Synthesis and Herbicidal Activity of [3*R**,5*S**,6*S**]-3-Benzyloxy-5-methoxy-1,7-dioxaspiro[5.5]undecane and [3*R**,5*S**,6*S**]-3-Methoxy-5-benzyloxy-1,7-dioxaspiro[5.5]undecane

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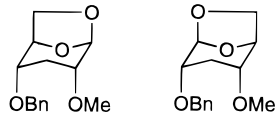
Received June 27, 1997[⊗]

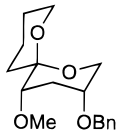
The synthesis of spiroacetals [3*R**,5*S**,6*S**]-3-benzyloxy-5-methoxy-1,7-dioaxaspiro[5.5]undecane **3** and [3*R**,5*S**,6*S**]-3-methoxy-5-benzyloxy-1,7-dioaxaspiro[5.5]undecane **4,** where the substituents on the spiroacetal assembly are in a 1,3-diaxial orientation, is described. Epoxidation of unsaturated spiroacetal **5** using dimethyldioxirane showed greater preference for the α-epoxide **11** over the *β*-epoxide **12**. Treatment of the α-epoxide **11** with lithium diethylamide in tetrahydrofuran afforded both the allylic alcohol **7** and the homoallylic alcohol **13** in approximately equal amounts. Use of a nonpolar solvent (hexane) suppressed the isomerization of the allylic alcohol **7** to the homoallylic alcohol **13**, affording a 21:1 ratio of **7:13**. Coordination of an oxygen lone pair with the electron-deficient lithium center of the reagent sets up a transition state in which abstraction of a *syn*-proton and opening of the epoxide leads to stereoselective formation of allylic alcohol **7** with a pseudoaxial hydroxyl group at C-5. The hydroxyl group liberated in the epoxide rearrangement step was then used to direct a second epoxidation to the lower face of the alkene. Thus, treatment of alcohol **7** with *m*-CPBA buffered with sodium acetate afforded α-*syn*-epoxy alcohol **9**. Subsequent epoxide opening using lithium aluminum hydride proceeded smoothly, affording *syn*-3,5-diaxial diol **10** and 4,5-diol **22**. Epoxy alcohol **9** was then treated with sodium hydride and methyl iodide or benzyl bromide, affording methyl ether **23** or benzyl ether **24,** respectively. Reduction of methoxy epoxide **23** with lithium aluminum hydride then afforded alcohol **25** together with the regioisomeric alcohol **27**. Benzyloxy epoxide **24** afforded alcohols **29** and **31**. Finally benzylation of alcohol **25** afforded bis-ether **3** whereas methylation of alcohol **29** afforded bis-ether **4**. Spiroacetals **3** and **4** were screened for herbicidal activity and exhibited significant activity against the weeds *Avena fatua, Setaria viridis, Amaranthus retroflexus*, and *Chenopodium album* when applied preemergence. Bis-ethers **3** and **4,** which contain alkoxy groups anchored in a 1,3-diaxial orientation on a spiroacetal ring, represent the first examples of herbicides based on a spiroacetal ring system.

The production of agrochemicals is a multibillion dollar global industry involving a large number of the world's leading chemical companies. The herbicide market provides a major contribution to the agrochemical industry with several major classes of compound, e.g. triazines, amides, carbamates, and ureas, contributing to the overall market share.[1] Shell has evaluated and filed patents[2] for a range of herbicidal oxygen containing mono- or bicyclic ring systems which bear an aryloxy group *β* to a ring oxygen atom. It was established that by locking the conformation of the heterocycle such that the aryloxy substituent was axial or pseudoaxial, the herbicidal activity could be increased. Further examples of the cyclic ether class of herbicide were reported by Sammes et al.[3] based on an 8-oxabicyclo[3.2.1]octane ring system bearing benzyloxy and methoxy groups locked in axial positions by the oxymethylene bridge. Furneaux et al.[4] later recognized the structural similarity between the 8-oxabicyclo[3.2.1]octane derivatives developed by Sammes and a series of 1,6-anhydro-3-deoxyhexose derivatives that they had previously synthesized. They therefore initiated a synthesis of the bis-ethers **1** and **2** in order to evaluate their herbicidal activity.

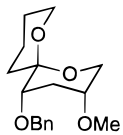


1

2



3



4

Given that the 1,7-dioxaspiro[5.5]undecane ring system is conformationally locked by the strong preference for the ring oxygens to adopt a bis-axial orientation with respect to each other,[5] it was decided to synthesize

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⊗ Abstract published in *Advance ACS Abstracts,* December 15, 1997.

(1) (a) Wood MacKenzie Consultants Ltd. *Reference Volume of the Agrochemical Service,* May 1994. (b) Mortimer, A. M. *Weed Control Handbook: Principles,* 8th ed.; Blackwell Scientific Publications: Oxford, 1990; p 1-42.

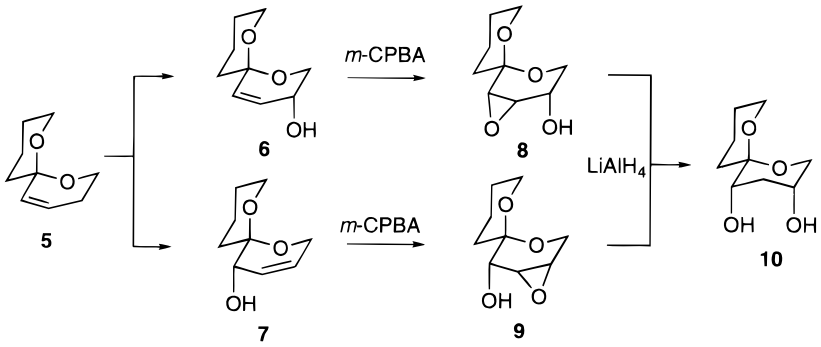
(2) Shell International Research, *Eur. Pat.* 0 081 893, 1983.

(3) Sammes, P. G.; Street, L. J.; Kirby, P. *J. Chem. Soc., Perkin Trans. 1,* **1983**, 2729.

(4) (a) Blattner, R. M.; Furneaux, R. H.; Mason, J.; Tyler, P. *Pestic. Sci.* **1991**, *31*, 419. (b) Furneaux, R. H.; Gainsford, G. J.; Shafizadeh, F.; Stevenson, T. T. *Carbohydr. Res.* **1986**, *146*, 113. (c) Henzell, R. F.; Furneaux, R. H.; Tyler, P. C. *Pestic. Sci.* **1990**, *30*, 59.

S0022-3263(97)01172-9 CCC: $15.00
Published on Web 01/07/1998

Scheme 1



spiroacetal analogues of the ribosugars **1** and **2** in order to evaluate their herbicidal activity. Introduction of axial benzyloxy and methoxy groups at C-3 and C-5 on the spiroacetal ring provides spiroacetal analogues **3** and **4** of the ribosugars **1** and **2**, which maintain the two important structural features of the carbohydrate-based herbicides: (i) the benzyloxy group is β to the ring oxygen and (ii) the C−O bond of the neighboring ring occupies an axial position on the ring bearing the alkoxy groups.

The presence of spiroacetals in a wide range of biologically active natural products has prompted a range of synthetic methods for their preparation largely based on the acid-catalyzed cyclization of dihydroxy ketones or compounds containing a masked carbonyl group.[6] The synthesis of spiroacetals **3** and **4**, however, requires placement of axial alkoxy groups at C-3 and C-5. Acid-catalyzed cyclization of an appropriately functionalized dihydroxy ketone precursor, however, would lead to competing formation of the corresponding diequatorial substituted ring system. The challenge of the present work, therefore, was to devise a method for functionalizing a 1,7-dioxaspiro[5.5]undecane ring system that avoided acidic conditions, which result in thermodynamically controlled equilibration of the spiro center. In line with our interest in the stereoselective functionalization of unsaturated spiroacetals, we undertook a synthesis of 3,5-diaxial substituted spiroacetals **3** and **4** making use of a base-induced rearrangement of an epoxyspiroacetal.[7] This latter rearrangement has hitherto been unreported on a 1,7-dioxaspiro[5.5]undecane ring system and offers a versatile method to functionalize spiroacetals in a stereocontrolled manner.

