Recl. Trav. Chim. Pays-Bas 114, 184–194 (1995)
SSDI 0165-0513(94)00014-3

0165-0513/95/4/5 184–11$9.50

Dispiroketals in synthesis (Part 16)[1]: Functionalised dispiroketals as new chiral auxiliaries; the synthesis of dihydroxylated dispiroketals in optically pure form and their application as bifunctional, C_2-symmetrical, chiral auxiliaries for highly stereoselective Michael additions

Barend C. B. Bezuidenhoudt [2], Grant H. Castle, Jean E. Innes and Steven V. Ley *

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB1 2EW, U.K.
(Received November 17, 1994)

Abstract. A range of rigid, architecturally complex diols derived from dispiroketals have been synthesised. A bifunctional, C_2-symmetrical, chiral auxiliary derived from these dihydroxylated dispiroketals has been used to induce a high degree of asymmetry in Michael additions of cuprates to a variety of di-α,β-unsaturated ester systems.

Introduction

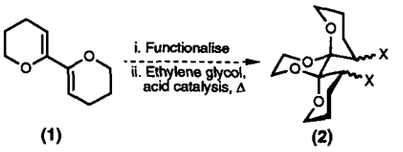
The dispiroketal (Dispoke)[3,4] protecting group has been shown to be of great utility for the protection of 1,2-diols by reaction with bis-dihydropyrans such as **1**.[4a] Examples include the preparation of a configurationally stable glyceraldehyde derivative[3], many applications in the field of carbohydrates[4], and the preparation of protected lactic acid derivatives whose enolates have been alkylated with a range of electrophiles to give the substituted adducts with moderate to excellent stereoselectivity[5]. If the bis-dihydropyran protecting agent bears substituents then these appended groups tend to adopt equatorial orientations which, in combination with the anomeric effects, dictates the configurations of the spirocentres. This approach has been used for chiral recognition of *trans*-1,2-diols in carbohydrates[6], to enantioselectively protect glycerol[7] and other *meso*-polyols[8].

It was envisaged that modification of the enol ether portions of a bis-dihydropyran prior to trapping with a diol would give rise to a variety of rigid, architecturally complex and diverse molecules (**2**) which may have applications in the field of asymmetric synthesis (Figure 1).

The preparation of enantiomerically pure materials is a crucial requirement for the modern synthetic organic chemist particularly in natural product synthesis. There has therefore been considerable interest in the exploitation of optically pure molecules which, by acting as chiral auxiliaries or modifiers, are able to influence the stereochemical outcome of chemical reactions. There is a constant need for new, cheap, low molecular weight chiral auxiliaries and chiral ligands and catalysts for asymmetric synthesis which are easily obtainable in both enantiomeric forms.

We envisaged that a wide range of chiral auxiliaries of three general classes, type **I**, type **II** and type **III**, may be synthesised from these diols (Figure 2).

Group A represents a reactive substituent upon which asymmetric reactions may be carried out. Group B can either be a bulky substituent to shield one stereoface of the reactive substituent or a group to direct the approach



Functionalisation method	X
Oxidation or Dihydroxylation	OH
Halogenation	Cl, Br, I
Aziridination	NR'R"

Figure 1.

of a reagent. The direction, or steering, of reactions by resident groups has been of considerable interest. An excellent example of such a reaction is the Simmons–Smith cyclopropanation[9]. Hydroxyl functions have been shown, in this case, to direct Zn/Cu carbenoid cyclopropanations of olefins[10] and such steering effects have also continued to be observed during more recent modifications to this system. The use of Zn/Ag rather than Zn/Cu, for example, results in cyclopropanation with greater procedural simplicity, higher yields and at lower temperatures[11]. Samarium carbenoids are effective with allylic alcohols at $-60°C$[12]. Peracid epoxidation has also been shown to be directed by resident hydroxyl groups[13].

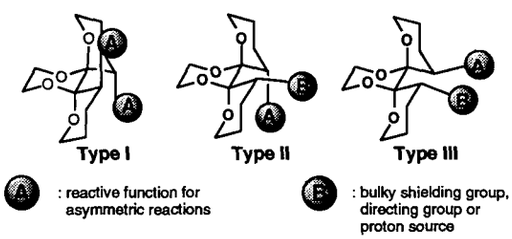
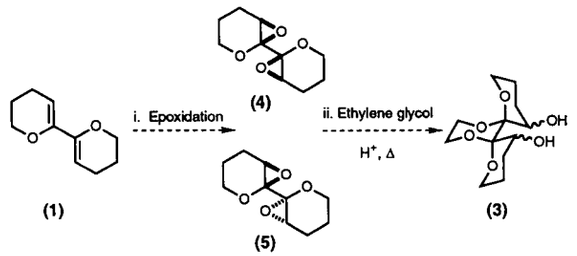


Figure 2.



Scheme 1.

Type-**II** auxiliaries were thought worthy of investigation since it was envisaged that one stereoface of the reactive portion A would be shielded by both B and the pyran ring to which B is attached. Type-**III** auxiliaries were also thought to be promising since, in molecular models of this system, A and B were found to be in extremely close proximity to one another.

The type-**I** system was, however, of particular interest since this type of system could potentially function as a C_2-symmetric, bifunctional chiral auxiliary. Bifunctional chiral auxiliaries are of interest because of their relatively low effective molecular weight which reduces the mass of the chiral auxiliary that has to be carried through a synthetic sequence[14].

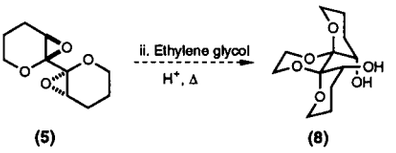
As part of our ongoing studies[1,15] to exploit dispiroketals for asymmetric synthesis we describe in this paper the oxidation (epoxidation and dihydroxylation) of bis-dihydropyrans and the application of the resulting diols as chiral auxiliaries for asymmetric Michael Additions.

Formation of dihydroxylated dispiroketals

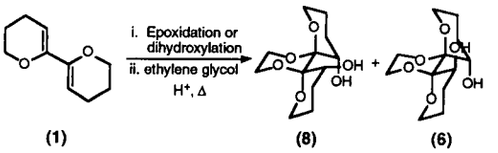
Our strategy for the synthesis of dihydroxylated dispiroketals **3** involved the epoxidation of the enol ether functions of bis-dihydropyran (5,5′,6,6′-tetrahydro-2,2′-bi-4*H*-pyran, **1**) to yield the diastereoisomeric diepoxides **4** and **5**. Acid-catalysed dispiroketalisation with a vicinal diol, such as ethylene glycol (ethane-1,2-diol), would then yield the diols **3** (Scheme 1).

Under thermodynamic conditions the dispiroketalisation reaction was expected to proceed to furnish diols in which anomeric stabilisation was maximised and steric repulsion minimised. The anomeric effect in pyran systems has been quantified as having a stabilising effect of approximately 1.4 kcal/mol[16]. A pyran ring system having an axial hydroxyl substituent has been found to be approximately 0.8 kcal/mol less stable than its equatorially substituted equivalent. It may therefore be concluded that maximisation of anomeric stabilisation would predominate over the minimisation of steric repulsion in such systems.

Epoxide **4** may give rise to two dispiroketal products, **6** and **7**, in which the maximum four anomeric stabilising effects are present, depending on which face of the diepoxide the ethylene glycol approaches (Figure 3). The hydroxyl functions present in diol **7** are both axially disposed and this diol should therefore be 1.6 kcal/mol less stable than the corresponding diol **6**, in which both hydroxyl groups are orientated equatorially. Molecular modelling[17] of these systems supports these arguments. Of these two diols, we therefore predicted the exclusive formation of diol **6** from such a dispiroketalisation reaction. Dispiroketalisation of **5** was expected to give rise to only one possible diastereomer, **8** (Scheme 2). Diepoxide **5** is a *meso* compound, and **8** would therefore be formed irrespective of which face of the diepoxide the ethylene glycol approaches. Its plane of symmetry can be seen if it is represented in an eclipsed form (Figure 4).



Scheme 2.



Scheme 3.

We therefore envisaged that epoxidation of bis-dihydropyran (**1**) followed by dispiroketalisation under thermodynamic conditions using acidic ethylene glycol would furnish a mixture of two diols **8** and **6** (Scheme 3).

The epoxidation of enol ethers has been found to be problematic, due to the lability of the resulting epoxides. *Danishefsky*[18], for example, has found, during investigations into the use of 1,2-anhydro sugars for the stereospecific construction of β-linked oligosaccharides, that direct epoxidation of glycals using standard peracid epoxidising agents resulted in further reaction of the desired 1,2-epoxy sugar with either solvent or acid (RCO_2H, derived from reduction of the peracid RCO_3H). His findings agreed with those of earlier studies of this reaction[19]. He was able to overcome this problem by using an anhydrous solution of the neutral, but highly reactive, 3,3-dimethyldioxirane which has been used as an oxidant for a wide variety of organic substrates[20]. In their synthesis of the ultimate carcinogen from aflatoxin B_1, for example, *Harris* and coworkers have reported the epoxidation of dihydrofurans and dihydropyrans using dimethyldioxirane[21]. This reagent was found to efficiently carry out the desired transformation in our analogous system.

When bis-dihydropyran (**1**) was treated with an approximately 0.05M solution of dimethyldioxirane in acetone at −78°C, and the resulting diepoxide intermediate treated with ethylene glycol under thermodynamic, catalytic acidic conditions, a 2/1 mixture of **8** and **6** was formed in 83% overall yield (Scheme 3 and Table I, Entry 1). The structures of both **8** and **6** were confirmed by X-ray crystallographic studies.

Raising the temperature of the dimethyldioxirane epoxidation to 0°C resulted in the formation of a 1/1 mixture of **6** to **8** in 82% overall yield (Scheme 3 and Table I, Entry 2).

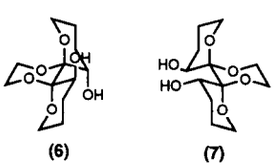


Figure 3.

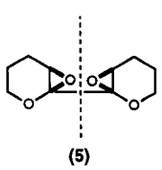


Figure 4.

Table I Yields and selectivities for formation of diols **6** *and* **8**.

Entry	Conditions	Overall yield	Ratio of **8**/**6**
	Epoxidation		
1	Dimethyldioxirane, −78°C	83%	2/1
2	Dimethyldioxirane, 0°C	82%	1/1
3	*m*CPBA, DCM, 0°C	62%	1/4
4	OsO_4, *t*-BuOH, H_2O, $K_3Fe(CN)_6$, 0°C	48%	1/3

Table II Yields for the formation of dihydroxylated butanediol dispiroketal adducts.

Temp.	Overall yield	Yield of **11**	Yield of **12**	Yield of **13**
0	86	22	16	48
−78	77	14	10	53

It was also possible to use other oxidants to prepare these diols. Bis-dihydropyran (**1**) was treated with 90% *m*CPBA (prepared from commercial 50–60% *m*CPBA [a] by the method of *Bortoloni* and co-workers[22]) at 0°C and the resulting intermediate was dispiroketalised using ethylene glycol and catalytic CSA [b] to obtain a 4/1 mixture of **6** and **8** in 62% overall yield (Scheme 3 and Table I, Entry 3).

Catalytic dihydroxylation reactions using osmium tetroxide and a cooxidant were also investigated. Bis-dihydropyran (**1**) was dihydroxylated with catalytic osmium tetroxide in the presence of potassium hexacyanoferrate(III), using the method of Sharpless. Treatment of the resulting intermediate with ethylene glycol under standard dihydroxylation conditions resulted in the formation of a 3/1 mixture of **6** and **8** in 48% overall yield (Scheme 3 and Table I, Entry 4).

We were therefore able to produce the diols **6** and **8** with a degree of selectivity.

With methodology for the preparation of either **6** or **8** in place, we turned our attention to obtaining diol **6** in optically pure form.

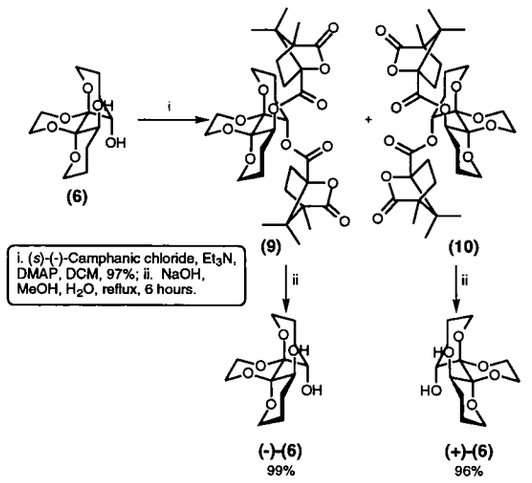
Classical resolution approach to enantiomerically pure dihydroxylated dispiroketals

Acylation of **6** with (*S*)-(−)-camphanic [c] chloride proceeded smoothly to furnish the easily separable dicamphanate esters **9** and **10** in 97% overall yield (Scheme 4). The hydrolysis of the separated esters furnished optically pure (−)-**6** and (+)-**6** in yields greater than 95%.

