **17** as an oil (7.03g, 98.5%). ^1H NMR ($CDCl_3$, 400 MHz) δ 4.49 (1H, t, J=5.2 Hz, H2'), 4.08 (2H, dd, J=10.8, 4.9 Hz, H4'-*ax*, H6'-*ax*), 3.77-3.70 (3H, m, H4'-*eq*, H6'-*eq*, H4), 2.10-2.01 (1H, m, H5'-*ax*), 1.59-1.54 (2H, m), 1.46-1.30 (5H, m, H5'-*eq*, 3×CH_2), 1.10 (3H, d, J=6.1 Hz, Me), 0.87 (9H, s, Me_3C), 0.02 (6H, s, Me_2Si); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 102.4 (C2'), 68.5 (C4), 66.9 (C4', C6'), 39.5, 35.2 (2×CH_2), 25.92 (Me_3), 25.89 (CH_2), 23.6 (Me), 20.2 (CH_2), 18.2 (Me_3CSi), -4.4, -4.7 (2×MeSi); IR (thin film) 2956, 2854, 1472, 1377, 1254, 1145 cm^{-1}; MS (EI) m/z 287.2 $(M-H)^+$, 273.2, 159.1, 133.1. Accurate mass calculated for $C_{15}H_{31}O_3Si$ $(M-H)^+$: 287.2042. Found 287.2043. $[\alpha]_D^{28}$ +7.7 (c=2.47, $CHCl_3$)

(4*S*)-1-(1,3-dioxan-2-yl)pentan-4-ol 18.

To a solution of **17** (7.03g, 24.4 mmol) in THF (25 ml) was added a 1.1 M solution of TBAF (31.1 ml, 34.2 ml) in THF. After 10 hours the mixture was diluted with ether, washed with water and brine then dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography (20% ether/petrol to 90% ether/petrol) to give the alcohol as an oil (3.99g, 94%). ^1H NMR ($CDCl_3$, 200 MHz) δ 4.52 (1H, t, J=4.9 Hz, H2'), 4.14-4.05 (2H, m), 3.81-3.69 (3H, m, H4, 2×H4', 2×H6'), 2.19-1.95 (1H, m), 1.68-1.28 (8H, m, 2×H1, 2×H2, 2×H3, 2×H5', OH), 1.18 (3H, d, J=6.1 Hz, Me); IR (thin film) 3424, 2961, 2852, 1461, 1377, 1244, 1144, 1076, 999 cm^{-1}; MS (EI) m/z 173.1 $(M-H)^+$, 157.1, 115.1, 100.1, 99.1. Accurate mass calculated for $C_9H_{17}O_3$ $(M-H)^+$: 173.1178. Found 173.1165. $[\alpha]_D^{30}$ +7.36 (c=1.55, $CHCl_3$)

(6*S*)-6-methyl-2-phenylsufonyltetrahydro-2*H*-pyran 19.

Freshly prepared benzenesulfinic acid[12] was dissolved in DCM (50 ml) and anhydrous calcium chloride added (13.93g). To this suspension was added the alcohol **18** (5.46g, 31.4 mmol) as a solution in DCM (20 ml) *via* cannula, the mixture then being stirred at room temperature for 3 hours. Filtration through celite and evaporation of the filtrate gave an oily residue (7.2g) which was purified by flash chromatography on Florisil® (30% ether/petrol to 50% ether/petrol) to give the sulfone **19** as a 2:1 mixture of *trans*/*cis* compounds (6.76g, 89%). MS (mixture, EI) m/z 241.1 (MH^+), 201.1, 194.9, 183.0, 157.1, 125.0, 99.0. Accurate mass calc. for $C_{12}H_{17}O_3S$ (MH^+): 241.0898. Observed 241.0901. ^1H NMR (*trans*-sulfone, 250 MHz, $CDCl_3$) δ 7.92-7.87 (2H, m, *meta*-H), 7.65 (1H, tt, J=7.3, 1.4 Hz, *para*-H), 7.59-7.52 (2H, m,

ortho-H), 4.67 (1H, dd, J=6.5, 1.6 Hz, H2), 4.53 (1H, qdd, J=6.3, 4.3, 2.3 Hz, H6), 2.52 (1H, dm, J=14.5 Hz), 1.96-1.82 (1H, m), 1.79-1.65 (2H, m), 1.38-1.14 (2H, m, 3×CH_2), 1.08 (3H, d, J=6.2 Hz, Me)

(2*S*)-3,4-dihydro-2-methyl-6-tri-n-butylstannyl-2*H*-pyran 20.