Results and Discussion

Our initial approach to the spiroacetal analogues **3** and **4** focused on the allylic oxidation of unsaturated spiroacetal **5**, which is readily prepared by the addition of the lithium acetylide of 1-trimethylsilyloxy-4-butyne to δ-valerolactone followed by partial hydrogenation and acid-catalyzed spirocyclization.[8] It was hoped that, depending on the choice of reagents, stereoselective allylic oxidation of olefin **5** could be effected with or without rearrangement of the double bond, leading to axial allylic alcohols **7** or **6,** respectively (Scheme 1). Hydroxyl-directed epoxidation of the allylic alcohols **6** or **7** would then provide epoxy alcohols **8** or **9**, respectively, which upon *trans*-diaxial ring opening with a hydride source should lead to the 3,5-diaxial diol **10**. Modification of this approach by introduction of a methyl or benzyl ether at an appropriate stage would then provide the desired spiroacetals **3** and **4**.

Having prepared olefin **5** using a thermodynamically controlled spirocyclization such that the most stable conformation was formed (in which each ring oxygen is axial with respect to the adjacent ring, thereby gaining maximum stability from the anomeric effect[5]), the allylic oxidation step was then investigated. Initial work focused on the allylic photooxidation of olefin **5**; however, use of a range of photosensitizers as well as chemically produced singlet oxygen afforded only recovered starting material.

Deslongchamps et al.[9] have successfully performed an allylic oxidation on a 1,7-dioxaspiro[5.5]undec-4-ene derivative of erythronolide A. Similar treatment of olefin **5** with selenium dioxide afforded only recovered starting material, and a number of selenium reagents, reoxidants, and reaction conditions also failed to effect the desired allylic oxidation. Alternative methods for achieving allylic oxidation of **5** such as CuBr/^{t}BuOOH, $Mn(OAc)_2$, $Hg(OAc)_2$, and CrO_3/dimethylpyrazole also met with no success.

Our attention next turned to the base-induced rearrangement of epoxide **11** as a method to prepare allylic alcohol **7** (Scheme 2). Given that the base-induced rearrangements of epoxides proceed stereoselectively via abstraction of the proton syn to the epoxide,[10] a stereoselective synthesis of alcohol **7** rested on a stereoselective epoxidation of olefin **5**. Treatment of spiroacetal olefin **5** with *m*-chloroperoxybenzoic acid (2 equiv) buffered with sodium acetate (2.1 equiv) using dichloromethane as solvent afforded the α-epoxide **11** and β-epoxide **12** in 42% and 33% yield, respectively. The major epoxide was

(5) (a) Kirby, A. J. *The Anomeric and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: New York, 1983. (b) *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; American Chemical Society Symposium Series, 539, American Chemical Society: Washington, DC, 1993. (c) Graczyk, P. P.; Mikolajczyk, M. *Top. Stereochem.* **1994**, *21*, 159. (d) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019.

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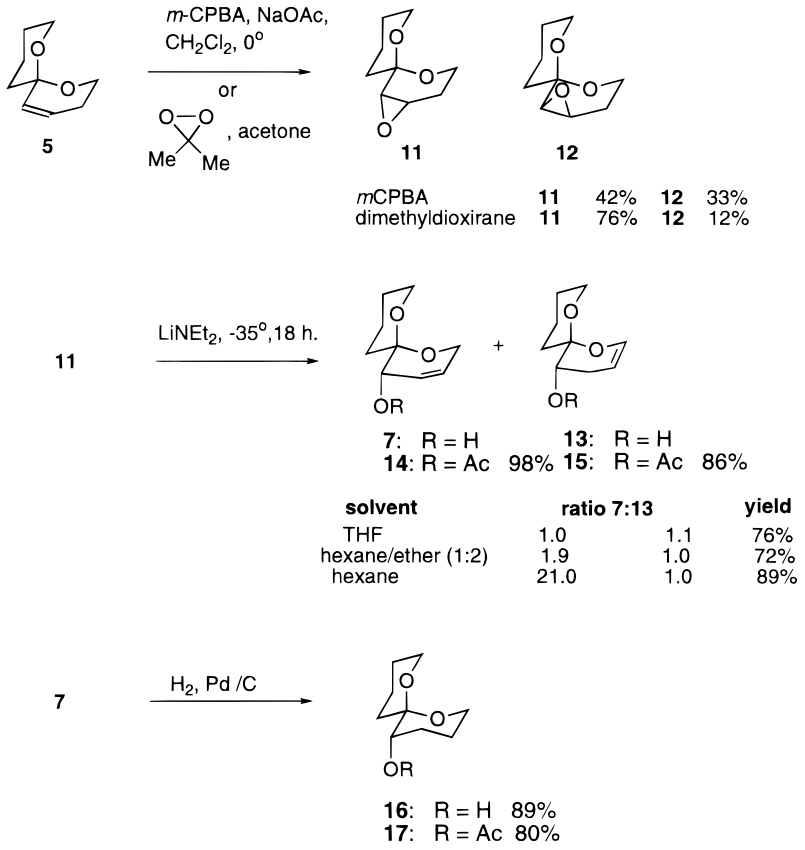
(11) Adams, W.; Bialas, J.; Hadjiorapogloui, *Chem. Ber.* **1991**, *124*, 2377.

Scheme 2



confirmed to be the α-epoxide **11** by subsequent transformations and ultimately X-ray crystallographic analysis of these derivatives (vide infra).

The epoxidation of **5** was then effected using dimethyldioxirane as it was felt that this more sterically sensitive oxidant would favor the formation of the desired α-epoxide **11**. Thus treatment of **5** with a solution of dimethyldioxirane[11] in acetone afforded epoxides **11** and **12** in 76% and 12% yield, respectively. As dimethyldioxirane is sensitive to steric factors, the oxygen is delivered chiefly to the lower less hindered α-face of the olefin **5** and this is reflected in the α:*β* epoxide product ratio of 6.3:1 compared to 1.3:1 using *m*-chloroperoxybenzoic acid. *m*-Chloroperoxybenzoic acid is capable of hydrogen bonding with oxygen substituents in the substrate; thus, a stabilized transition state such as that depicted in Figure 1 could be envisaged to be aiding attack from the more hindered *β*-face of olefin **5**.

Having successfully prepared epoxide **11**, its subsequent base opening to afford allylic alcohol **7** was investigated. Treatment of epoxide **11** with lithium diethylamide in tetrahydrofuran afforded the allylic alcohol **7** and homoallylic alcohol **13** in 37% and 39% yield, respectively.

In an attempt to optimize the yield of the allylic alcohol **7** at the expense of the homoallylic alcohol **13**, a variety of solvents was investigated. When epoxide **11** was isomerized using hexane/ether (1:2) as solvent, the allylic alcohol **7** and the homoallylic alcohol **13** were isolated in 47% and 25% yield, respectively. When hexane was employed as the solvent, the allylic alcohol **7** and the homoallylic alcohol **13** were isolated in 85% and 4% yield, respectively. Thus, use of a less polar solvent favors the formation of the allylic alcohol at the expense of the homoallylic alcohol. Coordination of an oxygen lone pair with the electron deficient lithium center of the reagent sets up a transition state (Figure 2) in which abstraction of a *syn*-proton and opening of the epoxide leads to stereoselective formation of allylic alcohol **7** with a pseudoaxial hydroxyl group at C-5. It is also of note that *β*-epoxide **12** failed to undergo analogous base-induced ring opening.