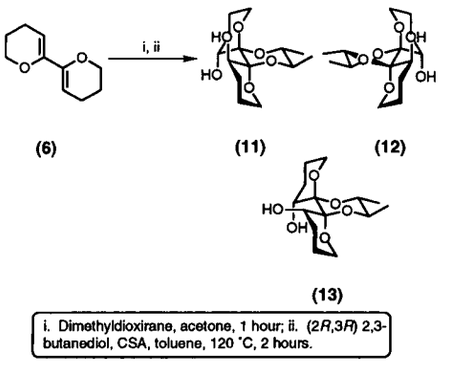
Both the acylation and hydrolysis reactions were high yielding and this approach was considered viable for gaining access to **6** in optically pure form.

The absolute stereochemistries of (+)-**6** and (−)-**6** were established by studies of the acid-catalysed, thermodynamically controlled formation of dihydroxylated dispiroketals **11**, **12** and **13** with an optically pure C_2-symmetrical diol, (2*R*,3*R*)-2,3-butanediol.

Dimethyldioxirane epoxidation of bis-dihydropyran (**1**) at both −78°C and 0°C followed by standard dispiroketalisation in the presence of two equivalents of (2*R*,3*R*)-butanediol gave the diols **11**, **12** and **13** (Scheme 5 and Table II). The structures of all these butanediol adducts were confirmed by X-ray crystallographic studies.



Scheme 4.



Scheme 5.

Transketalisation of **11** and **12** using ethylene glycol allowed the absolute stereochemistry of (+)-**6** and (−)-**6** to be determined with a high degree of certainty, since no mechanism for the epimerisation of the pyranyl hydroxyl functions could be envisaged (Scheme 6).

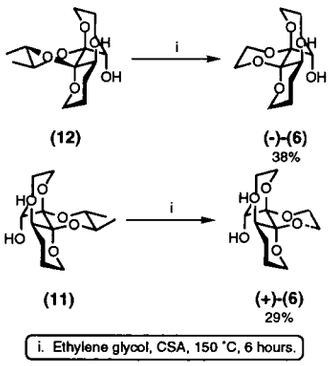
There are ongoing investigations within our group to discover other facile and cost-effective methods which allow the preparation of these diols in enantiomerically pure form on a large scale [d].

Type-I auxiliaries and their application to asymmetric Michael additions

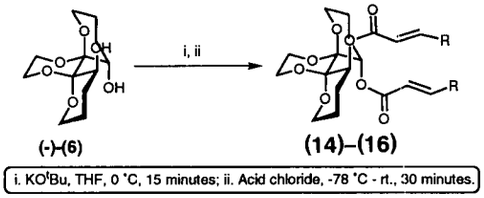
Whilst investigating the reactions of organocopper reagents RCu(I)[23] and R_2CuLi[24], *Gilman* noticed that α,β-unsaturated carbonyl compounds underwent 1,4-addition predominantly over 1,2-addition. This mode of reactivity has led to the extensive use of organocopper reagents in organic synthesis and many new classes of organocopper reagents have been developed, which differ dramatically in both reactivity and physical properties[25,26]. Stereoselective 1,4-additions to α,β-unsaturated carbonyl compounds have been commonly achieved using a variety of organocopper species and this area has recently been reviewed[27].

[a] *m*CPBA = 3-Chloroperbenzoic acid.
[b] CSA = (±)-10-camphorsulfonic acid.
[c] ω-Coamphanic acid = (1*S*)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2,2,1] heptane-1-carboxylic acid.

[d] Preliminary results indicate that the diastereomeric dicamphanate esters can be separated by fractional recrystallisation.



Scheme 6.

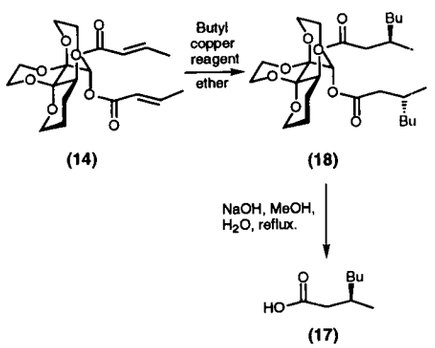


Scheme 7.

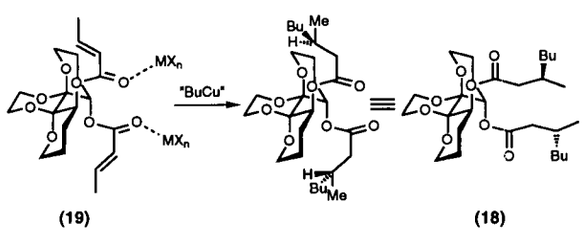
Preparation of type-I chiral auxiliaries

In order to assess the utility of **6** as a type-**I** chiral auxiliary, we required methods for its diacylation with a variety of saturated and unsaturated acylating agents.

We envisaged formation of the dianion with potassium *tert*-butoxide followed by a quench with an excess of the appropriate acid chloride. In order to ensure that base-mediated side reactions (bond migration, transesterification etc.) did not occur, no basic species, either butoxide or secondary alkoxide, could be present in the reaction mixture. Excess acid chloride, relative to the potassium *tert*-butoxide, was therefore used. In addition, to ensure that all alkoxide species would be rapidly converted into their corresponding (*E*)-but-2-enoic esters, the acid chloride was added to the dianion solution in one portion.



Scheme 8.



Scheme 9.

Table III Yields for the anionic acylation of (−)-6.

Acid chloride	R	Yield
(*E*)-but-2-enoyl chloride	Me **14**	78%
(*E*)-3-phenylprop-2-enoyl chloride	Ph **15**	94%
(*E*)-hept-2-enoyl chloride [a]	Bu **16**	74%

[a] (*E*)-hept-2-enoyl chloride was prepared from (*E*)-hept-2-enoic acid (see Experimental Section).

Table IV Addition of copper reagents to di-(E)*-butenoate* (**14**).

Entry	Butyl copper reagent	Temp. (°C)	Time (h)	Yield (%)	Config.	*ee* [a]
1	$BuCu \cdot BF_3 \cdot PBu_3$	−60	16	88	*R*	96%
2	$BuCu \cdot BF_3 \cdot PBu_3$	−45	16	63	*R*	89%
3	$Bu_2CuCNLi_2$, $ZnCl_2$	−60	16	80	*R*	63%
4	BuMgCl, CuBr·DMS, $ZnCl_2$ [b]	−60	16	40	*R*	28%
5	$Bu_2CuCNLi_2$	−60	16	82	*S*	35%

[a] The *ee* referred to in this table relates to the enantiomeric excess of the cleaved acid **17**. [b] DMS = dimethyl sulfide.

All the required unsaturated diesters (**14**, **15** and **16**) proved to be accessible by this facile method (Scheme 7 and Table III).

For our initial investigations, a variety of butyl copper reagents were chosen and their additions into the di-(*E*)-but-2-enoate derivative **14** were studied (Scheme 8). These copper species included organocopper reagents, copper-catalysed Grignard reagents, and heterocuprates (Table IV).

The *ee* of the cleaved acid **17** was efficiently estimated by analysis of the high-field ^1H and ^{13}C-NMR spectra of the di-Michael adduct **18**. The diastereotopic protons α to the ester carbonyl proved to be both highly distinctive and well resolved. The ratios of their intensities therefore allowed the effective measurement of stereofacial selectivity and hence enantiomeric excesses in these reactions [e]. The configuration of the cleaved Michael adduct was determined by comparison of the optical rotation of the cleaved acid with literature values (See Scheme 11 and Table VI).

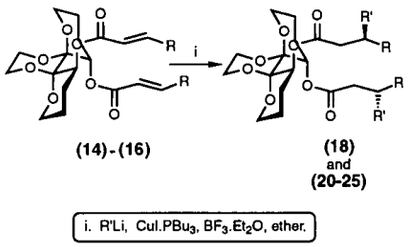
Several hypotheses were postulated on the basis of these preliminary results. Judging from the stereofacial selectivities observed for the reactions in Entries 1–4 (Table IV), the reaction was assumed to proceed via a Lewis acid complex (**19**) in which the two enoates adopt an s-(*E*) configuration. The *Si* (left-side) face of each enoate is thus shielded by the pyran ring of the dispiroketal to which it is not appended. The cuprate then approaches from the *Re* face of the (*E*)-but-2-enoate to give, in the case shown, the (*R*) product (Scheme 9).

Lewis-acid participation is supported by the result in Entry 5 involving the use of the heterocuprate reagent $Bu_2CuCNLi_2$. In this reaction, no strongly Lewis-acidic species is present, and a reversal of stereofacial selectivity was observed.

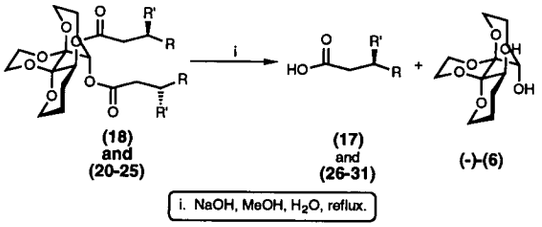
The highest selectivities were obtained using a butylcopper reagent developed by *Yamamoto*[28] in the presence of tributylphosphane (Entry 1 and Entry 2, Table IV). These preliminary results encouraged us to further investigate the conjugate addition of organocopper reagents to type I Michael acceptors **14**, **15** and **16** under these modified *Yamamoto* conditions (Scheme 10 and Table V).

As can be seen from entries 1, 4, 5 and 7 (Table V), Michael additions involving alkyl organocopper species all

[e] Although these particular diastereotopic protons were well-resolved it was impossible to fully assign the spectra of the minor diastereomer. Data is therefore given only for the major diastereomer.



Scheme 10.

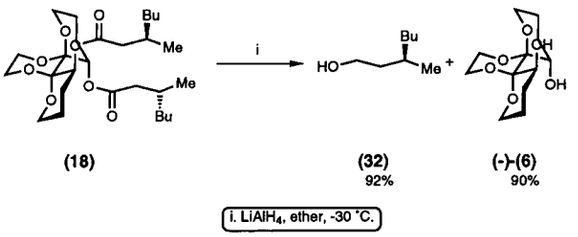


Scheme 11.

proceeded in high yield and with a high degree of stereoselectivity. The addition of the aryl organocopper species (Entry 2) to our system proceeded with reduced yield and selectivity. This organocopper species was relatively unreactive (the reaction proceeded only 68% towards completion) and required an elevated reaction temperature of −40°C, which may be responsible for the drop in stereoselectivity. The application of these modified *Yamamoto* conditions to *Fleming*'s (dimethylphenylsilyl)cuprate system[29] resulted in the formation of β-silyl esters in high yield but, again, with lowered stereoselectivity (Entries 3 and 6). The reason for this decrease in *ee* may be due to the use of a 50/50 THF/ether solvent system for these reactions or may be due to intrinsic differences between the nature of the silyl organocopper species and the alkyl organocopper species.

Cleavage of Michael adducts from the auxiliary

For the cleavage of the Michael adducts both hydrolytic (NaOH, MeOH, H_2O, reflux) (Scheme 11 and Table VI) and reductive ($LiAlH_4$, ether, −30°C) (Scheme 12) conditions were successfully applied to the Michael adducts



Scheme 12.

derived from the bifunctional auxiliary. Again, the recovered auxiliary and cleaved adduct could be obtained in pure form by extractive methods.

A single example of the reductive cleavage of the Michael adduct was carried out using lithium aluminium hydride. The adduct **18** was cleaved to give the diol (−)-**6** and 3-methylheptanol (**32**) in good yield (Scheme 12).

Concluding remarks

Additions of *Yamamoto*-type organocopper reagents to our type-**I** auxiliary system all proceeded with a high degree of selectivity. Trends observed within the series of reactions, however, remain difficult to explain. In the case of the aryl- and silylcuprates, for example, the stereofacial selectivity was found to be lower than for the alkylcopper equivalents and, although the stereochemical outcome of these reactions was consistent with our proposed bidentate chelate complex model, a firm mechanistic rationale has yet to be established to explain these results.

A considerable amount of work remains to be done in these areas, both to fully understand the factors governing the stereochemical outcome of these reactions and also to investigate their substrate generality.

Experimental section

General experimental

^{1}H-NMR spectra were recorded in $CDCl_3$, unless otherwise stated, on Bruker AM-200, Jeol GSX-270, Bruker AM-400 and Bruker AM-500 spectrometers. Residual protic solvent $CHCl_3$ (δ_H 7.26 ppm) was used as internal reference. Coupling constants were mea-

Table V Yields and selectivities for conjugate additions into type **I** *auxiliaries.*

Entry	R	R'	Temp. (°C)	Time (h)	Yield adduct	Config.	*ee* acid	Note
1	Me **14**	Bu	−60	16	88% **18**	*R*	94% **17**	
2	Me **14**	Ph	−40	16	68% **20**	*R*	81% **26**	[b]
3	Me **14**	$SiMe_2Ph$	−70	12	92% **21**	*R*	76% **27**	[a]
4	Ph **15**	Me	−60	16	83% **22**	*S*	92% **28**	
5	Ph **15**	Bu	−60	16	87% **23**	*R*	92% **29**	
6	Ph **15**	$SiMe_2Ph$	−70	12	91% **24**	*R*	71% **30**	[a]
7	Bu **16**	Me	−60	16	79% **25**	*S*	93% **31**	

[a] Yield based on recovered starting material. [b] Reaction carried out in 50% diethyl ether, 50% THF.