To a mixture of sulfone anomers (6.76g, 28.2 mmol) in THF (150 ml) at -78°C under argon was added a 1.6 M solution of n-butyllithium (21.1 ml, 33.8 mmol) in hexanes. After 1 hour, tri-n-butyltin chloride (8.56 ml, 31.6 mmol) was added slowly, then after a further 20 minutes the temperature was raised to -20°C for 30 minutes. The reaction mixture was poured into saturated sodium bicarbonate solution, extracted with ether and the combined organic extracts dried ($MgSO_4$) and evaporated. The resultant oil was taken up into chloroform (150 ml, passed through a short column of basic alumina) and Hünig's base (24.5 ml, 140.8 mmol) added. The solution was heated at reflux overnight then evaporated and the residue purified by flash chromatography on Florisil® eluting with neat petrol to give the vinyl stannane (8.17g, 75%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.29 (1H, ddd, J=4.3, 2.7, 1.3 Hz, H5; tin satellites $^3J(^{119}Sn\text{-}H)$=28 Hz), 3.83 (1H, dqd, J=9.5, 6.4, 2.4 Hz, H2), 2.15-2.06 (1H, m, H4-*ax*), 2.00-1.92 (1H, m, H4-*eq*), 1.83-1.76 (1H, m, H3), 1.62-1.43 (7H, m, H3, 6×H2'), 1.34 (6H, sextet, J=7.3 Hz, 6×H3'), 1.21 (3H, d, J=6.3 Hz, Me), 0.94-0.88 (15H, m, incl. 9H, t, J=7.1 Hz, 9×H4'; 6×H1'); Accurate mass calculated for $C_{18}H_{37}OSn$ (MH^+): 389.1866. Found 389.1866. $[\alpha]_D^{28}$ -6.67 (c=1.125, $CHCl_3$).

(2*S*,2'*S*)-2,2'-dimethyl-3,3',4,4'-tetrahydro-bi-2*H*-pyran 21.

The vinyl stannane **20** (5.92g, 15.3 mmol) was placed under argon, dissolved in THF (50 ml) and cooled to -78°C. A 1.5 M solution of n-butyllithium (12.2 ml, 18.3 mmol) in hexanes was added dropwise. After 35 minutes anhydrous copper (II) chloride (2.26g, 16.83 mmol) and palladium dichloride *bis*-acetonitrile complex (224 mg, 0.87 mmol) were added in one portion. After 40 minutes the reaction mixture was raised to -25°C for 30 minutes. It was then poured into a mixture of saturated ammonium chloride and 880 ammonia (100 ml, 4:1 ratio), which was then extracted with ether (×3). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo*, and purification of the residue by flash chromatography on Florisil® (neat petrol to 20% ether/petrol) gave the *bis*-dihydropyran **21** as a white solid (890 mg, 60 %). MPt. 54-57°C without recrystallisation; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.22 (2H, t, J=3.8 Hz, H5, H5'), 4.0-3.87 (2H, m, H2, H2'), 2.22-2.04 (4H, m, 2×H3, 2×H3'), 1.88-1.77 (2H, m, H4, H4'), 1.61-1.45 (2H, m, H4, H4'), 1.32 (6H, d, J=6.4 Hz, 2×Me); IR (thin film) 2969, 2912, 1625, 1445, 1276, 1210, 1174, 1073 cm^{-1}; MS (EI) m/z 194 (M^+), 125, 97, 69, 57, 55; Analysis calculated for $C_{12}H_{18}O_2$: C 74.19, H 9.34. Found C 74.10, H 9.47. $[\alpha]_D^{28}$ -94.9 (c=1.0, $CHCl_3$).

(2*S*,6*S*,7*R*,9*S*)-2,9-dimethyl-1,8,13,16-tetraoxadispiro[5.0.5.4]-hexadecan-14-one 22.

Glycolic acid (188 mg, 2.5 mmol), *bis*-dihydropyran **21** (145 mg, 0.82 mmol) and a trace of a radical inhibitor [4,4'-thio*bis*-(6-*tert*-butyl-3-methyl-phenol)[15]] were dissolved in THF (1.1 ml). To this solution was added pyridinium *para*-toluenesufonate (PPTS, 29 mg) and the mixture stirred at room temperature for

3 days. The clear yellow solution was poured into saturated sodium bicarbonate solution which was then extracted with DCM (×3). The combined extracts were dried ($MgSO_4$), evaporated and the residue purified by flash chromatography (10% ether/petrol to 20% ether/petrol) to give **22** (151 mg, 75%). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.32 (1H, d, J=17.5 Hz), 4.16 (1H, d, J=17.5 Hz, 2×H15), 4.07 (1H, dqd, J=11.5, 6.2, 2.2 Hz), 3.74 (1H, dqd, J=11.3, 6.2, 2.2 Hz, H2, H9), 2.09-1.20 (12H, m, 6×CH_2), 1.15 (3H, d, J=6.2 Hz, Me), 1.14 (3H, d, J=6.2 Hz, Me); IR (thin film) 2936, 1753, 1200, 1050, 964 cm^{-1}; MS (EI) m/z 271.2 (MH^+), 211.1, 196.1, 156.1, 141.1, 128.1. Accurate mass calculated for $C_{14}H_{23}O_5$ (MH^+): 271.1545. Found 271.1547. $[\alpha]_D^{28}$ -81.25 (c=0.48, $CHCl_3$).

(2*S*,6*R*,7*R*,9*S*,15*S*)-15-benzyl-2,9,15-trimethyl-1,8,13,16-tetraoxadispiro[5.0.5.4]-hexadecan-14-one 24.