Allylic alcohol **7** and homoallylic alcohol **13** were converted to their corresponding acetate derivatives in order to confirm the assignment of the stereochemistry at C-5. Thus, treatment of alcohols **7** and **13** with acetic anhydride, triethylamine, and 4-(dimethylamino)pyridine (catalytic quantity) in dichloromethane afforded the acetates **14** and **15,** respectively. In the ^{1}H NMR spectrum recorded for allylic acetate **14**, 5-H resonated as a doublet at δ_H 4.85, ($J_{5,4}$ = 5.3 Hz). The magnitude

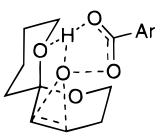


Figure 1.

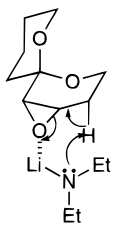
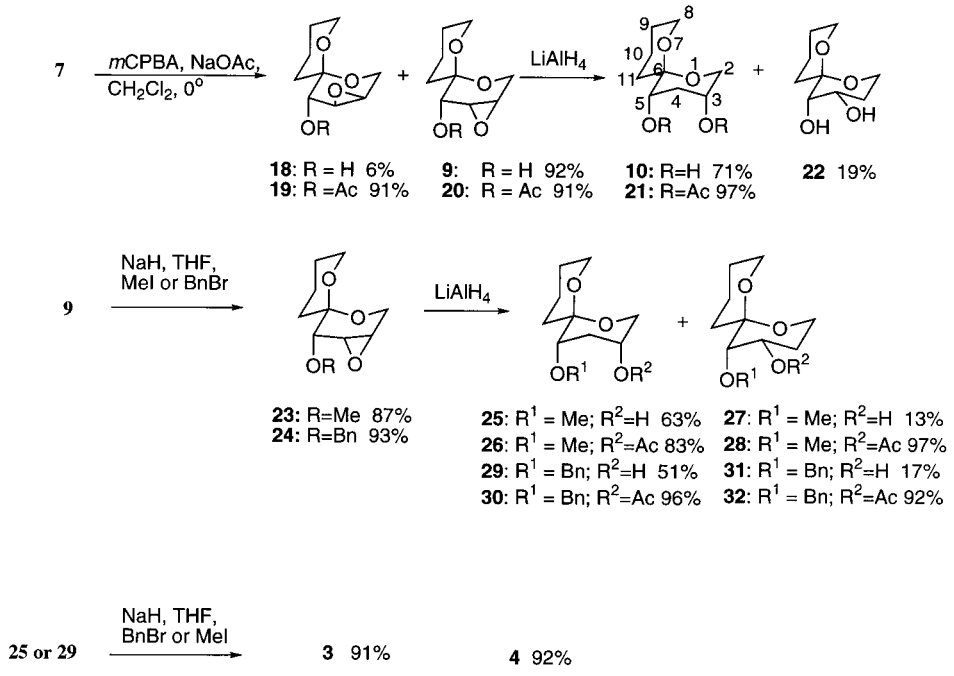


Figure 2.

Scheme 3



of the vicinal coupling suggested that 5-H adopts a pseudoequatorial position; therefore, the C-5 alkoxy substituent is pseudoaxial.

To confirm further the stereochemical environment of 5-H, the allylic alcohol **7** was converted to the saturated analogue **16** and subsequently saturated acetate **17**. Using methanol as solvent, allylic alcohol **7** was reduced under a hydrogen atmosphere over 5% palladium on charcoal to the saturated spiroacetal **16** in 89% yield. Conversion of the saturated alcohol **16** to the acetate derivative **17** was then effected in 80% yield by treatment with acetic anhydride and triethylamine. The ^{1}H NMR spectrum of **17** exhibited a one proton triplet[16] at δ_H 4.68 ($J_{5,4} = 2.9$ Hz) which is assigned to 5-H, thereby providing evidence that 5-H is equatorial.

After successfully preparing allylic alcohol **7,** its subsequent epoxidation to afford epoxy alcohols **9** and **18** was investigated (Scheme 3). It was envisaged that the directing effect of the hydroxyl group in alcohol **7** would direct a peroxy acid to the α-face of the olefin. Thus, treatment of allylic alcohol **7** with *m*-chloroperoxybenzoic acid buffered with sodium acetate in dichloromethane afforded *syn*-epoxy alcohol **9** and *anti*-epoxy alcohol **18** in 92% and 6% yield, respectively.

The NMR spectra of the acetate derivatives **20** and **19** did not aid the assignment of the stereochemistry; thus, crystals of **9** were grown for X-ray crystallographic analysis. The crystal structure[12] confirmed the syn relationship between the hydroxyl group at C-5 and the 3,4-epoxide for the major epoxide isolated. The unsubstituted pyran ring adopted a chair conformation with the oxygen atom of the epoxy-substituted ring assuming an axial orientation with respect to the unsubstituted ring, thereby gaining maximum stability from the anomeric effect.[5]

Upon conclusively establishing that the major epoxide formed from allylic alcohol **7** was the desired α-*syn*-epoxy alcohol **9**, subsequent epoxide opening to furnish *syn*-3,5-diaxial diol **10** was investigated. When conformational effects are not complicated by steric or polar effects, *trans*-diaxial reduction of the epoxide occurs to generate the axial alcohol[13] rather that the equatorial alcohol (Fürst−Plattner rule 1951). Treatment of *syn*-epoxy alcohol **9** with lithium aluminum hydride in tetrahydrofuran at room temperature for 12 h afforded *syn*-3,5-diaxial diol **10** and 4,5-diol **22** in 71% and 19% yield, respectively.

The ^{1}H NMR spectrum recorded for *syn*-3,5-diaxial diol **10** was assigned with the aid of 2D COSY and HETCOR experiments, and 4,5-diol **22** had identical physical and spectroscopic properties to those reported in the literature.[14] The diacetate derivative **21** of diol **10** was prepared using standard conditions to provide further confirmation of the stereochemistry of the substituents at C-3 and C-5, and the X-ray structure obtained for diacetate **21** confirmed the assignment of stereochemistry based on the NMR data.[12] The two tetrahydropyran rings assumed chair conformations with the oxygen atoms of the tetrahydropyran rings adopting positions axial with respect to the adjacent ring, thus gaining maximum stability from the anomeric effect.[5] The 1,3-diaxial orientation of the acetate groups in **21** and hence the hydroxyl groups in diol **10** was therefore conclusively assigned.

Having successfully cleaved the major epoxy alcohol **9** to afford the diaxial 3,5-diol **10** as the major product, the acid-catalyzed equilibration of the diaxial 3,5-diacetate **21** to the diequatorial 3,5-diacetate **33** was investigated (Scheme 4).[6] Treatment of a solution of diaxial 3,5-diacetate **21** in dichloromethane with camphorsulfonic acid (2.0 equiv) under reflux for 90 h afforded diaxial 3,5-diacetate **21** and diequatorial 3,5-diacetate **33** in 56% and 37% yield, respectively.

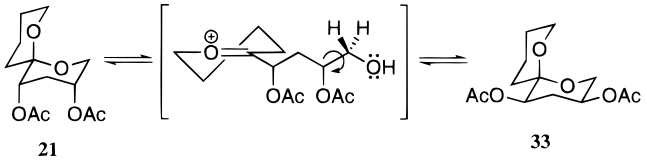
Our attention then turned to completing the synthesis of the spiroacetal bis-ethers **3** and **4**. Treatment of a

(12) For full details of the crystal structure, see: Brimble, M. A.; Johnston, A. D.; Hambley, T. W.; Turner, P. *Aust. J. Chem.* **1997**, *50*, 123.