Table VI Hydrolytic cleavage of Michael adducts from auxiliary (−)-**6**.

Entry	R	R'	Yield	Config.	*ee*	$[\alpha]_D$	$[\alpha]_D^{lit}$	Yield [a]
1	Me	Bu **18**	95% **17**	*R*	94%	+4.1	+3.84[31]	92%
2	Me	Ph **20**	87% **26**	*R*	81%	+42.6	+51.1[31]	95%
3	Me	$SiMe_2Ph$ **21**	89% **27**	*R*	76%	−10.7	−12.0[32]	97%
4	Ph	Me **22**	97% **28**	*S*	92%	−48.5	−51.1[31]	93%
5	Ph	Bu **23**	90% **29**	*R*	92%	−26.2	−27.8[31]	91%
6	Ph	$SiMe_2Ph$ **24**	89% **30**	*R*	71%	+4.3	+6.0[32]	94%
7	Bu	Me **25**	93% **31**	*S*	93%	−3.6	−3.84[31]	92%

[a] Yield of recovered (−)-**6**.

sured in Hz. ^{13}C-NMR spectra were recorded in $CDCl_3$ unless otherwise stated, at 100 MHz, 62.5 MHz and at 50 MHz on Bruker AM-400, Bruker AM-250 and Bruker AM-200 spectrometers, respectively, using the resonance of $CDCl_3$ (δ_C 77.0 ppm) as internal reference. Infrared spectra were recorded on Perkin-Elmer 983G or FTIR 1620 spectrometers. Mass spectra were recorded using VG-707B, VG 12-253 and VG ZAB-E instruments at the Department of Chemistry, Imperial College, London, at the SERC Mass Spectrometry service in Swansea and also on a Kratos MS890MS spectrometer at the Department of Chemistry, University of Cambridge. Microanalyses were determined in the microanalytical laboratories at Imperial College, London, at the University of Cambridge and at MEDAC Ltd, Department of Chemistry, Brunel University. Melting points were determined on a Reichert hot stage apparatus and are uncorrected. Optical rotations were measured with an Optical Activity AA-1000 polarimeter. Flash chromatography was performed on Merck 9385 Kieselgel 60 silica (230–400 mesh). Analytical thin layer chromatography was performed on silica using pre-coated glass-backed plates (Merck Kieselgel F_{254}) and visualised by ultraviolet radiation, acidic ammonium molybdate or potassium permanganate. All reactions were carried out under argon unless otherwise stated. Diethyl ether and tetrahydrofuran solvents were distilled from sodium benzophenone ketyl; benzene, dichloromethane, toluene and acetonitrile from calcium hydride and methanol from magnesium methoxide. Petrol refers to petroleum ether b.p. 40–60°C, and ether to diethyl ether which were both distilled prior to use. Other solvents and reagents were purified by standard procedures as necessary. Aqueous solutions are saturated unless specified otherwise.

(5S,6R*,7R*,12R*) 1,8,13,16-Tetraoxadispiro[5.0.5.4]hexadecane-5,12-diol* (**8**) *and (5S*,6R*,7R*,12S*)-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane-5,12-diol* (**6**)

Method 1. Bis-dihydropyran (**1**) (350 mg, 2.1 mmol) in dichloromethane (2 ml) was added dropwise over 2 min to a solution of dimethyldioxirane[20] (approximately 0.05 M in acetone, 120 ml, 6 mmol) at −78°C. The reaction was stirred at this temperature for 1 h during which time the yellow colour of the solution diminished in intensity. Having allowed the solution to come to room temperature, the solvent was removed *in vacuo* to yield a white solid residue. This residue was suspended in toluene (10 ml) and ethylene glycol (2 ml, excess) then (*d,l*)-camphorsulfonic acid (200 mg, cat.) were added. The solution was then heated at 120°C for 1 h with vigorous strirring and then quenched by pouring the reaction mixture into saturated aqueous sodium bicarbonate solution (10 ml). The aqueous phase was extracted with dichloromethane (3×200 ml), the combined organic phases were dried ($MgSO_4$), and the solvent removed *in vacuo* to yield a pale yellow crystalline solid. This crude product was purified by flash column chromatography on silica gel with 10% methanol in diethyl ether as eluent to yield, in order of elution, the unsymmetrical diol **8** (284 mg, 1.09 mmol, 52%) as a colourless blocks; m.p. 210–211°C (from toluene); IR ν_{max} (thin film)/cm^{-1}: 3460 (OH), 3400 (OH), 2960, 2940, 1435, 1325, 1280, 1220, 1090, 1060, 1021, 980, 950; δ_H (270 MHz; $CDCl_3$) 1.5–2.2 (8H, m, 2×H-3, 2×H-4, 2×H-10, and 2 H-11), 3.4–4.1 (9H, m, 2×H-2, 2×H-9, H-12, 2×H-14, and 2 H-15), 4.39 (1H, dd, *J* 10.3, 5.2, H_{ax}-5); δ_C (125 MHz; DMSO-d_6): 18.2, 24.3, 26.0, 26.3 (C-3, C-4, C-10, and C-11), 57.2 (C-2), 57.3 (C-9), 59.2 (C-5), 60.2 (C-15), 64.8 (C-14), 68.4 (C-12), 94.5 (C-7), 96.8 (C-6); *m / z* (EI): 260 $(M)^+$, 242 $(M-H_2O)^+$, 222, 189, 180, 144, 116, 99, 71, 57; Found: $(M)^+$ 260.1270; $C_{12}H_{20}O_6$ requires: *M*, 260.1260. Found: C, 55.21%; H, 7.54%. $C_{12}H_{20}O_6$ requires: C, 55.37%; H, 7.74%; and the symmetrical diol **6** (169 mg, 0.65 mmol, 31%) as a colourless plates; m.p. 188°C (from toluene); ν_{max} (film)/cm^{-1} 3519 (OH), 3498 (OH), 2936, 2883, 1278, 1125, 1081, 1051, 1000, 975, 940; δ_H (500 MHz; $CDCl_3$) 1.6–1.8 (6H, m, H_{eq}-3, 2×H-4, H_{eq}-10, and 2×H-11), 1.83–1.92 (2H, m, H_{ax}-3 and H_{ax}-10), 3.65 (2H, m, H_{eq}-14 and H_{eq}-15), 3.3–3.8 (4H, m, 2×H-2 and 2×H-9), 3.90 (2H, dd, *J* 10.6, 5.1, H_{ax}-5 and H_{ax}-12), 4.13 (2H, m, H_{ax}-14 and H_{ax}-15); δ_C (67.5 MHz; $CDCl_3$) 24.5 and 25.9 (C-3 and C-10, C-4 and C-11), 58.6 and 60.3 (C-2 and C-9, C-5 and C-12), 68.0 (C-14 and C-15), 96.9 (C-6 and C-7); *m / z* (EI) 260 $(M)^+$, 242 $(M-H_2O)^+$, 189, 180, 171, 144, 116, 99, 71, 57, 44; Found: $(M)^+$ 260.1259. $C_{12}H_{20}O_6$ requires: *M*, 260.1260. Found: C, 55.13%; H, 7.64%. $C_{12}H_{20}O_6$ requires: C, 55.37%; H, 7.74%.

Method 2. Bis-dihydropyran (**1**) (350 mg, 2.1 mmol) in dichloromethane (2 ml) was added dropwise over 2 min to a solution of dimethyldioxirane (approximately 0.05 M in acetone, 120 ml, 6 mmol) at −0°C. The reaction was stirred at this temperature for 1 h during which time the yellow colour of the solution diminished in intensity. Having allowed the solution to come to room temperature, the solvent was removed *in vacuo* to yield a white solid residue. This residue was suspended in toluene (10 ml) and ethylene glycol (2 ml, excess) then (*d,l*)-camphorsulfonic acid (200 mg, cat.) were added. The solution was then heated at 120°C for 1 h with vigorous stirring and then quenched by pouring the reaction mixture into saturated aqueous sodium bicarbonate solution (10 ml). The aqueous phase was extracted with dichloromethane (3×200 ml), the combined organic phases were dried ($MgSO_4$), and the solvent was removed *in vacuo* to yield a pale yellow crystalline solid. This crude product was purified by flash column chromatography on silica gel with 10% methanol in diethyl ether as eluent to yield, in order of elution, the desired unsymmetrical diol **8** (213 mg, 0.82 mmol, 39%) as colourless blocks and the desired symmetrical diol **6** (235 mg, 0.90 mmol, 43%) as a colourless plates, both identical in all respects to that reported above.

Method 3. A solution of *m*CPBA [~90% prepared by washing commercial 50–60% *m*CPBA (250 g) in ether (1 l) with phosphate buffer solution by the method of *Bortoloni* et al.[22], (9.70 g, 56.2 mmol, 2.1 eq.)] in dry ether (30 ml) was added over 30 min to a solution of bis-dihydropyran (**1**) (4.45 g, 26.8 mmol) in dry dichloromethane (100 ml) at 0°C under argon. The resulting pale yellow solution was stirred at 0°C for 2 h. After allowing the reaction to come to room temperature, the solvent was removed *in vacuo*, the resulting yellow solid was suspended in toluene (30 ml) and ethylene glycol (30 ml) then (*d,l*)-camphorsulfonic acid (2 g, excess) were added. The solution was heated at 120°C for 2 h and quenched by pouring into saturated aqueous sodium bicarbonate solution (30 ml). The aqueous phase was extracted with dichloromethane (4×400 ml), the combined organic phases dried ($MgSO_4$), and the solvent removed *in vacuo* to yield a pale yellow oil. This crude product was purified by flash column chromatography on silica gel with 10% methanol in diethyl ether as eluent to yield, in order of elution, the unsymmetrical diol **8** (0.98 g, 3.77 mmol, 14%) as colourless blocks and the symmetrical diol **6** (3.3 g, 12.7 mmol, 48%) as a colourless plates, both identical in all respects to that isolated above.

Method 4. To a solution of bis-dihydropyran (**1**) (200 mg, 1.2 mmol) in *tert*-butanol (10 ml) and water (10 ml) was added potassium hexacyannoferrate(III) (2.8 g, 7.2 mmol, 6 eq.), potassium carbonate (1.0 g, 7.2 mmol, 6 eq.) and a solution of osmium tetroxide (one crystal, cat.) in *tert*-butanol (200 μl). The resulting orange suspension was stirred at room temperature for 7 h, during which time it turned pale green/brown in colour. The reaction was quenched by the addition of a saturated aqueous solution of sodium sulfite (5 ml) and stirred for 10 min. The resulting pale blue suspension was lyophilised to give an off white solid which was washed with 20% methanol in dichloromethane (400 ml) and the filtrate was concentrated *in vacuo* to yield a pale yellow oil. This oil was dissolved in toluene (10 ml) and treated sequentially with ethylene glycol (2 ml, excess) and (*d,l*)-camphorsulphonic acid (100 mg, cat.) before heating reflux for 2 h. The resulting brown solution was cooled to room temperature and poured into saturated aqueous sodium bicarbonate solution (5 ml). The organic and aqueous layers were separated and the aqueous phase extracted with dichloromethane (4×100 ml). The combined organic layers were dried ($MgSO_4$), and the solvent removed *in vacuo* to yield a brown solid. The crude product was purified by flash chromatography on silica gel with 10% methanol in diethyl ether as eluent to yield, in order of elution, the unsymmetrical diol **8** (34 mg, 0.132 mmol, 11%) as colourless blocks and the symmetrical diol **6** (115 mg, 0.444 mmol, 37%) as colourless plates, both identical in all respects to that isolated above.