To a solution of diisopropylamine (0.075 ml, 0.53 mmol) in THF (1.5 ml) at -78°C under argon was added a 1.6 M solution of n-butyllithium (0.33 ml, 0.53 mmol) in hexanes. After 20 minutes a solution of **22** (110 mg, 0.41 mmol) in THF (1.5 ml) was added dropwise, the flask then being rinsed with THF (1.5 ml). 35 minutes later iodomethane was added (*ca* 1.5 eq.), the reaction being stirred for 20 minutes before quenching with saturated ammonium chloride solution. The mixture was extracted with DCM, the organic extracts combined, dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow oil. This was purified by flash chromatography (10% ether/petrol) to give (in order of elution) an inseparable mixture of **23a** and **23b** (85 mg, 73%, **23a**:**23b** = 10:1 by ^{1}H NMR) and recovered starting material **22** (27 mg, 23%).

The mixture of **23a** and **23b** (80 mg, 0.28 mmol) was azeotropically dried with toluene (×3), placed under argon and dissolved in THF (2 ml). This solution was added *via* cannula (rinsed through with 0.5 ml THF) to a cold (-78°C) solution of LDA (0.56 mmol) in THF (1.5 ml) prepared as above. DMPU (0.5 ml) was added and the mixture stirred for 30 minutes, then a further portion of n-butyllithium solution (0.21 ml, 2 eq.) was added. After 20 minutes benzyl bromide (160 µl, 5eq.) was added, reaction being complete in 15 minutes by tlc. The reaction mixture was poured into saturated ammonium chloride solution which was then extracted with DCM (×4). The combined organic extracts were dried ($MgSO_4$) and evaporated *in vacuo* and the oil obtained was purified by flash chromatography (5% ether/petrol) to give **24** (73 mg, 70%) as a colourless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.50-7.19 (5H, m, ArH), 4.12-4.00 (1H, m), 3.79 (1H, dqd, J=11.3, 6.4, 2.2 Hz, H2, H9), 3.31 (1H, d, J=13.0 Hz), 2.85 (1H, d, J=13.0 Hz, PhCH_2), 2.16-1.39 (12H, m, 6×CH_2), 1.36 (3H, s, 15-Me), 1.12 (3H, d, J=6.2 Hz), 1.04 (3H, d, J=6.3 Hz, 2-Me, 9-Me). IR (thin film) 2935, 1818, 1745, 1444, 1198, 1052 cm^{-1}; MS (EI) 375.2 (MH^+), 302.2, 283.3, 195.1, 146.1. Accurate mass calculated for $C_{22}H_{31}O_5$ (MH^+): 375.2171. Found 375.2173. $[\alpha]_D^{24}$ -67.4 (c=1.0, $CHCl_3$).

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REFERENCES AND NOTES

1. Dispiroketals in Synthesis (Part 9): Edwards, P. J.; Entwistle, D. A.; Perry, E. J.; Ley, S. V. *Tetrahedron Asymm.* **1994**, in press.

2. For a resolution approach see: Davies, A. G.; Ebeid, F. M.; Kenyon, J. *J. Chem. Soc.* **1957**, 3154-3157. For another enolate approach to this problem see reference 3 below.

3. a) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313-1324. b) Seebach, D. in *Modern Synthetic Methods 1986*; Scheffold, R. Ed.; Springer-Verlag; Berlin, Heidelberg, New York, Tokyo, 1986; pp. 125-257.

4. For the preliminary account of this work see: Downham, R.; Kim, K. S.; Ley, S. V.; Woods, M. *Tetrahedron Lett.* **1994**, *35*, 769-72.

5. Woods, M. *Spiroketals in Synthesis*, University of London 1992.

6. X-ray crystallographic data for **3** have been deposited at the Cambridge Crystallographic Data Centre.

7. Mukhopadhgay, T.; Seebach, D. *Helv. Chim. Acta.* **1982**, *65*, 385.

8. Kobayashi, M.; Koga, K.; Yamada, S. *Chem. Pharm. Bull.* **1972**, *20*, 1898-1905.

9. Heathcock, C. H.; Pirrung, M. C.; Sohn, J. E. *J. Org. Chem.* **1979**, *44*, 4294-4299.

10. Boons, G-J.; Entwistle, D. A.; Ley, S. V.; Woods, M. *Tetrahedron Lett.* **1993**, *34*, 5649-5652.

11. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

12. Sodium phenylsulfinate is treated with 3N sulfuric acid and extracted with ether (×3), the combined organic extracts dried ($MgSO_4$) and evaporated *in vacuo* to give the acid, which is unstable if stored for a prolonged period of time.

13. Purchased from Macherey-Nagel, Düren.

14. It is necessary to use crystalline lactic acid (Sigma) because of the requirement for anhydrous conditions to avoid *bis*-dihydropyran hydrolysis.

15. Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T.; Inoue, S.; Sugiura, S.; Kakoi, H. *J. C. S. Chem. Comm.* **1972**, 64-65.

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