(13) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1956**, 3289.

(14) Brimble, M. A. and Nairn, M. R., *Aust. J. Chem.* **1993**, *46*, 195.

Scheme 4



CSA, CH_2Cl_2, reflux, 90 h., **21** 56% **33** 37%

solution of *syn*-epoxy alcohol **9** with sodium hydride followed by methyl iodide or benzyl bromide afforded the methyl ether **23** or the benzyl ether **24** in 87% and 93% yield, respectively. The methoxy alcohols **25** and **27** were then prepared via reductive opening of *syn*-methoxy epoxide **23** with lithium aluminum hydride in 63% and 13% yield, respectively.

To confirm that the major methoxy alcohol isolated was that in which the methoxy group at C-5 was axial and syn to the hydroxyl group at C-3, both methoxy alcohols **25** and **27** were converted to their acetate derivatives **26** and **28** under standard conditions in 83% and 97% yield, respectively. In methoxy acetate **26**, the stereochemistry for 3-H was assigned indirectly from the clean coupling patterns of 4ax-H and by analogy with the fact that hydride opening of *syn*-epoxy alcohol **9** afforded 3,5-diol **10** with the substituents in a *syn*-3,5-diaxial orientation. 4ax-H resonated as a double double doublet at δ_H 2.04 (J_{gem} = 15.5 Hz, $J_{4ax,5}$ = 3.3 Hz, and $J_{4ax,3}$ = 3.3 Hz), suggesting that 3-H was in a pseudoequatorial position and therefore 3-OAc was pseudoaxial. For methoxy acetate **28**, 5-H resonated as a doublet at δ_H 3.23 ($J_{5,4}$ = 2.2 Hz), suggesting that 5-H was in a pseudoequatorial orientation and that 4-H assumed an axial position.

The benzyloxy alcohols **29** and **31** were prepared via reductive ring opening of *syn*-benzyloxy epoxide **24** using lithium aluminum hydride in 51% and 17% yield, respectively. To confirm that the major benzyloxy alcohol isolated was that in which the benzyloxy group at C-5 was axial and syn to the hydroxyl group at C-3, benzyloxy alcohols **29** and **31** were converted to their acetate derivatives **30** and **32** under standard conditions in 96% and 92% yield, respectively. Assignment of stereochemistry for benzyloxy acetate **30**, however, was provided upon conversion to the methyl ether **4** (vide infra).

The ^{1}H NMR spectrum for benzyloxy acetate **32** exhibited a doublet at δ_H 3.52 ($J_{5,4}$ = 2.5 Hz) assigned to 5-H, suggesting that 5-H was in a pseudoequatorial orientation. 4-H resonated as a double double doublet at δ_H 5.28 ($J_{4,3ax}$ = 12.2 Hz, $J_{4,3eq}$ = 4.8 Hz, and $J_{4,5}$ = 2.5 Hz), establishing that 4-H was in a pseudoaxial orientation. Hence, the stereochemistry of **32** was established to be that in which the benzyloxy group at C-5 was axial and the acetate at C-4 was equatorial.

Following the successful synthesis of methoxy alcohol **25** and benzyloxy alcohol **29**, subsequent conversion to the bis-ethers **3** and **4** was effected. Treatment of methoxy alcohol **25** in tetrahydrofuran, with sodium hydride, followed by benzyl bromide afforded bis-ether **3** in 91% yield. In the ^{1}H NMR spectrum for **3**, 5-H resonated as a double doublet at δ_H 3.01 ($J_{5,4eq}$ = 4.9 Hz, $J_{5,4ax}$ = 4.2 Hz), suggesting that 5-H was in a pseudoequatorial orientation and that the methoxy group at C-5 was in a pseudoaxial position as desired. 4ax-H resonated as a double double doublet at δ_H 1.97 (J_{gem} = 14.4 Hz, $J_{4ax,5}$ = 4.2 Hz and $J_{4ax,3}$ = 4.2 Hz), suggesting that 3-H was in a pseudoequatorial position. 4eq-H resonated as a double double double doublet at δ_H 2.04 (J_{gem} = 14.4 Hz, $J_{4eq,5}$ = 4.9 Hz, $J_{4eq,3}$ = 4.9 Hz, and $J_{4eq,2eq}$ = 1.5 Hz), providing further evidence that 3-H was pseudoequatorial and that the benzyloxy group at C-3 was pseudoaxial, as desired.

Table 1. Postemergent Weed Control 13 days after Treatment

		percent weed control			
analogue	rate, g ai/ha	AMARE	CHEAL	AVEFA	SETVI
3	2000	0	0	0	65
4	2000	65	65	35	65

Table 2. Preemergent Weed Control 20 days after Treatment

		percent weed control			
analogue	rate, g ai/ha	AMARE	CHEAL	AVEFA	SETVI
3	2000	0	0	65	90
4	2000	65	90	90	90

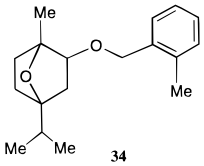
Treatment of a solution of benzyloxy alcohol **29** in tetrahydrofuran, with sodium hydride, followed by methyl iodide afforded bis-ether **4** in 92% yield. In the ^{1}H NMR spectrum for **4**, 5-H resonated as a double doublet at δ_H 3.18 ($J_{5,4ax}$ = 4.2 Hz and $J_{5,4eq}$ = 3.9 Hz), suggesting that 5-H was in a pseudoequatorial position and that the benzyloxy group at C-5 was in a pseudoaxial position as desired. 4ax-H resonated as a double double doublet at δ_H 1.92 (J_{gem} = 14.6 Hz, $J_{4ax,5}$ = 3.9 Hz and $J_{4ax,3}$ = 3.9 Hz), suggesting that 3-H was in a pseudoequatorial position and 4eq-H resonated as a double double double doublet at δ_H 2.09 (J_{gem} = 14.6 Hz, $J_{4eq,5}$ = 4.2 Hz, $J_{4eq,3}$ = 4.2 Hz, and $J_{4eq,2eq}$ = 1.6 Hz), providing further evidence that the methoxy group at C-3 was pseudoaxial as desired.

After successfully synthesizing the spiroacetal bis-ethers **3** and **4**, preliminary screening for herbicidal and plant growth regulatory activity was investigated. Compounds were tested in glasshouses at ZENECA Research Station at Jealotts Hill, Berkshire, UK. Those showing herbicidal activity progressed to screens in which they were applied both pre- and postemergence to four weeds. Weeds included in the tests were AVEFA, *Avena fatua* (Wild oat); SETVI, *Setaria viridis* (Green foxtail); AMARE, *Amaranthus retroflexus* (Redroot pigweed); and CHEAL, *Chenopodium album* (Fat hen). The results are summarized in Tables 1 and 2.

Spiroacetal **4** at 2000 g of active ingredient per hectare applied preemergence, controlled *Avena fatua* (Wild oat), *Setaria viridis* (Green foxtail), and *Chenopodium album* (Fat hen) all at 90% weed control, but did not control *Amaranthus retroflexus* (Redroot pigweed). ZENECA advised that there appears to be potential for control of preemergent grasses and broadleaved weed; however previous ZENECA testing of related chemicals suggests that at lower application rates and in heavier soils **4** may not be as effective. Crop selectivity is also unlikely to be achieved.

Spiroacetal herbicide regioisomer **3** at 2000 g of active ingredient per hectare (ai/ha) was less potent than **4** and only controlled *Setaria viridis* (Green foxtail) at 90% weed control.

The closest commercial herbicide to the spiroacetals **3** and **4** is cinmethylin (SD 95481) **34**, a novel herbicide developed for the selective preemergence control of many annual grass weeds in a wide range of temperate and



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tropical crops.[15] Cinmethylin **34** inhibits meristematic growth both in roots and shoots of plants and is readily metabolized. The compound has low mammalian toxicity and shows no tendency to accumulate in the environment.