(5S,6R,7R,12S,1'S,4'R,1''S,4''R)-5,12-bis[4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptyl-1-carbonyloxy]-1,8,13,16-tetraoxadispiro-5.0.5.4]hexadecane (**9**) *and (5R,6S,7S,12R,1'S,4'R,1''S,4''R)-5,12-bis-[4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptyl-1-carbonyloxy]-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane* (**10**)

Triethylamine (21.4 ml, 15.6 g, 153 mmol, 20 eq.), (*S*)-(−)-camphanic chloride (8.32 g, 38.4 mmol, 5 eq.) and 4-dimethylaminopyridine (20 mg, cat.) were added to a solution of the diol **6** (2 g, 7.68 mmol) in dichloromethane (10 ml) at room temperature. The resulting pale yellow precipitous solution was stirred at room temperature for 13 h. The reaction was then quenched by the addition of saturated sodium bicarbonate solution (50 ml) and the resulting solution was stirred at room temperature for 30 min. Dichloromethane (50 ml) was then added and the layers separated. The aqueous layer was extracted with dichloromethane (3×100 ml), the combined organic phases dried ($MgSO_4$), and the solvent removed *in vacuo* to yield a pale

yellow oil. This crude product was purified by flash column chromatography on silica gel with 5% iso-propanol in hexane as eluent to yield the desired (−)-dicamphanate **9** (1.96 g, 3.16 mmol, 41%) as colourless needles; m.p. 201–202°C (from toluene); $[\alpha]_D^{24}$ −116.5 (*c* 1.20, chloroform); ν_{max} (thin film)/cm^{-1} 2966, 2878, 1789 (C=O lactone), 1728 (C = O ester), 1271, 1108, 1105, 1063, 927, 733; δ_H (400 MHz; $CDCl_3$) 0.97 (6H, s, Me-4′ and Me-4″), 1.07 and 1.09 (6H, s, Me-7′ and Me-7″ and 6H, s, Me-7′ and Me-7″), 1.5–1.8 (8H, m, 2×H-3, 2×H-4, 2×H-10, 2×H-11), 1.8–2.0 (6H, m, 2×H-5′, 2×H-5″, H-6′ and H-6″), 2.34 (2H, m, H-6′ and H-6″), 3.4–3.5 (4H, m, 2×H-2 and 2×H-9), 3.52 (2H, m, H_{eq}-14 and H_{eq}-15), 4.01 (2H, m, H_{ax}-14 and H_{ax}-15), 5.29 (2H, dd, J 11.5, 5.2, H_{ax}-5 and H_{ax}-12); δ_C (100 MHz; $CDCl_3$) 7.0 (Me-4′ and Me-4″), 16.4 (Me-7′ and Me-7″), 16.6 (Me-7′ and Me-7″), 24.0, 25.7, 28.8, 31.0 (C-3, C-4, C-10, C-11, C-5′, C-5″, C-6′ and C-6″), 53.8, 54.8, 58.4, 59.2 (C-2, C-9, C-14, C-15, C-4′, C-4″, C-7′ and C-7″), 67.9 (C-5 and C-12), 91.0 (C-1′ and C-1″), 95.7 (C-6 and C-7), 166.5 (C-3′ and C-3″), 178.5 (O-*C*O-C-1′ and O-*C*O-C-1″); *m/z* (EI) 620 $(M)^+$, 549, 422, 334, 306, 225, 181, 171, 153, 137, 126, 109, 99, 83, 71, 55; found: $(M)^+$ 620.2835; $C_{32}H_{44}O_{12}$ requires: *M*, 620.2833.; found: C, 62.10%; H, 7.21%. $C_{32}H_{44}O_{12}$ requires: C, 61.92%, H, 7.15%, and the (+)-dicamphanate **10** (2.01 g, 3.24 mmol, 42%) as colourless blocks; m.p. > 240 °C (from toluene); $[\alpha]_D^{23}$ +90.5 (*c* 1.20, chloroform); ν_{max} (thin film)/cm^{-1} 2967, 2876, 1789 (C=O lactone), 1749 (C=O ester), 1317, 1271, 1169, 1110, 1091, 1065, 935; δ_H (400 MHz; $CDCl_3$) 0.94 (6H, s, Me-4′ and Me-4″), 1.02 and 1.09 (6H, s, Me-7′ and Me-7″ and 6H, s, Me-7′ and Me-7″), 1.5–2.0 (14H, m, 2×H-3, 2×H-4, 2×H-10, 2×H-11, 2×H-5′, 2×H-5″, H-6′ and H-6″), 2.49 (2H, m, H-6′ and H-6″), 3.4–3.6 (6H, m, 2×H-2, 2×H-9, H_{eq}-14 and H_{eq}-15), 4.00 (2H, m, H_{ax}-14 and H_{ax}-15), 5.46 (2H, dd, J 11.0, 5.4, H_{ax}-5 and H_{ax}-12); δ_C (100 MHz; $CDCl_3$) 9.8 (Me-4′ and Me-4″), 16.7 (Me-7′ and Me-7″), 17.0 (Me-7′ and Me-7″), 23.8, 25.8, 29.0, 30.4 (C-3, C-4, C-10, C-11, C-5′, C-5″, C-6′ and C-6″), 53.8, 54.8, 58.5, 59.3 (C-2, C-9, C-14, C-15, C-4′, C-4″, C-7′ and C-7″), 67.5 (C-5 and C-12), 91.5 (C-1′ and C-1″), 95.7 (C-6 and C-7), 165.7 (C-3′ and C-3″), 178.5 (O-*C*O-C-1′ and O-*C*O-C-1″); *m/z* (EI) 620 $(M)^+$, 549, 422, 334, 306, 225, 171, 153, 126, 99, 83, 71, 55; found: $(M)^+$ 620.2837; $C_{32}H_{44}O_{12}$ requires: *M*, 620.2833.; found: C, 62.10%; H, 7.18%. $C_{32}H_{44}O_{12}$ requires: C, 61.92%, H, 7.15%; and mixed fractions (410 mg, 0.662 mmol, 8.6%).

*Preparation of (−)-***6**

To a solution of the dicamphanate (**9**) (2.0 g, 3.23 mmol) in methanol (6.5 ml) was added 3N sodium hydroxide solution (3.2 ml). The resulting colourless solution was heated under reflux for 12 h and then allowed to come to room temperature. After removal of the methanol *in vacuo* and dilution of the aqueous solution with brine (15 ml), the aqueous layer was extracted with dichloromethane (3×10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude diol. This crude product was purified by flash column chromatography to yield the diol (−)-**6** (824 mg, 3.17 mmol, 96%) as colourless plates; $[\alpha]_D^{24}$ −165 (*c* 0.85, chloroform) which was spectroscopically identical to that isolated previously.

*Preparation of (+)-***6**

To a solution of the dicamphanate **10** (2.0 g, 3.23 mmol) in methanol (6.5 ml) was added 3N sodium hydroxide solution (3.2 ml). The resulting colourless solution was heated under reflux for 12 hours and then allowed to come to room temperature. After removal of the methanol *in vacuo* and dilution of the aqueous solution with brine (15 ml), the aqueous layer was extracted with dichloromethane (3×10 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude diol. This crude product was purified by flash column chromatography to yield the diol (+)-**6** (781 mg, 3.00 mmol, 93%) as colourless prisms $[\alpha]_D^{27}$ +166 (*c* 1.35, chloroform) which was spectroscopically identical to that isolated previously.

(5S,6R,7R,12S,14R,15R)-14,15-Dimethyl-1,8,13,16-tetraoxadispiro [5.0.5.4]hexadecane-5,12-diol (**12**), *(5R,6S,7S,12R,14R,15R)-14,15-dimethyl-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane-5,12-diol* (**11**) *and (5R,6S,7S,12S,14R,15R)-14,15-dimethyl-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane-5,12-diol* (**13**)

To a solution of dimethyldioxirane (*ca.* 0.05 M in acetone, 240 ml, 12 mmol) at 0°C was added bis-dihydropyran (**1**) (700 mg, 4.21 mmol) in ether (1 ml). The resulting pale yellow solution was stirred at this temperature for 2 h. The solvent was then removed *in vacuo* to give a white solid. This solid was suspended in toluene (10 ml), treated with (*2R,3R*)-(−)-butane-2,3-diol (770 μl, 759 mg, 8.42 mmol) and CSA (250 mg) before heating under reflux under argon for 2 h. The resulting brown solution was cooled to room temperature and poured into saturated sodium bicarbonate solution (20 ml). The organic and aqueous layers were separated and the aqueous was extracted with dichloromethane (4×100 ml). The combined organic layers were dried ($MgSO_4$), and the solvent removed *in vacuo* to yield a brown oil. The crude product was purified by flash column chromatography on silica gel with ether as eluent to yield, in order of elution, the diol **12** (193 mg, 0.674 mmol, 16%) as colourless blocks; m.p. 208°C (from ether/petrol); $[\alpha]_D^{26}$ −73 (*c* 0.77, chloroform); ν_{max} (film)/cm^{-1} 3508 (OH), 2949, 1147, 1091, 1072, 1051, 1022, 998, 925, 632; δ_H (400 MHz; $CDCl_3$) 1.19 (6H, d, *J* 5.7, Me-14 and Me-15), 1.6–1.9 (8H, m, 2×H-3, 2×H-4, 2×H-10 and 2×H-11), 3.63 (2H, dd, *J* 11.2, 4.7, H_{ax}-5, H_{ax}-12), 3.8–3.9 (4H, m, 2×H-2, 2×H-9), 4.0–4.1 (4H, m, H_{ax}-14, H_{ax}-15, 2×O*H*); δ_C (100 MHz; $CDCl_3$) 18.7 (Me-14 and Me-15), 24.6 (C-3 and C-10), 25.9 (C-4 and C-11), 60.0 (C-2 and C-9), 68.6 (C14 and C15), 73.3 (C-5 and C-12), 98.5 (C-6 and C-7); *m/z* (EI) 288 $(M)^+$, 270 $(M-H_2O)^+$, 200, 188, 145, 127, 117, 99, 71, 56, 44; found: $(M)^+$ 288.1581; $C_{14}H_{24}O_6$ requires: *M*, 288.1573. Found: C, 57.99%; H, 8.43%; $C_{14}H_{24}O_6$ requires: C, 58.32%, H, 8.39%; the diol **11** (266 mg, 0.926 mmol, 22%) as colourless blocks; m.p. 178–179°C (from ether); $[\alpha]_D^{26}$ +130 (*c* 0.92, chloroform); ν_{max} (film)/cm^{-1} 3506 (OH), 2975, 2938, 2882, 1088, 1070, 1048, 1001, 568; δ_H (400 MHz; $CDCl_3$) 1.17 (6H, d, *J* 5.3, Me-14 and Me-15), 1.6–1.9 (8H, m, 2×H-3, 2×H-4, 2×H-10, 2×H-11), 3.6–3.7 (4H, m, 2×H-2, 2×H-9), 3.77 (2H, m, H_{ax}-14 and H_{ax}-15), 3.88 (2H, dd, *J* 5.4, 9.9, H_{ax}-5 and H_{ax}-12), 4.13 (2H, s, O*H*); δ_C (100 MHz; $CDCl_3$) 16.8 (Me-14 and Me-15), 24.6 (C-3 and C-10), 26.0 (C-4 and C-11), 60.8 (C-2 and C-9), 68.0 (C14 and C15), 69.0 (C-5 and C-12), 97.3 (C-6 and C-7); *m/z* (EI) 288 $(M)^+$, 270 $(M-H_2O)^+$, 200, 188, 145, 127, 117, 99, 71, 56, 44; found: $(M)^+$ 288.1571; $C_{14}H_{24}O_6$ requires: *M*, 288.1573; found: C, 58.31%; H, 8.51%. $C_{14}H_{24}0_6$ requires: C, 58.32%, H, 8.39% and the diol **13** (582 mg, 2.02 mmol, 48%) as colourless blocks; m.p. 209–210°C (from ether); $[\alpha]_D^{26}$ +111 (*c* 1.37, chloroform); ν_{max} (film)/cm^{-1} 3464 (OH), 3349 (OH), 2962, 2929, 2893, 1083, 1068, 1014, 668; δ_H (400 MHz; $CDCl_3$) 1.00 (3H, d, *J* 5.9, Me-15), 1.15 (3H, d, *J* 5.9, Me-14), 1.5–2.2 (8H, m, 2×H-3, 2×H-4, 2×H-10, 2×H-11), 3.7–3.7 (6H, m, 2×H-2, 2×H-9, H-14, H-15), 3.83 (1H, bt, *J* 2.3, H_{eq}-12), 4.07 (1H, s, O*H*), 4.32 (1H, dd, *J* 10.4, 5.6, H_{ax}-5); δ_C (100 MHz; $CDCl_3$) 16.6 (Me-14 and Me-15), 18.8 (C-10), 24.9 (C-11), 26.0, 26.1 (C-3 and C-4), 60.0, 60.7 (C-2 and C-9), 66.9 (C-5), 68.1 (C-15), 68.5 (C-12), 69.5 (C-14), 95.3 (C-7), 97.8 (C-6); *m/z* (EI) 288 $(M)^+$, 270 $(M-H_2O)^+$, 200, 188, 145, 127, 117, 99, 71, 56, 44; Found: $(M)^+$ 288.1567. $C_{14}H_{24}O_6$ requires: *M*, 288.1573; Found: C, 58.13%; H, 8.49%. $C_{14}H_{24}O_6$ requires: C, 58.32%; H, 8.39%.

*Preparation of (−)-***6**

The diol **12** (100 mg, 0.347 mmol) was added to ethylene glycol (2 ml, excess) followed by CSA (500 mg) and the solution heated at 150°C for 5 h. The resulting brown oil was poured into saturated sodium bicarbonate solution (10 ml) and stirred vigourously for 5 min. Dichloromethane (50 ml) was then added, the layers separated and the aqueous phase extracted with dichloromethane (3×50 ml). The combined organic layers were dried ($MgSO_4$), and the solvent removed *in vacuo* to yield a brown oil. This crude product was purified by flash column chromatography on silica gel with ether as eluent to yield the diol (−)-**6** (34 mg, 0.132 mmol, 38%) as colourless plates; $[\alpha]_D^{25}$ −168 (*c* 1.46, chloroform) identical in all respects to that isolated previously.

*Preparation of (+)-***6**

The diol **11** (100 mg, 0.347 mmol) was added to ethylene glycol (2 ml, excess) followed by CSA (500 mg) and the solution heated at 150°C for 5 h. The resulting brown oil was poured into saturated sodium bicarbonate solution (10 ml) and stirred vigourously for 5 min. Dichloromethane (50 ml) was then added, the layers separated and the aqueous phase extracted with dichloromethane (3×50 ml). The combined organic layers were dried ($MgSO_4$), and the solvent removed *in vacuo* to yield a brown oil. This crude product was purified by flash column chromatography on silica gel with ether as eluent to yield the diol (+)-**6** (26 mg, 0.101 mmol, 29%) as colourless plates; $[\alpha]_D^{25}$ +163 (*c* 0.81, chloroform) identical in all respects to that isolated previously.

General procedure for the diacylation of the diols with Michael acceptors

Potassium *tert*-butoxide (2.25 g, 20.0 mmol, 4 eq.) was added portionwise over 2 min to a solution of the diol (−)-**6** (1.31 g, 5.0 mmol) in

THF (20 ml) at 0°C under argon. The resulting orange suspension was stirred for 10 min and cooled to −78°C before treatment with the appropriate acid chloride (6 eq.) dropwise over 2 min. The reaction was stirred at −78°C for 2 h, allowed to come to room temperature, and stirred for a further 2 h before quenching by the addition of water (10 ml). The layers were separated and the aqueous phase extracted with dichloromethane (3×50 ml). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed *in vacuo* to yield a golden brown crystalline solid. The crude product was purified by flash column chromatography on silica gel with 50% ether/petrol as eluent, to yield the desired diester.

(*5S,6R,7R,12S,2'E,2''E*)-*5,12-bis(but-2-enoyloxy)-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane* (**14**). The general diacylation procedure outlined above was followed using (*E*)-but-2-enoyl chloride (2.89 ml, 3.15 g, 30.1 mmol, 6 eq.) to yield **14** (1.46 g, 3.9 mmol, 78%) as colourless plates; m.p. 202°C (from iso-propanol/hexane); $[\alpha]_D^{27}$ −197 (*c* 0.23, chloroform); ν_{max} (film)/cm^{-1} 3015, 2991, 1714 (C=O), 1659 (C=C), 1319, 1229, 1194, 1181, 1162, 1095, 1064, 1044, 928, 753; δ_H (200 MHz; $CDCl_3$) 1.4–2.1 (8H, m, 2×H-3, 2×H-4, 2×H-10 and 2×H-11), 1.87 (6H, dd, *J* 6.8, 1.8, 3×H-4' and 3×H-4''), 3.3–3.6 (4H, m, 2×H-2 and 2×H-9), 3.60 (2H, m, H_{eq}-14 and H_{eq}-15), 4.10 (2H, m, H_{ax}-14 and H_{ax}-15), 5.55 (2H, dd, *J* 11.1, 5.1, H-5 and H-12), 5.94 (2H, dq, *J* 15.3, 1.6, H-2' and H-2''), 6.95 (2H, dq, *J* 15.4, 6.9, H-3' and H-3''); δ_C (50 MHz; $CDCl_3$) 17.8 (C-4' and C-4''), 24.2 (C-3 and C-10), 25.3 (C-4 and C-11), 58.5 (C-2 and C-9), 59.7 (C-14 and C-15), 66.7 (C-5 and C-12), 96.1 (C-6 and C-7), 123.4 (C-2' and C-2''), 143.8 (C-3' and C-3''), 165.8 (C-1' and C-1''); *m/z* (EI) 396 $(M)^+$, 325, 311, 256, 212, 142, 113, 99, 69; found: $(M)^+$ 396.1780; $C_{20}H_{28}O_8$ requires *M*, 396.1784; found: C, 60.41%; H, 7.12%. $C_{20}H_{28}O_8$ requires C, 60.59%; H, 7.12%.

(E)-*hept-2-enoyl chloride*. (*E*)-Hept-2-enoic acid (12.8 g, 100 mmol) was dissolved in dichloromethane (50 ml), then cooled to −20°C before treatment under argon with DMF (500 μl, cat.), then oxalyl chloride (16.7 ml, 25.4 g, 200 mmol, 2 eq.), dropwise, over 20 min. The reaction was allowed to come to room temperature and stirred for 2 h. The oxalyl chloride and dichloromethane were removed by distillation at atmospheric pressure, before isolation of the desired product by fractional distillation under reduced pressure. The desired acid chloride **33** was obtained as a colourless oil; b.p. 73°C at 17 mmHg (5.30 g, 36.1 mmol, 36%) which was identical in all respects to that described in the literature[30].

(*5S,6R,7R,12S,2'E,2''E*)-*5,12-bis(Hept-2-enoyloxy)-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane* (**16**). The general diacylation procedure outlined above was applied to the diol (−)-**6** (1.10 g, 4.23 mmol) using (*E*) hept-2-enoyl chloride (3.72 g, 25.4 mmol, 6 eq.) to yield the diester **16** (1.38 g, 2.88 mmol, 74%) as colourless needles; m.p. 52°C (from petrol); $[\alpha]_D^{26}$ −159 (*c* 0.62, chloroform); ν_{max} (film)/cm^{-1} 2956, 2930, 2873, 1720 (C=O), 1654, 1316, 1276, 1212, 1080, 1065, 1046, 972, 925, 668; δ_H (200 MHz; $CDCl_3$) 0.80 (6H, t, *J* 7.1, 3×H-7' and 3×H-7''), 1.0–1.9 (16H, m, 2×H-3, 2×H-4, 2×H-10, 2×H-11, 2×H-5', 2×H-6', 2×H-5'', 2×H-6''), 2.09 (4H, m, 2×H-4', 2×H-4''), 3.2–3.6 (4H, m, 2×H-2, 2×H-9), 3.51 (2H, m, H_{eq}-14 and H_{eq}-15), 4.01 (2H, m, H_{ax}-14 and H_{ax}-15), 5.46 (2H, dd, *J* 11.0, 4.8, H-5 and H-12), 5.81 (2H, d, *J* 15.6, H-2' and H-2''), 6.88 (2H, dt, *J* 15.4, 6.9, H-3' and H-3''); δ_C (50 MHz; $CDCl_3$) 13.6 (C-7' and C-7''), 21.9, 24.0 (C-5', C-6', C-5'', C-6''), 25.0 (C-3 and C-10), 29.9 (C-4 and C-11), 31.5 (C-4' and C-4''), 58.3 (C-2 and C-9), 59.5 (C-14 and C-15), 66.5 (C-5 and C-12), 96.0 (C-6 and C-7), 121.6 (C-2' and C-2''), 148.7 (C-3' and C-3''), 165.8 (C-1' and C-1''); *m/z* (EI) 480 $(M)^+$, 352, 299, 265, 197, 155, 111, 99, 71, 55; found: $(M)^+$ 480.2688; $C_{26}H_{40}O_8$ requires *M*, 480.2723; found: C, 64.97%; H, 8.47%; $C_{26}H_{40}O_8$ requires C, 64.98%; H, 8.39%.

(*5S,6R,7R,12S,2'E,2''E*)-*5,12-bis(3-Phenylprop-2-enoyloxy)-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane* (**15**). The general diacylation procedure outlined above was applied to the diol (−)-**6** (1.10 g, 4.23 mmol) using (*E*)-3-phenylprop-2-enoyl chloride (3.72 g, 25.4 mmol, 6 eq.) to yield the diester **15** (2.06 g, 3.98 mmol, 94%) as colourless plates; m.p. 189°C (from iso-propanol/hexane); $[\alpha]_D^{27}$ −67 (*c* 0.26, chloroform); ν_{max} (film)/cm^{-1} 3019, 2976, 2952, 1701 (C=O), 1635, 1448, 1360, 1310, 1281, 1214, 1075, 1025, 971, 756; δ_H (200 MHz; $CDCl_3$) 1.6–2.1 (8H, m, 2×H-3, 2×H-4, 2×H-10, 2×H-11), 3.3–3.7 (4H, m, 2×H-2, 2×H-9), 3.65 (2H, m, H_{eq}-14 and H_{eq}-15), 4.15 (2H, m, H_{ax}-14 and H_{ax}-15), 5.70 (2H, dd, *J* 10.8, 5.1, H-5 and H-12), 6.59 (2H, d, *J* 15.9, H-2' and H-2''), 7.38 (4H, m, 4×H_{meta}-Ar), 7.54 (6H, m, 4×H_{ortho}-Ar and 2×H_{para}-Ar), 7.72 (2H, d, *J* 16.0, H-3' and H-3''); δ_C (50 MHz; $CDCl_3$) 24.2 (C-3 and C-10), 25.2 (C-4 and C-11), 58.6 (C-2 and C-9), 59.8 (C-14 and C-15), 67.2 (C-5 and C-12), 96.2 (C-6 and C-7), 118.9 (C-2' and C-2''), 128.1 (4×C_{meta}-Ar), 128.8 (4×C_{ortho}-Ar), 130.0 (2×C_{para}-Ar), 134.7 (2×C_{ipso}-Ar), 144.3 (C-3' and C-3''), 166.4 (C-1' and C-1''); *m/z* (EI) 520 $(M)^+$, 372, 319, 285, 257, 246, 202, 175, 131, 103, 71, 51; found: $(M)^+$ 520.2112; $C_{30}H_{32}O_8$ requires: *M*, 520.2097; found: C, 69.06%; H, 6.14%; $C_{30}H_{32}O_8$ requires C, 69.22%; H, 6.20%.

(*5S,6R,7R,12S,3'R,3''R*)-*5,12-bis(3-Methylheptanoyloxy)-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane* (**18**). Butyllithium free from hexane [prepared by removal of solvent from commercial butyllithium (2.5 M in hexanes, 2.06 ml, 5.16 mmol, 20 eq.) under high vacuum] in ether (2 ml) was added to a solution of copper(I) iodide tributylphosphane complex[31] (2.02 g, 5.16 mmol, 20 eq.) in ether (1 ml) at −78°C under argon. The resulting pale brown suspension was allowed to come slowly to −20 °C then recooled to −78°C before treatment with boron trifluoride etherate (635 μl, 732 mg, 5.16 mmol, 20 eq.) added dropwise over 10 min. The solution was stirred at −78°C for 1 h and then treated with **14** (96 mg, 0.258 mmol) in ether (1 ml). The resulting brown solution was stirred at −78°C for 2 h and then at −65°C for 16 h. The reaction was quenched by the addition of concentrated aqueous ammonia solution (2 ml) in saturated aqueous ammonium chloride solution (8 ml) at −78°C and allowed to come slowly to room temperature. The solution was stirred vigorously for 10 min to ensure complete aerial oxidation of copper(I) salts and the aqueous layer was then extracted with dichloromethane (2×50 ml). The combined organic layers were dried ($MgSO_4$), and the solvent was removed *in vacuo* to yield a yellow oil. This crude product was purified by flash column chromatography on silica gel with 2% ether in petrol then 50% ether in petrol as eluent to yield the diester **18** (116 mg, 0.227 mmol, 88%) as a colourless oil; $[\alpha]_D^{27}$ −96 (*c* 1.0, chloroform); ν_{max} (film)/cm^{-1} 2961, 2872, 1731 (C=O), 1163, 1089, 1078, 1064; δ_H (400 MHz; $CDCl_3$) 0.85 (6H, t, *J* 6.9, 3×H-7' and 3×H-7''), 0.89 (6H, d, *J* 6.6, Me-3' and Me-3''), 1.1–1.4 (14H, m, H-3', 2×H-4', 2×H-5', 2×H-6', H-3'', 2×H-4'', 2×H-5'' and 2×H-6''), 1.4–2.0 (8H, m, 2×H-3, 2×H-4, 2×H-10 and 2×H-11), 2.11 (2H, dd, *J* 15.6, 8.2, H_AH_B-2' and H_AH_B-2''), 2.23 (2H, dd, *J* 15.6, 5.8, H_AH_B-2' and H_AH_B-2''), 3.4–3.6 (4H, m, 2×H-2 and 2×H-9), 3.59 (2H, m, H_{eq}-14 and H_{eq}-15), 4.07 (2H, m, H_{ax}-14 and H_{ax}-15), 5.47 (2H, dd, *J* 11.3, 5.0, H-5 and H-12); δ_C (100 MHz; $CDCl_3$) 14.0 (C-7' and C-7''), 19.6 (Me-3' and Me-3''), 22.7 (C-6' and C-6''), 24.2 (C-5' and C-5''), 25.3 (C-3 and C-10), 29.1 (C-4 and C-11), 29.8 (C-4' and C-4''), 36.2 (C-3' and C-3''), 41.6 (C-2' and C-2''), 58.4 (C-2 and C-9), 59.7 (C-14 and C-15), 66.6 (C-5 and C-12), 96.0 (C-6 and C-7), 172.2 (C-1' and C-1''); *m/z* (EI) 512 $(M)^+$, 342, 312, 280, 128, 147, 126, 118, 99, 91, 71, 51; found: $(M)^+$ 512.3351; $C_{28}H_{48}O_8$ requires: *M*, 512.3349.