Conclusion

In summary, synthesis of the spiroacetal bis-ethers **3** and **4** in which the alkoxy groups are in a 1,3-diaxial arrangement has been achieved. Reductive ring opening of epoxides **23** and **24** followed by alkylation with methyl iodide or benzyl bromide afforded the required bis-ethers **3** and **4**. The precursor to these epoxides was obtained via stereocontrolled hydroxyl-assisted epoxidation of allylic alcohol **7**, which in turn was prepared via base-induced ring opening of α-epoxide **11** using lithium diethylamide. X-ray crystal structures obtained for **9** and **21** provided conclusive evidence for the assignment of stereochemistry at C-3 and C-5 throughout the synthesis. Further explanation for the herbicidal activity of spiroacetals **3** and **4** awaits a detailed understanding of the mode of action of these compounds as herbicides, which to date is unavailable. The herbicidal activity observed for **4** is encouraging and structural analogues of **4** will be prepared in due course in order to establish a more detailed structure−activity profile for this class of compound.

Experimental Section

General Experimental Procedures. Chemicals and reagents were purchased from the Aldrich Chemical Co. and used without further purification. Melting points were determined on a Kofler hotstage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 200 or 400 MHz and 50 or 100 MHz, respectively. All ^{13}C NMR spectra were assigned with the aid of DEPT (distortionless enhancement by polarization transfer) and HETCOR (heteronuclear correlation spectroscopy) experiments. Low-resolution mass spectra were recorded using an ionization potential of 70 eV, using chemical ionization with ammonia as the reagent gas, desorption electron impact (DEI), or desorption chemical ionization (DCI) with ammonia as reagent gas. Flash chromatography was performed using Merck Kieselgel 60 or Riedel-de Haen Kieselgel (both 230−400 mesh) with the indicated solvents. Thin-layer chromatography (TLC) was performed using 0.2 mm thick precoated silica gel plates (Merck Kieselgel 60 F_{254} or Riedel-de Haen Kieselgel S F_{254}). Compounds were visualized by ultraviolet fluorescence or by staining with iodine or vanillin in methanolic sulfuric acid. Spiroacetal **5** was prepared according to the published procedure.[8]

[4*S,5*S**,6*S**]- and [4*R**,5*R**,6*S**]-4,5-Epoxy-1,7-dioxaspiro[5.5]undecane (11 and 12). (a) Using *m*-chloroperoxybenzoic Acid.** A solution of (+)-1,7-dioxaspiro[5.5]undec-4-ene **5** (163 mg, 1.0 mmol) in dry dichloromethane (7 mL) was cooled to 0 °C in an ice/water bath. Sodium acetate (175 mg, 2.1 mmol) was added followed by *m*-chloroperoxybenzoic acid (750 mg, 50% w/w, 2.0 mmol) in five portions over 1 min. The reaction mixture was allowed to warm to room temperature and stirred for 48 h under a drying tube. After filtration through a short pad of Celite, the mixture was washed with sodium sulfite (10% w/v), saturated sodium hydrogen carbonate, and water and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a pale tan solid that was purified by flash chromatography using hexanes−ethyl acetate (8:2) as eluent to afford [4*S**,5*S**,6*S**]-epoxide **11** (77 mg, 42%) as colorless needles: mp 48−49 °C; IR (Nujol) 1274 [CO (epoxide)], 1010 (CO), 892 [CO (epoxide)] cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.47−1.78 (7 H, m, 9-, 10-, 11-CH_2, 3eq-H), 1.97−2.06 (1 H, m, 3ax-H), 2.76 (1 H, dd, $J_{5,4}$ = 4.0 Hz, $J_{5,3eq}$ = 0.9 Hz, 5-H), 3.29 (1 H, dd, $J_{4,5}$ = 4.0 Hz, $J_{4,3ax}$ = 4.5 Hz, 4-H), 3.39 (1 H, ddd, $J_{2eq,2ax}$ = 11.0 Hz, $J_{2eq,3ax}$ = 7.1 Hz, $J_{2eq,3eq}$ = 0.88 Hz, 2eq-H), 3.59−3.73 (3 H, m, 8-CH_2, 2ax-H); ^{13}C NMR ($CDCl_3$) 17.6, 22.7, 25.0, 31.9 (CH_2, C-3, C-9, C-10, C-11), 50.5 (CH, C-4), 52.9 (CH, C-5), 54.9 (CH_2, C-2), 60.9 (CH_2, C-8), 93.7 (C, C-6); MS (EI) *m*/*z* 170 (M^+, 3). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.27, H, 8.43. [4*R**,5*R**,6*S**]-Epoxide **12** (61 mg, 33%) was also generated as a colorless oil: IR (film) 2945, 2870 (CH), 1271 [CO (epoxide)], 1012 (CO), 896, 826 [CO (epoxide)] cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.45−1.78 (6 H, m, 9-, 10-, 11-CH_2), 1.84−1.92 (2 H, m, 3-CH_2), 3.01 (1 H, d, $J_{5,4}$ = 4.0 Hz, 5-H), 3.26−3.29 (1 H, m, 4-H), 3.36−3.41 (1 H, m, 2eq-H), 3.57−3.69 (2 H, m, 2ax-H, 8eq-H), 3.74 (1 H, ddd, $J_{8ax,8eq}$ = 11.3 Hz, $J_{8ax,9ax}$ = 11.3 Hz, $J_{8ax,9eq}$ = 2.7 Hz, 8ax-H); ^{13}C NMR ($CDCl_3$) 18.1, 24.8, 24.9, 34.5 (CH_2, C-3, C-9, C-10, C-11), 50.2 (CH, C-4), 54.9 (CH_2, C-2), 55.3 (CH, C-5), 60.9 (CH_2, C-8), 92.8 (C, C-6); MS (CI, NH_3) *m*/*z* 171 (M + H, 100); HRMS calcd for $C_9H_{14}O_3$ (M + H), 171.1021, found 171.1019.

(b) Using Dimethyldioxirane. To a solution of spiroacetal **5** (160 mg, 1.0 mmol) in acetone (10 mL) was added dimethyldioxirane[11] (11.0 mL, 1.1 mmol as a 0.1 mmol/mL solution in acetone) and the reaction mixture allowed to stir for 16 h at room temperature. Removal of the solvent under reduced pressure afforded a colorless oil, which was dissolved in dichloromethane and dried over sodium sulfate. Removal of the solvent under reduced pressure and purification by flash chromatography using hexanes−ethyl acetate (8:2) as eluent gave epoxide **11** (140 mg, 76%) and epoxide **12** (22 mg, 12%) which had identical analytical and spectroscopic properties to those reported above.