(*5S,6R,7R,12S,3'R,3''R*)-*5,12-bis(3'-Phenylheptanoyloxy)-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane* (**23**). Butyllithium free from hexane [prepared by removal of solvent from commercial butyllithium (2.5 M in hexanes, 2.06 ml, 5.16 mmol, 20 eq.) under high vacuum] in ether (2 ml) was added to a solution of copper(I) iodide tributylphosphane complex (2.02 g, 5.16 mmol, 20 eq.) in ether (1 ml) at −78°C under argon. The resulting pale brown suspension was allowed to come slowly to −20°C then recooled to −78°C before treatment with boron trifluoride etherate (635 μl, 732 mg, 5.16 mmol) added dropwise over 10 min. The solution was stirred at −78°C for 1 h and then treated with **15** (134 mg, 0.258 mmol) in ether (1 ml). The resulting brown solution was stirred at −78°C for 2 h and then at −65°C for 16 h. The reaction was quenched by the addition of concentrated aqueous ammonia solution (2 ml) in saturated aqueous ammonium chloride solution (8 ml) at −78°C and allowed to come to room temperature. The solution was stirred vigorously for 10 min to ensure complete aerial oxidation of copper(I) salts and the aqueous layer was then extracted with dichloromethane (2×50 ml). The combined organic layers were dried ($MgSO_4$) and the solvent was removed *in vacuo* to yield a yellow oil. This crude product was purified by flash column chromatography on silica gel with 2% ether in petrol then 50% ether in petrol as eluent to yield the diester **23** (143 mg, 0.224 mmol, 87%) as a colourless oil; $[\alpha]_D^{26}$ −84 (*c* 0.90, chloroform); ν_{max} (film)/cm^{-1} 2925, 2853, 1723 (C=O), 1160, 1093; δ_H (400 MHz; $CDCl_3$) 0.79 (6H, t, *J* 7.0, 3×H-7' and 3×H-7''), 1.0–1.8 (20H, m, 2×H-3, 2×H-4, 2×H-10, 2×H-11, 2×H-4', 2×H-5', 2×H-6', 2×H-4'', 2×H-5'' and 2×H-6''), 2.55 (2H, dd, *J* 16.2, 7.1, H_AH_B-2' and H_AH_B-2''), 2.61 (2H, dd, *J* 15.8, 7.8, H_AH_B-2' and H_AH_B-2''), 3.2–3.6 (3H, m, 2×H-2, 2×H-9, H-3' and H-3''), 3.59 (2H, m, H_{eq}-14 and H_{eq}-15), 4.06 (2H, m, H_{ax}-14 and H_{ax}-15), 5.36 (2H, dd, *J* 11.2, 5.3, H-5 and H-12), 7.0–7.4 (10H, m, 10×H-Ar); δ_C (100 MHz; $CDCl_3$) 13.4 (C-7' and C-7''), 22.6 (C-6' and C-6''), 24.2 (C-3 and C-10), 25.0 (C-4 and C-11), 29.5 (C-5' and C-5''), 36.0 (C-4' and C-4''), 41.4 (C-2' and C-2''), 41.8 (C-3' and C-3''), 58.5 (C-2 and C-9), 59.8 (C-14 and C-15), 66.7 (C-5 and C-12), 96.0 (C-6 and C-7), 126.1 (2×C_{para}-Ar), 127.6 (4×C_{ortho}-Ar), 128.2 (4×C_{meta}-Ar), 144.4

(2×C_{ipso}-Ar), 171.4 (C-1′ and C-1″); *m/z* (EI) 636 $(M)^+$, 578, 372, 343, 246, 233, 171, 147, 126, 118, 99, 91, 71, 51; found: $(M)^+$ 636.3664; $C_{38}H_{52}O_8$ requires: *M*, 636.3662.

(*5S,6R,7R,12S,3′R,3″R*)-*5,12-bis(3-Phenylbutanoyloxy)-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane* (**22**). Methyllithium (1.4 M in ether, 2.74 ml, 3.85 mmol, 40 eq.) was added dropwise to a solution of copper(I) iodide tributylphosphane complex (1.55 g, 3.94 mmol, 41 eq.) in ether (1 ml) at −78°C under argon dropwise over 5 min. The resulting pale brown suspension was allowed to come slowly to −20°C then recooled to −78°C before treatment with boron trifluoride etherate (472 μl, 545 mg, 3.84 mmol, 40 eq.) added dropwise over 10 min. The resulting brown solution was stirred at −78°C for 1 h and then treated with the diester (**15**) (50 mg, 0.096 mmol) in ether (1 ml). The resulting pale brown solution was stirred at −78°C for 2 h and then at −45°C for 16 h. The reaction was quenched by the addition of concentrated aqueous ammonia (5 ml) in saturated ammonium chloride solution (20 ml) at −78°C, allowed to come slowly to room temperature and stirred vigourously for 30 min to ensure aerial oxidation of residual copper(I) salts. The aqueous layer was then extracted with dichloromethane (2×50 ml), dried ($MgSO_4$), and the solvent was removed *in vacuo* to yield a pale yellow oil. This crude product was purified by flash column chromatography on silica gel with 2% ether in petrol then 40% ether in petrol as eluent to yield the diester **22** (44 mg, 0.0797 mmol, 83%) as a colourless oil; $[\alpha]_D^{26}$ −73 (*c* 0.32, chloroform); ν_{max} (film)/cm^{-1} 2958, 1722 (C=O), 1094, 1078; δ_H (400 MHz; $CDCl_3$) 1.29 (6H, t, *J* 7.0, 3×H-4′ and 3×H-4″), 1.3–2.0 (8H, m, 2×H-3, 2×H-4, 2×H-10 and 2×H-11), 2.61 (4H, d, *J* 7.3, 2×H-2′ and 2×H-2″), 3.2–3.6 (6H, m, 2×H-2, 2×H-9, H-3′ and H-3″), 3.57 (2H, m, H_{eq}-14 and H_{eq}-15), 4.06 (2H, m, H_{ax}-14 and H_{ax}-15), 5.44 (2H, dd, *J* 11.8, 5.7, H-5 and H-12), 7.1–7.3 (10H, m, 10×H-Ar); δ_C (100 MHz; $CDCl_3$) 22.3 (C-4 and C-4′), 24.2 (C-3 and C-10), 25.3 (C-4 and C-11), 36.1 (C-2′ and C-2″), 42.5 (C-3′ and C-3″), 58.4 (C-2 and C-9), 59.7 (C-14 and C-15), 66.8 (C-5 and C-12), 95.9 (C-6 and C-7), 126.2 (2×C_{para}-Ar), 126.9 (4×C_{ortho}-Ar), 128.4 (4×C_{meta}-Ar), 146.4 (2×C_{ipso}-Ar), 171.3 (C-1′ and C-1″); *m/z* (EI) 552 $(M)^+$, 335, 301, 273, 191, 164, 147, 127, 105, 91, 78, 55; found: $(M)^+$ 552.2719; $C_{32}H_{40}O_8$ requires: *M*, 552.2723.

(*5S,6R,7R,12S,3′S,3″S*)-*5,12-bis(3-Methylheptanoyloxy)-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane* (**25**). Methyllithium (1.4 M in ether, 2.74 ml, 3.84 mmol, 40 eq.) was added dropwise over 5 min to a solution of copper(I) iodide tributylphosphane complex (1.55 g, 3.94 mmol, 41 eq.) in ether (1 ml) at −78°C under argon. The resulting pale brown suspension was allowed to come slowly to −20°C then recooled to −78°C before treatment with boron trifluoride etherate (472 μl, 545 mg, 3.84 mmol, 40 eq.), added dropwise over 10 min. The resulting brown solution was stirred at −78°C for 1 h and then treated with the diester **16** (46 mg, 0.096 mmol) in ether (1 ml). The resulting brown solution was stirred at −78°C for 2 h and then at −45°C for 16 h. The reaction was quenched by the addition of concentrated aqueous ammonia (5 ml) in saturated ammonium chloride solution (20 ml) at −78°C, allowed to come to room temperature and stirred vigourously for 30 min to ensure aerial oxidation of residual copper(I) salts. The aqueous layer was then extracted with dichloromethane (2×50 ml), dried ($MgSO_4$), and the solvent was removed *in vacuo* to yield a pale yellow oil. This crude product was purified by flash column chromatography on silica gel with 2% ether in petrol then 20% ether in petrol as eluent to yield the diester **25** (39 mg, 0.0759 mmol, 79%) as a colourless oil; $[\alpha]_D^{27}$ −102 (*c* 0.76, chloroform); ν_{max} (film)/cm^{-1} 2959, 1727 (C=O), 1160, 1084, 1077, 1063, 924, 714; δ_H (400 MHz; $CDCl_3$) 0.86 (6H, t, *J* 6.8, 3×H-7′ and 3×H-7″), 0.93 (6H, d, *J* 6.7, Me-3′ and Me-3″), 1.1–1.4 (14H, m, H-3′, 2×H-4′, 2×H-5′, 2×H-6′, H-3″, 2×H-4″, 2×H-5″ and 2×H-6″), 1.5–2.0 (8H, m, 2×H-3, 2×H-4, 2×H-10 and 2×H-11), 2.08 (2H, dd, *J* 15.6, 7.8, $H_A$$H_B$-2′ and $H_A$$H_B$-2″), 2.31 (2H, dd, *J* 15.7, 6.1, $H_A$$H_B$-2′ and $H_A$$H_B$-2″), 3.4–3.6 (4H, m, 2×H-2 and 2×H-9), 3.60 (2H, m, H_{eq}-14 and H_{eq}-15), 4.08 (2H, m, H_{ax}-14 and H_{ax}-15), 5.46 (2H, dd, *J* 11.4, 5.1, H-5 and H-12); δ_C (100 MHz; $CDCl_3$) 14.1 (C-7′ and C-7″), 19.8 (Me-3′ and Me-3″), 22.6 (C-6′ and C-6″), 24.4 (C-5′ and C-5″), 25.1 (C-3 and C-10), 29.0 (C-4 and C-11), 29.6 (C-4′ and C-4″), 36.5 (C-3′ and C-3″), 41.3 (C-2′ and C-2″), 58.3 (C-2 and C-9), 59.7 (C-14 and C-15), 66.2 (C-5 and C-12), 96.3 (C-6 and C-7), 172.5 (C-1′ and C-1″); *m/z* (EI) 512 (M)+, 342, 312, 280, 128, 147, 126, 118, 99, 91, 71, 51; found: $(M)^+$ 512.3344; $C_{28}H_{48}O_8$ requires: *M*, 512.3349.

(*5S,6R,7R,12S,3′S,3″S*)-*5,12-bis(3′-Phenylbutanoyloxy)-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane* (**20**). Phenyllithium (1.8 M in ether, 5.61 ml, 10.1 mmol, 40 eq.) was added to a solution of copper(I) iodide tributylphosphane complex (4.06 g, 10.4 mmol, 41 eq.) in ether (4 ml) at −78°C under argon. The resulting pale brown suspension was allowed to come slowly to −20°C and recooled to −78°C before treatment with boron trifluoride etherate (1.24 ml, 1.43 g, 10.1 mmol, 40 eq.) added dropwise over 20 min. The solution was stirred at −78°C for 1 h and then treated with the diester **14** (100 mg, 0.253 mmol) in ether (2 ml). The resulting brown solution was stirred at −78°C for 2 h then at −45°C for 16 h. The reaction was quenched by the addition of concentrated aqueous ammonia (7 ml) in saturated ammonium chloride solution (28 ml) at −78°C, the solution was allowed to come slowly to room temperature and stirred vigourously for 30 min to ensure aerial oxidation of residual copper(I) salts. The aqueous layer was then extracted with dichloromethane (2×60 ml), dried ($MgSO_4$), and the solvent removed *in vacuo* to yield a pale yellow oil. This crude product was purified by flash column chromatography on silica gel with 2% ether in petrol then 40% ether in petrol as eluent to yield, in order of elution, the diester **20** (85 mg, 0.0154 mmol, 61%) as a colourless oil; $[\alpha]_D^{27}$ −88 (*c* 0.65, chloroform); ν_{max} (film)/cm^{-1} 2925, 2853, 1732 (C=O), 1453, 1377, 1159, 1092, 700; d_H (400 MHz; $CDCl_3$) 1.26 (6H, t, *J* 7.3, 3×H-4′ and 3×H-4″), 1.3–1.9 (8H, m, 2×H-3, 2×H-4, 2×H-10 and 2×H-11), 2.59 (4H, d, *J* 7.3, 2×H-2′ and 2×H-2″), 3.13 (2H, dd, *J* 10.8, 4.5, H_{eq}-2 and H_{eq}-9), 3.28 (2H, m, H-3′ and H-3″), 3.39 (2H, m, H_{eq}-14 and H_{eq}-15), 3.2–3.6 (2H, m, H_{ax}-2 and H_{ax}-9), 4.06 (2H, m, H_{ax}-14 and H_{ax}-15), 5.44 (2H, dd, *J* 11.8, 5.7, H-5 and H-12), 7.1–7.3 (10H, m, 10×H-Ar); δ_C (100 MHz; $CDCl_3$) 22.1 (C-4 and C-4′), 24.1 (C-3 and C-10), 25.1 (C-4 and C-11), 36.1 (C-2′ and C-2″), 42.4 (C-3′ and C-3″), 58.4 (C-2 and C-9), 59.6 (C-14 and C-15), 66.7 (C-5 and C-12), 95.8 (C-6 and C-7), 126.2 (2×C_{para}-Ar), 126.8 (4×C_{ortho}-Ar), 128.4 (4×C_{meta}-Ar), 145.9 (2×C_{ipso}-Ar), 171.3 (C-1′ and C-1″); *m/z* (EI) 552 $(M)^+$, 335, 301, 273, 191, 147, 127, 105, 99, 91, 78, 71, 55; found: $(M)^+$ 552.2719; $C_{32}H_{40}O_8$ requires: *M*, 552.2723, the monoadduct (23 mg, 0.0531 mmol, 21%), and recovered starting material (**14**) (9.0 mg, 0.0228 mmol, 9%).