[5*S,6*S**]-1,7-Dioxaspiro[5.5]undec-3-en-5-ol and [5*S**,6*S**]-1,7-Dioxaspiro-[5.5]undec-2-en-5-ol (7 and 13).** To a solution of dry diethylamine (0.9 mL, 8.72 mmol) in dry hexane (40 mL) under a nitrogen atmosphere at −35 °C, was added dropwise *n*-butyllithium (3.3 mL of a 2.41 mol L^{-3} solution in hexane, 7.93 mmol), and the resultant suspension stirred for 0.5 h. To this was added [4*S**,5*S**,6*S**]-epoxide **11** (1.35 g, 7.93 mmol) via a closed solid addition tube. The suspension was allowed to warm to room temperature and stirred for an additional 16 h. After quenching with sodium dihydrogen phosphate solution (10% w/v), the reaction mixture was extracted with ethyl acetate, washed with water, and dried over sodium sulfate. Removal of the solvent under reduced pressure gave an orange oil that was purified by flash chromatography using hexanes−ethyl acetate (6:4) as eluent to afford [5*S**,6*S**]-alcohol **7** (1.15 g, 85%) as colorless needles: mp 54−56 °C; IR (Nujol) 3650−3210 (OH), 1655 (C=C), 1081, 1046, 1008 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.45−1.57 (3 H, m, 9-CH_2, 11ax-H), 1.64−1.79 (2 H, m, 10-CH_2), 1.94 (1 H, d, $J_{OH,5}$ = 10.3 Hz, O*H*), 1.96−2.01 (1 H, m, 11eq-H), 3.52 (1 H, dd, $J_{5,OH}$ = 10.3 Hz, $J_{5,4}$ 2.9 = Hz, 5-H), 3.65 (1H, ddd, $J_{8ax,8eq}$ = 11.3, $J_{8ax,9ax}$ = 11.3, $J_{8ax,9eq}$ = 3.1 Hz, 8ax-H), 3.71−3.75 (1 H, m, 8eq-H), 4.05 (1 H, d, $J_{2eq,2ax}$ = 16.4 Hz, 2eq-H), 4.12 (1 H, dd, $J_{2ax,2eq}$ = 16.4 Hz, $J_{2ax,3}$ = 1.8 Hz, 2ax-H), 5.89−5.90 (2 H, m, 3-H, 4-H); ^{13}C NMR ($CDCl_3$) 18.3, 24.9, 30.3 (CH_2, C-9, C-10, C-11), 60.2 (CH_2, C-2), 62.9 (CH_2, C-8), 66.9 (CH, C-5), 96.9 (C, C-6), 124.6, 128.7 (CH, C-3, C-4); MS (CI, NH_3) *m*/*z* 171 (M + H, 30), 153 (M + H − H_2O, 100), 101 (M − C_4H_5O, 45). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.51, H, 8.28. [5*S**,6*S**]-Alcohol **13** (66 mg, 4%) was generated as colorless prisms: mp 45−46 °C; IR (Nujol) 3700−3100 (OH), 1655 (C=C), 1017 (C−O) cm^{-1}; ^{1}H NMR

(15) Grayson, B. T.; Williams, K. S.; Freehauf, P. A.; Pease, R. R.; Ziesel, W. T.; Sereno, R. L.; Reinsfielder, R. E. *Pestic. Sci.* **1987**, *21*, 143.

(16) The observation of a triplet for 5-H suggests that **17** is a twisted chair due to the dihedral angles between 5-H and the two protons at C-4 (and therefore the coupling constants) being identical.

($CDCl_3$) 1.44 (1 H, ddd, $J_{11ax,11eq}$ = 13.5 Hz, $J_{11ax,10ax}$ = 13.5 Hz, $J_{11ax,10eq}$ = 4.7 Hz, 11ax-H), 1.50−1.81 (4 H, m, 9-, 10-CH_2), 1.91 (1 H, dddd, $J_{4eq,4ax}$ = 17.4 Hz, $J_{4eq,5}$ = 4.0 Hz, $J_{4eq,3}$ = 4.0 Hz, $J_{4eq,2}$ = 1.0 Hz, 4eq-H), 2.00−2.03 (2 H, m, 11eq-H and O*H*), 2.42 (1 H, dddd, $J_{4ax,4eq}$ = 17.4 Hz, $J_{4ax,5}$ = 4.5 Hz, $J_{4ax,3}$ = 2.5 Hz, $J_{4ax,2}$ = 2.5 Hz, 4ax-H), 3.58 (1 H, ddd, $J_{5,OH}$ = 8.5 Hz, $J_{5,4ax}$ = 4.5 Hz, $J_{5,4eq}$ = 4.0 Hz, 5-H), 3.66 (1 H, dt, $J_{8eq,8ax}$ = 11.5 Hz, $J_{8eq,9}$ = 1.9 Hz, 8eq-H), 3.79 (1 H, ddd, $J_{8ax,8eq}$ = 11.5 Hz, $J_{8ax,9ax}$ = 11.7 Hz, $J_{8ax,9eq}$ 3.2 Hz, 8ax-H), 4.65−4.68 (1 H, m, 3-H), 6.25 (1 H, br, d, $J_{2,3}$ = 6.2 Hz, 2-H); ^{13}C NMR ($CDCl_3$) 17.9, 24.9 (CH_2, C-9, C-10), 25.8 (CH_2, C-4), 29.4 (CH_2, C-11), 61.8 (CH_2, C-8), 68.5 (CH, C-5), 96.9 (C, C-6), 98.6 (CH, C-3), 139.9 (CH, C-2); MS (EI) *m*/*z* 170 (M^+, 8). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.30, H, 8.19.

[5*S,6*S**]-1,7-Dioxaspiro[5.5]undec-3-en-5-yl Acetate (14).** To a solution of [5*S**,6*S**]-alcohol **7** (22 mg, 0.13 mmol) in dichloromethane (2 mL) was added triethylamine (26 mg, 0.26 mmol), acetic anhydride (20 mg, 0.19 mmol), and 4-(dimethylamino)pyridine (3 mg). The reaction mixture allowed to stand at room temperature for 1 h and then quenched with water, extracted with dichloromethane, and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a pale yellow oil that was purified by flash chromatography using hexanes−ethyl acetate (9:1) as eluent to afford acetate **14** (27 mg, 98%) as a colorless oil: IR (film) 2943−2870 (CH), 1735 (C═O), 1081, 1046, 1025 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.38 (1 H, ddd, $J_{11ax,11eq}$ = 12.7 Hz, $J_{11ax,\ 10ax}$ = 12.7 Hz, $J_{11ax,10eq}$ = 4.6 Hz, 11ax-H), 1.50−1.62 (3 H, m, 9-CH_2, 10-H), 1.73−1.85 (2 H, m, 11eq-H, 10-H′), 2.04 (3 H, s, Ac), 3.65 (1 H, ddd, $J_{8ax,8eq}$ = 11.3 Hz, $J_{8ax,9ax}$ = 11.3 Hz, $J_{8ax,9eq}$ = 2.9 Hz, 8ax-H), 3.71−3.75 (1 H, m, 8eq-H), 4.14 (2 H, m, 2-CH_2), 4.85 (1 H, d, $J_{5,4}$ = 5.3 Hz, 5-H), 5.77−5.81 (1 H, m, 4-H), 6.03 (1 H, dt, $J_{3,4}$ = 10.2, $J_{3,2}$ = 2.4 Hz, 3-H); ^{13}C NMR ($CDCl_3$) 17.9 (CH_2, C-9), 20.9 (CH_3, Me), 24.8, 30.3 (CH_2, C-10, C-11), 60.1 (CH_2, C-2), 62.7 (CH_2, C-8), 67.7 (CH, C-5), 95.4 (C, C-6), 120.4 (CH, C-4), 130.8 (CH, C-3), 170.3 (C, C═O); MS (CI, NH_3) *m*/*z* 213 (M + H, 60). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.26; H, 7.60. Found: C, 61.97, H, 7.62.