(*5S,6R,7R,12S,3′S,3″S*)-*5,12-bis[3-(dimethylphenylsilyl)-butanoyloxy]-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane* (**21**). To a suspension of finely sliced lithium metal (555 mg, 80 mmol) in degassed (ultrasound and argon) THF (10 ml) at −20°C was added dimethylphenylsilyl chloride (824 mg, 800 μl, 4.84 mmol, 40 eq.). The resulting deep red solution was stirred at −10°C for 24 h. This was then added via cannula to a solution of copper(I) iodide tributylphosphane complex (2.08 g, 5.31 mmol, 44 eq.) in ether (5 ml) at −78°C. The resulting deep red/brown solution was allowed to come slowly to −40°C and stirred for 20 min before recooling to −78°C. Boron trifluoride etherate (594 μl, 68 5mg, 4.82 mmol, 40 eq.) was added dropwise over 10 min, the reaction was allowed to warm slowly to −50°C and then recooled to −78°C. Diester **14** (50 mg, 0.126 mmol) in ether (5 ml) was then added dropwise over 20 min. The resulting deep purple/brown solution was stirred at −70°C for 16 h, quenched by the addition of concentrated aqueous ammonia solution (4 ml) in saturated ammonium chloride (16 ml), allowed to come to room temperature and stirred vigourously for 30 min to ensure aerial oxidation of residual copper(I) salts. The layers were then separated and the aqueous layer was extracted with dichloromethane (3×100 ml). The combined organic phases were dried ($MgSO_4$), and the solvent was removed *in vacuo* to yield a yellow oil. This crude product was purified by flash column chromatography on silica gel with 2% ether in petrol then 30% ether in petrol as eluent to yield the disilane **21** (81 mg, 0.116 mmol, 92%) as a colourless oil; $[\alpha]_D^{27}$ −79 (*c* 1.21, chloroform); ν_{max} (film)/cm^{-1} 2965, 2872, 1735 (C=O), 1463, 1083, 1012, 964; δ_H (400 MHz; $CDCl_3$) 0.24 (6H, s, $Me_A$$Me_B$PhSi-3′ and $Me_A$$Me_B$PhSi-3″), 0.26 (6H, s, $Me_A$$Me_B$PhSi-3′ and $Me_A$$Me_B$PhSi-3″), 0.96 (6H, d, *J* 7.3, 3×H-4′ and 3×H-4″), 1.3–1.9 (10H, m, 2×H-3, 2×H-4, 2×H-10, 2×H-11, H-3′ and H-3″), 2.08 (2H, dd, *J* 16.7, 12.0, $H_A$$H_B$-2′ and $H_A$$H_B$-2″), 2.23 (2H, dd, *J* 16.7, 2.4, $H_A$$H_B$-2′ and $H_A$$H_B$-2″), 2.88 (2H, dd, *J* 10.2, 3.7, H_{ax}-2 and H_{ax}-9), 3.32 (2H, dt, *J* 10.4, 2.4, H_{eq}-2 and H_{eq}-9), 3.53 (2H, m, H_{eq}-14 and H_{eq}-15), 3.96 (2H, m, H_{ax}-14 and H_{ax}-15), 5.46 (2H, dd, *J* 11.7, 4.8, H-5 and H-12), 7.2–7.4 (6H, m, 4×H_{ortho}-Ar and 2×H_{para}-Ar), 7.4–7.6 (4H, m, 4×H_{meta}-Ar); *m/z* (+FAB) 669 $(MH)^+$, 447, 359, 288, 243, 205, 181, 155, 135; found: $(MH)^+$ 699.3275; $C_{36}H_{53}O_8Si_2$ requires: *MH*, 669.3278.

(*5S,6R,7R,12S,3′R,3″R*)-*5,12-bis[3-(Dimethylphenylsilyl)-3-phenylpropanoyloxy]-1,8,13,16-tetraoxadispiro[5.0.5.4]hexadecane* (**24**). To a suspension of finely sliced lithium metal (555 mg, 80 mmol) in degassed (ultrasound and argon) THF (10 ml) at −20°C was added dimethylphenylsilyl chloride (824 mg, 800 μl, 4.84 mmol, 40 eq.). The resulting deep red solution was stirred at −10°C for 24 h. This was then added *via* cannula to a solution of copper(I) iodide tributylphosphane complex (2.08 g, 5.31 mmol, 44 eq.) in ether (5 ml) at

−78°C. The resulting deep red/brown solution was allowed to come slowly to −40°C and stirred for 20 min before recooling to −78°C. Boron trifluoride etherate (594 μl, 68 5 mg, 4.82 mmol, 40 eq.) was added dropwise over 10 min, the reaction warmed slowly to −50°C and then recooled to −78°C. Diester **15** (66 mg, 0.126 mmol) in ether (5 ml) was then added dropwise over 20 min. The resulting deep purple/brown solution was stirred at −60°C for 16 h, quenched by the addition of concentrated aqueous ammonia solution (4 ml) in saturated ammonium chloride (16 ml), allowed to come slowly to room temperature and stirred vigourously for 30 min to ensure aerial oxidation of residual copper(I) salts. The layers were then separated and the aqueous layer extracted with dichloromethane (3×100 ml). The combined organic phases were dried ($MgSO_4$), and the solvent removed *in vacuo* to yield a yellow oil. This crude product was purified by flash column chromatography on silica gel with 2% ether in petrol then 30% ether in petrol as eluent to yield the disilane **24** (91 mg, 0.115 mmol, 91%) as a colourless oil; $[\alpha]_D^{27}$ −117 (*c* 0.91, chloroform); ν_{max} (film)/cm^{-1} 2941, 2875, 1728 (C=O), 1353, 1277, 1151, 1080, 700; δ_H (400 MHz; $CDCl_3$) 0.12 (6H, s, Me_AMe$_B$PhSi-3′ and Me_AMe$_B$PhSi-3″), 0.23 (6H, s, Me$_A$$Me_B$PhSi-3′ and Me$_A$$Me_B$PhSi-3″), 0.8–1.8 (8H, m, 2×H-3, 2×H-4, 2×H-10 and 2×H-11), 2.37 (2H, dd, *J* 13.9, 4.9, H-3′ and H-3″), 2.81 (4H, m, 2×H$_A$H$_B$-2′ and 2×H$_A$H$_B$-2″), 3.1–3.4 (4H, m, 2×H-2 and 2×H-9), 3.52 (2H, m, H_{eq}-14 and H_{eq}-15), 3.93 (2H, m, H_{ax}-14 and H_{ax}-15), 5.22 (2H, dd, *J* 11.7, 4.9, H-5 and H-12), 6.7–7.5 (20H, m, 20×H-Ar); δ_C (100 MHz; $CDCl_3$) −6.0 (2×Me_AMe$_B$Si) −3.9 (2×Me$_A$$Me_B$Si), 24.2 (C-3 and C-10), 24.9 (C-4 and C-11), 32.1 (C-3′ and C-3″), 34.5 (C-2′ and C-2″), 58.4 (C-2 and C-9), 59.6 (C-14 and C-15), 66.8 (C-5 and C-12), 95.8 (C-6 and C-7), 124.7, 124.8, 127.6, 127.7, 127.9, 128.0, 128.1, 129.2, 134.1, 134.2, 137.1, 141.7 (24×C-Ar), 172.1 (C-1′ and C-1″); *m*/*z* (+FAB) 793 (MH)$^+$, 512, 424, 353, 243, 199, 162, 155, 135; found: (MH)$^+$ 793.3595; $C_{46}H_{57}O_8Si_2$ requires: *MH*, 793.3592.

General procedure for the hydrolytic cleavage of the Michael adducts from the chiral auxiliary

To a solution of the diester (0.1 mmol) in methanol (2 ml) was added 3N sodium hydroxide solution (1 ml). The resulting colourless solution was heated under reflux for 12 h and then allowed to come to room temperature. After removal of the methanol *in vacuo* and dilution the aqueous residue with water (5 ml), the aqueous layer was extracted with dichloromethane (3×20 ml). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to yield the recovered diol auxiliary (−)-**6**. The aqueous phase was then acidified to pH 1 with 3N hydrochloric acid solution and was then extracted with dichloromethane (3×20 ml). The combined organic extracts were washed with brine (10 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield the desired acid.

(3R)-*3-Methylheptanoic acid* (**17**). The general saponification procedure outlined above was followed using the diester **18** (86 mg, 0.167 mmol) to yield the carboxylic acid **17** (46 mg, 0.334 mmol, 95%) as a colourless oil; $[\alpha]_D^{27}$ +4.1 (*c* 0.91, benzene), lit.[31] $[\alpha]_D^{27}$ +3.84 (benzene); ν_{max} (film)/cm^{-1} 3700–2200 (br, CO_2H), 2928, 1711 (C=O), 1461, 1410, 1265, 742, 705; δ_H (400 MHz; $CDCl_3$) 0.88 (3H, t, *J* 7.2, 3×H-7), 0.94 (3H, d, *J* 6.7, Me-3), 1.2–1.5 (7H, m, H-3, 2×H-4, 2×H-5, 2×H-6), 2.12 (1H, dd, *J* 14.9, 8.2, H_AH_B-2), 2.34 (1H, dd, *J* 14.9, 5.9, H$_A$$H_B$-2); δ_C (100 MHz; $CDCl_3$) 14.1 (C-7), 19.6 (Me-3), 22.7 (C-6), 29.1 (C-4), 30.1 (C-3), 36.3 (C-5), 41.5 (C-2), 179.2 (C-1); *m*/*z* (EI) 144 (M)$^+$, 129, 115, 101, 87, 84, 60, 55, 45; found: (M)$^+$ 144.1143; $C_8H_{16}O_2$ requires: *M*, 144.1150, and recovered diol (−)-**6** (40 mg, 0.155 mmol, 92%) identical in all respects to that isolated previously.

(3R)-*3-Phenylheptanoic acid* (**29**). The general saponification procedure outlined above was followed using the diester **23** (76 mg, 0.119 mmol) to yield the carboxylic acid **29** (44.3 mg, 0.216 mmol, 90%) as a colourless oil; $[\alpha]_D^{27}$ −26.2 (*c* 0.71, benzene), lit.[31] $[\alpha]_D$ −27.8; ν_{max} (film)/cm^{-1} 3700–2200 (br, CO_2H), 2916, 1713 (C=O), 1462, 1454, 1383, 699; δ_H (400 MHz; $CDCl_3$) 0.83 (3H, t, *J* 7.1, 3×H-7), 1.1–1.5 (4H, m, 2×H-5 and 2×H-6), 1.5–1.7 (2H, m, 2×H-4), 2.62 (2H, m, H_AH_B-2 and H$_A$$H_B$-2), 3.04 (1H, m, H-3), 7.1–7.3 (5H, m, 5×H-Ar); δ_C (100 MHz; $CDCl_3$) 13.9 (C-7), 22.6 (C-6), 29.5, 29.7 (C-2 and C-4), 35.9 (C-5), 41.8 (C-3), 126.2 (C_{para}-Ar), 127.4, 128.5 (2×C_{ortho}-Ar and 2×H_{meta}-Ar), 144.0 (C_{ipso}-Ar), 178.1 (C-1); *m*/*z* (EI) 206 (M)$^+$, 150, 104, 91, 74, 59, 45; found: (M-CH$_4$)$^+$ 206.0767; $C_{13}H_{18}O_2$ requires: *M*, 206.0763 and recovered diol (−)-**6** (28.3 g, 0.109 mmol, 91%) identical in all respects to that isolated previously.

(3R)-*3-Phenylbutanoic acid* (**28**). The general saponification procedure outlined above was followed using the diester **22** (102 mg, 0.185 mmol) to yield the carboxylic acid **28** (53 g, 0.321 mmol, 87%) as a colourless oil; $[\alpha]_D^{27}$ −48.5 (*c* 1.1, benzene), lit.[31] $[\alpha]_D^{25}$ −51.1 (benzene); ν_{max} (film)/cm^{-1} 3700–2200 (br, CO_2H), 2848, 1713 (C=O), 1415, 1350, 847, 761; δ_H (400 MHz; $CDCl_3$) 1.32 (3H, t, *J* 7.0, 3×H-4), 2.58 (1H, dd, *J* 15.5, 8.2, H_AH_B-2), 2.67 (1H, dd, *J* 15.5, 6.9, H$_A$$H_B$-2), 3.70 (1H, m, H-3), 7.1–7.4 (5H, m, 5×H-Ar); δ_C (100 MHz; $CDCl_3$) 21.9 (C-4), 36.2 (C-2), 42.6 (C-3), 126.5 (C_{para}-Ar), 126.7, 128.6 (2×C_{ortho}-Ar and 2×H_{meta}-Ar), 138.4 (C_{ipso}-Ar), 188.1 (C-1); *m*/*z* (EI) 164 (M)$^+$, 149, 118, 85, 77, 60; found: (M)$^+$ 164.0838; $C_{10}H_{12}O_2$ requires: *M*, 164.0837 and recovered diol (−)-**6** (46 mg, 0.175 mmol, 95%) identical in all respects to that isolated previously.