[5*S,6*S**]-1,7-Dioxaspiro[5.5]undec-2-en-5-yl Acetate (15).** Acetate **15** was prepared from alcohol **13** (44 mg, 0.26 mmol), triethylamine (53 mg, 0.52 mmol), acetic anhydride (40 mg, 0.39 mmol), and 4-(dimethylamino)pyridine (3 mg) using the procedure described for acetate **14**. Removal of the solvent under reduced pressure gave a pale yellow oil that was purified by flash chromatography using hexanes−ethyl acetate (9:1) as eluent to afford acetate **15** (47 mg, 86%) as a colorless oil: IR (film) 3019−2850 (CH), 1727 (C═O), 1219 (CO) 1029 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.33−1.41 (1 H, ddd, $J_{11ax,11eq}$ = 14.1 Hz, $J_{11ax,10ax}$ = 14.1 Hz, $J_{11ax,10eq}$ = 4.5 Hz, 11ax-H), 1.51−1.64 (3 H, m, 9-CH_2 and 10-H) 1.76−1.86 (2 H, m, 10-H′, 11eq-H), 1.93 (1 H, dd, $J_{4eq,4ax}$ = 18.2, $J_{4eq,3}$ = 4.1 Hz, 4eq-H), 2.05 (3 H, s, Ac), 2.44 (1 H, dddd, $J_{4ax,4eq}$ = 18.2 Hz, $J_{4ax,5}$ = 4.7 Hz, $J_{4ax,3}$ = 2.3 Hz, $J_{4ax,2}$ = 2.3 Hz, 4ax-H), 3.63−3.67 (1 H, m, 8eq-H), 3.77 (1 H, ddd, $J_{8ax,8eq}$ = 11.6 Hz, $J_{8ax,9ax}$ = 11.6 Hz, $J_{8ax,9eq}$ = 2.9 Hz, 8ax-H), 4.69−4.71 (1 H, m, 3-H), 4.87 (1 H, d, $J_{5,4ax}$ = 4.7 Hz, 5-H), 6.27 (1 H, dd, $J_{2,3}$ = 5.2 Hz, $J_{2,4ax}$ = 2.3 Hz, 2-H); ^{13}C NMR ($CDCl_3$) 17.8, 24.8, 30.8 (CH_2, C-9, C-10, C-11), 21.1 (CH_3, Ac), 23.1 (CH_2, C-4), 61.5 (CH_2, C-8), 69.4 (CH, C-5), 94.8 (C, C-6), 98.7 (CH, C-3), 139.6 (CH, C-2), 170.4 (C, C═O); MS (EI) *m*/*z* 170 (M^+, 10). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.26; H, 7.60. Found: C, 62.21, H, 7.60.

[5*S,6*S**]-1,7-Dioxaspiro[5.5]undecan-5-ol (16).** To a solution of [5*S**,6*S**]-alcohol **7** (10 mg, 0.06 mmol) in methanol (5 mL) was added 5% palladium on charcoal (2 mg) and potassium carbonate (20 mg, 0.14 mmol) and the reaction flask was flushed with hydrogen. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 6 h. After filtration through a short Celite pad, the solvent was removed at reduced pressure to give a colorless oil that was purified by flash chromatography using pentane−diethyl ether (9:1) as eluent to afford spiroacetal **16** (9 mg, 89%) as colorless needles: mp 73−75 °C; IR (Nujol) 3620−3150 (OH), 1100, 1050, 1040 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.33−2.10 (11 H, m, 3-, 4-, 9-, 10-, 11-CH_2, O*H*), 3.42 (1 H, dt, $J_{5,OH}$ = 8.2 Hz, $J_{5,4}$ = 3.2 Hz, 5-H), 3.57−3.75 (4 H, m, 2-, 8-CH_2); ^{13}C NMR ($CDCl_3$) 18.1, 19.2, 24.9, 25.7, 30.9 (CH_2, C-3, C-4, C-9, C-10, C-11), 59.9, 60.6 (CH_2, C-2, C-8), 69.8 (CH, C-5), 96.2 (C, C-6); MS (CI, NH_3) *m*/*z* 173 (M + H, 30). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.83, H, 9.48.

[5*S,6*S**]-1,7-Dioxaspiro[5.5]undec-5-yl Acetate (17).** Acetate **17** was prepared from alcohol **16** (4 mg, 0.02 mmol), triethylamine (5 mg, 0.05 mmol), acetic anhydride (3 mg, 0.03 mmol), and 4-(dimethylamino)pyridine (1 mg) using the procedure described for acetate **14**. Removal of the solvent under reduced pressure gave a colorless oil that was purified by flash chromatography using pentane−diethyl ether (9:1) as eluent to afford acetate **17** (4 mg, 80%) as a colorless oil: IR (film) 3031−2843 (CH), 1728 (C═O), 1213 (CO), 1034 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.23−2.06 (10 H, m, 3-, 4-, 9-, 10-, 11-CH_2), 2.08 (3 H, s, Ac), 3.62−3.76 (4 H, m, 2-, 8-CH_2), 4.68 (1 H, t, $J_{5,4}$ = 2.9 Hz, 5-H); ^{13}C NMR ($CDCl_3$) 18.0, 19.7, 23.6, 24.9, 31.4 (CH_2, C-3, C-4, C-9, C-10, C-11), 21.2 (CH_3, Ac), 59.9, 60.5 (CH_2, C-2, C-8), 71.1 (CH, C-5), 94.8 (C, C-6), 170.4 (C, C═O); MS (CI, NH_3) *m*/*z* 215 (M + H, 100); HRMS calcd for $C_{11}H_{18}O_4$ (M + H) 215.1283, found 215.1290.

[3*S**,4*S**,5*S**,6*S**]-3,4-Epoxy-1,7-dioxaspiro[5.5]undecan-5-ol and [3*R**,4*R**,5*S**,6*S**]-3,4-Epoxy-1,7-dioxaspiro[5.5]undecan-5-ol (9 and 18).

A solution of [5*S**,6*S**]-olefin **7** (1.15 g, 6.76 mmol) in dry dichloromethane (50 mL) under a nitrogen atmosphere was cooled to 0 °C in an ice/water bath. Sodium acetate (1.11 g, 13.53 mmol) was added, followed by *m*-chloroperoxybenzoic acid (2.56 g, 50% w/w, 7.42 mmol) in five portions over 1 min. The reaction mixture was allowed to warm to room temperature and stirred for 72 h. After filtration through a short Celite pad, the mixture was washed with sodium sulfite (10% w/v), saturated sodium hydrogen carbonate, and water and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a white solid that was purified by flash chromatography using hexanes−ethyl acetate (6:4) as eluent to afford [3*S**,4*S**,5*S**,6*S**]-epoxide **9** (1.16 g, 92%) as colorless prisms: mp 129.5−131.5 °C; IR (Nujol) 3650−3100 (OH), 1270 (CO), 1085 (CO), 885 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.39 (1 H, ddd, $J_{11ax,11eq}$ = 14.0 Hz, $J_{11ax,10ax}$ = 14.0 Hz, $J_{11ax,10eq}$ = 5.2 Hz, 11ax-H), 1.48−1.70 (4 H, m, 9-, 10-CH_2), 1.87 (1 H, dt, $J_{11eq,11ax}$ = 14.0 Hz, $J_{11eq,10}$ = 2.8 Hz, 11eq-H), 2.37 (1 H, d, $J_{OH,5}$ = 11.1 Hz, O*H*), 3.34 (1 H, d, $J_{3,4}$ = 3.4 Hz, 3-H), 3.47−3.58 (3 H, m, 4-H, 5-H, 8ax-H), 3.65−3.68 (1 H, m, 8eq-H), 3.82 (1 H, d, $J_{2eq,2ax}$ = 13.4 Hz, 2eq-H), 3.93 (1 H, d, $J_{2ax,2eq}$ = 13.4 Hz, 2ax-H); ^{13}C NMR ($CDCl_3$) 18.1, 24.8 (CH_2, C-9, C-10), 29.9 (CH_2, C-11), 51.2 (CH, C-4), 51.9 (CH, C-3), 57.3 (CH_2, C-2), 61.8 (CH_2, C-8), 65.7 (CH, C-5), 95.2 (C, C-6); MS (CI, NH_3) *m*/*z* 187, (M + H, 100). The structure of this compound was also confirmed by X-ray crystallography.[12] Anal. Calcd for $C_9H_{14}O_4$: C, 58.06; H, 7.58. Found: C, 57.99, H,7.29. [3*R**,4*R**,5*S**,6*S**]-Epoxide **18** (75 mg, 6%) was also afforded as a colorless oil: IR (film) 3650−3000, (OH), 2943, 2860 (CH), 1260 (CO), 1036 (CO), 907, 805 [CO (epoxide)] cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.48−1.83 (6 H, m, 9-, 10-, 11-CH_2), 2.35 (1 H, d, $J_{OH,5}$ = 6.8 Hz, O*H*), 3.22 (1 H, dd, $J_{3,2eq}$ = 3.0 Hz, $J_{3,4}$ = 4.0 Hz, 3-H), 3.25 (1 H, d, $J_{4,3}$ = 4.0 Hz, 4-H), 3.66 (1 H, d, $J_{5,OH}$ = 6.8 Hz, 5-H), 3.70−3.77 (2 H, m, 8-CH_2), 3.92 (1H, dd, $J_{2eq,2ax}$ = 13.7 Hz, $J_{2eq,3}$ = 3.0 Hz, 2eq-H), 4.07 (1 H, d, $J_{2ax,2eq}$ = 13.7 Hz, 2ax-H); ^{13}C NMR ($CDCl_3$) 17.9, 24.7, 26.3 (CH_2, C-9, C-10, C-11), 49.3 (CH, C-3), 53.2 (CH, C-4), 60.2 (CH_2, C-2), 61.9 (CH_2, C-8), 68.9 (CH, C-5), 97.1 (C, C-6); MS (CI, NH_3) *m*/*z* 187 (M + H, 100). Anal. Calcd for $C_9H_{14}O_4$: C, 58.06; H, 7.58. Found: C, 58.16; H,7.46.