(3S)-*3-Methylheptanoic acid* (**31**). The general saponification procedure outlined above was followed using the diester **25** (92 mg, 0.180 mmol) to yield the carboxylic acid **31** (48 mg, 0.334 mmol, 93%) as a colourless oil which was spectroscopically identical to that isolated previously; $[\alpha]_D^{27}$ −3.6 (*c* 1.03, benzene), lit.[31] $[\alpha]_D^{24}$ −3.84 (benzene) and recovered diol (−)-**6** (43 g, 0.165 mmol, 92%) identical in all respects to that isolated previously.

(3S)-*3-Phenylbutanoic acid* (**26**). The general saponification procedure outlined above was followed using the diester **20** (51 mg, 0.092 mmol) to yield the carboxylic acid **26** (27 mg, 0.164 mmol, 89%) as a colourless oil which was spectroscopically identical to that isolated previously; $[\alpha]_D^{27}$ +42.6 (*c* 0.72, benzene), lit.[31] $[\alpha]_D^{25}$ +51.1 (benzene); and recovered diol (−)-**6** (23 mg, 0.089 mmol, 97%) identical in all respects to that isolated previously.

(3S)-*3-(Dimethylphenylsilyl)butanoic acid* (**27**). The general saponification procedure outlined above was followed using the diester **21** (142 mg, 0.203 mmol) to yield the carboxylic acid **27** (73 mg, 0.353 mmol, 87%) as a colourless oil; $[\alpha]_D^{27}$ −10.7 (*c* 0.92, chloroform), lit.[32] $[\alpha]_D$ −12.0 (chloroform); ν_{max} (film)/cm^{-1} 3300–2200 (br, CO_2H), 2918, 1708 (C=O), 1600, 1427, 1250, 817, 699; δ_H (200 MHz; $CDCl_3$) 0.26 (3H, s, Me_AMe$_B$PhSi-3), 0.29 (3H, s, Me$_A$$Me_B$PhSi-3), 1.00 (3H, d, *J* 7.2, 3×H-4), 1.39 (1H, m, H-3), 2.08 (1H, dd, *J* 16.0, 11.3, H_AH_B-2), 2.40 (1H, dd, *J* 16.1, 3.4, H$_A$$H_B$-2), 7.3–7.5 (5H, m, 5×H-Ar); *m*/*z* (EI) 206 (M-CH$_4$)+, 146, 107, 91, 59; found: (M)$^+$ 206.0762; $C_{12}H_{18}O_2Si$ requires: *M*, 206.0763 and recovered diol (−)-**6** (51 mg, 0.197 mmol, 97%) identical in all respects to that isolated previously.

(3R)-*3-(Dimethylphenylsilyl)-3-phenylpropanoic acid* (**30**). The general saponification procedure outlined above was followed using the diester **24** (113 mg, 0.142 mmol) to yield the carboxylic acid **30** (68 mg, 0.254 mmol, 89%) as a colourless oil; $[\alpha]_D^{27}$ +4.3 (*c* 0.97, chloroform), lit.[32] $[\alpha]_D$ +6.0 (chloroform); ν_{max} (film)/cm^{-1} 3500–2300 (br, CO_2H), 2926, 1714 (C=O), 1265, 818, 744, 701; δ_H (400 MHz; $CDCl_3$) 0.21 (3H, s, Me_AMe$_B$Si), 0.25 (3H, s, Me$_A$$Me_B$Si), 2.64 (1H, t, *J* 7.4, H_AH_B-2), 2.77 (1H, dd, *J* 26.3, 12.8, H-3), 2.93 (1H, t, *J* 7.7, H$_A$$H_B$-2), 6.9–7.5 (10H, m, 10×H-Ar); δ_C (100 MHz; $CDCl_3$) −5.5, −4.1 (Me_AMe$_B$Si and Me$_A$$Me_B$Si), 30.6 (C-3), 32.0 (C-2), 125.1, 126.4, 127.5, 127.8, 128.1, 128.6, 129.4, 134.1, 136.3, 140.1, 141.4 (12×C-Ar); *m*/*z* (EI) 269 (M-Me)$^+$, 206, 150, 135, 104, 78, 51; found: (M−Me)$^+$ 269.0996; $C_{16}H_{17}O_2Si$ requires: *M*, 269.0997 and recovered (−)-diol (−)-**6** (35 g, 0.134 mmol, 94%).

(3R)-*3-methylheptanol* (**32**). To a solution of the diester (**18**) (48 mg, 9.4×10^{-5} mmol) in ether (1 ml) at −30°C under argon was added lithium aluminium hydride (1.0 M in ether, 184 μl, 0.188 mmol, 2 eq.) dropwise over 1 min. The solution was allowed to come slowly to room temperature and stirred for 2 h before recooling to −30°C. The reaction was then quenched by the portionwise addition of sodium sulfate decahydrate (250 mg) over 1 min. The reaction was allowed to come slowly to room temperature and 3N hydrochloric acid solution (5 ml) then 5% dichloromethane in petrol (20 ml) were added. The layers were separated and the aqueous layer extracted with 5% dichloromethane in petrol (3×10 ml). The combined organic extracts were washed with saturated sodium bicarbonate solution (10 ml), dried ($MgSO_4$) and concentrated *in vacuo* to yield the alcohol **32** (22 mg, 0.174 mmol, 92%) as a colourless oil; $[\alpha]_D^{27}$ +3.2 (benzene), lit.[31] $[\alpha]_D^{25}$ +2.76; ν_{max} (film)/cm^{-1} 3500–2300 (br, CO_2H), 2926, 1714, 1265, 818, 744, 701; δ_H (200 MHz; $CDCl_3$) 0.8–0.9 (6H, m, 3×H-7 and Me-3), 1.1–1.9 (9H, m, 2×H-2, H-3, 2×H-4, 2×H-5 and 2×H-6), 3.63 (2H, dt, *J* 2.4, 6.7, 2×H-1); δ_C (50 MHz; $CDCl_3$) 13.7 (C-7), 19.6 (Me-3), 22.9 (C-6), 29.1 (C-4), 29.4 (C-3), 36.8 (C-5), 39.9 (C-2), 61.0 (C-1); *m*/*z* (EI) 130 (M)$^+$, 112 (M-H$_2$O)$^+$, 99, 57, 45; found: (M)$^+$ 130.1357. $C_8H_{18}O$ requires: *M*, 130.1358. The aqueous layer was then extracted with dichloromethane (3×20 ml). The combined dichloromethane extracts were then washed with saturated sodium bicarbonate solution (10 ml), dried

($MgSO_4$) and concentrated *in vacuo* to yield the recovered diol auxiliary (−)-**6** (22 g, 0.084 mmol, 90%) identical in all respects to that isolated previously.

Acknowledgements

We thank the E.P.S.R.C. for funding (to *G.H.C.*) and Glaxo Research and Development for a Studentship (to *J.E.I.*). Further financial support was provided by the F.R.D., Pretoria (to *B.C.B.B.*) and the BP endowment (to *S.V.L.*). This work was also funded with support from the European Communities Human Mobility Program "Stereoselective Organic Synthesis" CHRX-CT92-0067. We thank Dr. *S.G. Davies*, Oxford University, for useful discussions.

References

[1] *G. Genicot* and *S.V. Ley*, Synthesis 1275 (1994).
[2] On study leave from the Department of Chemistry, The University of the Orange Free State, P.O. Box 339, Bloemfontein 9300, Republic of South Africa.
[3] *S.V. Ley, M. Woods* and *A. Zanotti-Gerosa*, Synthesis 52 (1992).
[4a] *R. Leslie, S.V. Ley, P.D. Tiffen* and *M. Woods*, Tetrahedron Lett. **33**, 4767 (1992);
[b] *A.B. Hughes, S.V. Ley, H.W.M. Priepke* and *M. Woods*, Tetrahedron Lett. **35**, 773 (1994);
[c] *G-J. Boons, R. Leslie, S.V. Ley* and *L.L. Yeung*, Tetrahedron Lett. **34**, 8523 (1993).
[5] *R. Downham, K-S. Kim, S.V. Ley* and *M. Woods*, Tetrahedron Lett. **35**, 769 (1994).
[6] *D.A. Entwistle, A.B. Hughes, S.V. Ley* and *G. Visentin*, Tetrahedron Lett. **35**, 777 (1994).
[7] *G.-J. Boons, D.A. Entwistle, S.V. Ley* and *M. Woods*, Tetrahedron Lett. **34**, 5649 (1993).
[8] *P.J. Edwards, D.A. Entwistle, C. Genicot, K-S. Kim* and *S.V. Ley*, Tetrahedron Lett. **35**, 7443 (1994).
[9] *H.E. Simmons* and *R.D. Smith*, J. Am. Chem. Soc. **81**, 4256 (1959).
[10a] *R. Ginsig* and *A.D. Cross*, J. Am. Chem. Soc. **87**, 4629 (1965);
[b] *J.M. Denis, C. Girard* and *J.M. Conia*, Synthesis 549 (1972);
[c] *E.P. Blanchard, H.E. Simmons* and *J.S. Taylor*, J. Org. Chem. **30**, 4321 (1965);
[d] *J.M. Conia* and *J.C. Limasset*, Tetrahedron Lett. 3151 (1965).
[11] *E.J. Corey, J.G. Reid, A.G. Myers* and *R.W. Hahl*, J. Am. Chem. Soc. **109**, 918 (1987).
[12] *G. Molander* and *J.B. Etter*, J. Org. Chem. **52**, 3944 (1987).
[13a] *H.B. Henbest* and *R.A.L. Wilson*, J. Chem. Soc. 1958 (1957);
[b] *B.A. McKittrick* and *B. Genen*, Tetrahedron Lett. **26**, 4895 (1985);
[c] *A.S. Narula*, Tetrahedron Lett. **22**, 2017 (1981);
[d] *R.B. Dehnel* and *G.H. Witham*, J. Chem. Soc., Perkin Trans. I, 953 (1979).
[14] *S.G. Davies, A.J. Edwards, G.B. Evans* and *A.A. Mortlock*, Tetrahedron **50**, 6621 (1994).
[15a] *B.C.B. Bezuidenhoudt, G.H. Castle* and *S.V. Ley*, Tetrahedron Lett. **35**, 7447 (1994);
[b] *B.C.B. Bezuidenhoudt, G.H. Castle, J.V. Geden* and *S.V. Ley*, Tetrahedron Lett. **35**, 7451 (1994).
[16a] *G. Descotes, M. Lissac, J. Delman, J. Duplan* and *C.R. Hebd*, Séances Acad. Sci., Ser. C **267**, 1240 (1968);
[b] *N. Beaulieu, R.A. Dickinson* and *P. Deslongchamps*, Can. J. Chem. **58**, 2531 (1980).
[17] Macromodel, the Batchmin program and the associated documentation are available from *W.C. Still*, Columbia University, New York. For details of the MM2 force field see: *N.L. Allinger*, J. Am. Chem. Soc. **99**, 8127 (1977). For details of MOPAC see: (a) *M.J.S. Dewar, E.G. Zoebish, E.F. Healy* and *J.J.P. Stewart*, J. Am. Chem. Soc. **107**, 8127 (1985); (b) *M.J.S. Dewar*, J. Mol. Struct. **100**, 41 (1983) and references therein.
[18] *R.L. Halcomb* and *S.J. Danishefsky*, J. Am. Chem. Soc. **111**, 6661 (1989).
[19] See *inter alia.*: (a) *F. Sweet* and *R.K. Brown*, Can. J. Chem. **44**, 1571 (1966); (b) *H.B. Wood* and *H.G. Fletcher*, J. Am. Chem. Soc. **79**, 3234 (1957).
[20] For reviews see: (a) *R.W. Murray*, Chem. Rev. **89**, 1187 (1989); (b) *W. Adam, R. Curci* and *J. Edwards*, Acc. Chem. Res. **22**, 205 (1989).
[21] *S.W. Baertschi, K.D. Raney, M.P. Stone* and *T.M. Harris*, J. Am. Chem. Soc. **110**, 7929 (1988).
[22] *O. Bortoloni, S. Campestrini, F. Di Furia* and *G. Modena*, J. Org. Chem. **52**, 5093 (1987).
[23] *H. Gilman* and *J.M. Straley*, Recl. Trav. Chim. Pays-Bas **55**, 821 (1936).
[24] *H. Gilman, R.G. Jones* and *L.A. Woods*, J. Org. Chem. **17**, 1630 (1952).
[25] For a collection of papers dealing with the applications of organocopper and cuprate reagents see: Tetrahedron **45(2)** (1989), *B.H. Lipshutz*, Ed.
[26] *G.H. Posner*, "An Introduction to Synthesis using Organocopper Reagents", Wiley, New York, 1980.
[27] *B.E. Rossiter* and *N.M. Swingle*, Chem. Rev. **92**, 771 (1992).
[28a] *Y. Yamamoto* and *K. Maruyama*, J. Am. Chem. Soc. **100**, 3240 (1978);
[b] *Y. Yamamoto* and *K. Maruyama*, J. Am. Chem. Soc. **99**, 8068 (1977).
[29] *D.J. Ager, I. Fleming* and *S.K. Patel*, J. Chem. Soc., Perkin Trans. I, 2520 (1981).
[30] Dictionary of Organic Compounds, 5th Edition, Chapman and Hall, New York (1982).
[31] *G.B. Kauffman* and *L.A. Teter*, Inorg. Synth. 7, 9 (1963).