[3*R,5*S**,6*S**]-1,7-Dioxaspiro[5.5]undecane-3,5-diol and [4*S**,5*S**,6*S**]-1,7-Dioxaspiro[5.5]undecane-4,5-diol (10 and 22).** A solution of [3*S**,4*S**,5*S**,6*S**]-epoxide **9** (40 mg, 0.21 mmol) in dry tetrahydrofuran (3.0 mL) under a nitrogen atmosphere was cooled to 0 °C in an ice/water bath. Lithium aluminum hydride (35 mg, 0.92 mmol) was added in three portions over 1 min, and the reaction mixture allowed to stir at 0 °C for 1 h then room temperature for 12 h. After quenching with sodium dihydrogen phosphate solution (10% w/v), the reaction mixture was extracted with ethyl acetate, and the combined extracts were washed with water and dried over sodium sulfate. Removal of the solvent under reduced

pressure gave a colorless oil, which was purified by flash chromatography using hexanes−ethyl acetate (2:1) as eluent to afford [3*R**,5*S**,6*S**]-diol **10** (28 mg, 71%) as colorless plates: mp 59−60 °C; IR (film) 3750−3200 (OH), 2938, 2800 (CH), 1109, 1043 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.37 (1 H, ddd, $J_{11ax,11eq}$ = 13.5 Hz, $J_{11ax,10ax}$ = 13.5 Hz, $J_{11ax,10eq}$ = 4.7 Hz, 11ax-H), 1.52−1.85 (4 H, m, 9-, 10-CH_2), 1.94 (1 H, dddd, $J_{4eq,4ax}$ = 14.5 Hz, $J_{4eq,5}$ = 3.0 Hz, $J_{4eq,3}$ = 3.0 Hz, $J_{4eq,2eq}$ = 3.0 Hz, 4eq-H), 2.09 (1 H, dt, $J_{11eq,11ax}$ = 13.5 Hz, $J_{11eq,10}$ = 3.2 Hz, 11eq-H), 2.14 (1 H, ddd, $J_{4ax,4eq}$ = 14.5 Hz, $J_{4ax,5}$ = 3.0 Hz, $J_{4ax,3}$ = 3.0 Hz, 4ax-H), 3.45 (1 H, dd, $J_{5,OH}$ = 8.2, $J_{5,4}$ = 3.0 Hz, 5-H), 3.64−3.72 (4 H, m, 8-CH_2, 2eq-H, 3-H), 3.82 (1 H, dd, $J_{2ax,2eq}$ = 12.1 Hz, $J_{2ax,3}$ = 1.4 Hz, 2ax-H), 3.89 (1 H, br, s, 3-OH), 3.93 (1 H, d, $J_{OH,\ 5}$ = 8.2 Hz, 5-OH); ^{13}C NMR ($CDCl_3$) 18.1, 24.9 (CH_2, C-9, C-10), 30.8 (CH_2, C-4), 31.1 (CH_2, C-11), 60.9 (CH_2, C-8), 64.8 (CH_2, C-2), 65.3 (CH, C-3), 70.3 (CH, C-5), 96.6 (C, C-6); MS (CI, NH_3), *m*/*z* 189 (M + H, 60). Anal. Calcd for $C_9H_{16}O_4$: C, 57.44; H, 8.57. Found: C, 57.16, H, 8.70. [4*S**,5*S**,6*S**]-Diol **22** (8 mg, 19%) was also formed as colorless needles: 121−124 °C (lit.[14] mp 124−125 °C). Diol **22** had identical spectroscopic properties to those previously published.[14]

[3*S,5*R**,6*S**]-1,7-Dioxaspiro[5.5]undec-3,5-diyl Diacetate (33).** To a solution of [3*R**,5*S**,6*S**]-diacetate **21** (47 mg, 0.17 mmol) in dichloromethane (7.0 mL) was added (1*S*)−(+)-10-camphorsulfonic acid (80 mg, 0.34 mmol), and the resultant solution was heated under reflux for 90 h. Removal of the solvent under reduced pressure afforded a tan oil that was purified by flash chromatography using hexanes−ethyl acetate (6:4) as eluent to afford [3*R**,5*S**,6*S**]-diacetate (**21**) (28 mg, 56%) as colorless needles, which had identical physical and spectroscopic properties to those reported previously (vide supra), and [3*S**,5*R**,6*S**]-diacetate **31** (19 mg, 37%) as a colorless oil: IR (film) 1730 (C=O), 1079 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.40−1.97 (7 H, m, 9-, 10-, 11-CH_2, 4eq-H), 2.03 (3 H, s, Ac), 2.11 (3 H, s, Ac), 2.14−2.22 (1 H, m, 4ax-H), 3.44 (1 H, dd, $J_{2ax,2eq}$ = 10.8 Hz, $J_{2ax,3ax}$ = 10.8 Hz, 2ax-H), 3.68−3.80 (3 H, m, 2eq-H, 8-CH_2), 4.69 (1 H, dd, $J_{5,4ax}$ = 12.0 Hz, $J_{5,4eq}$ = 6.6 Hz, 5-H), 4.91 (1 H, dddd, $J_{3ax,4ax}$ = 10.8 Hz, $J_{3ax,2ax}$ = 10.8 Hz, $J_{3ax,2eq}$ = 5.6 Hz, $J_{3ax,4eq}$ = 5.6 Hz, 3-H); ^{13}C NMR ($CDCl_3$) 17.9, 24.0 (CH_2, C-9, C-10), 20.8, 21.9 (CH_3, 2 Ac), 27.3 (CH_2, C-4), 30.1 (CH_2, C-11), 61.4 (CH_2, C-8), 61.8 (CH_2, C-2), 65.7 (CH, C-3), 69.1 (CH, C-5), 95.3 (C, C-6), 170.1, 170.8 (C, 2 C=O); MS (CI, NH_3) *m*/*z* 273 (M + H, 70), 213 (M + H − CH_2-CO_2H + H, 75), 195 (15), 172 (42), 153 (100), 135 (25), 114 (35), 101 (80); HRMS calcd for $C_{13}H_{20}O_6$ (M + H) 273.1338, found 273.1338.

[3*S,4*S**,5*S**,6*S**]-3,4-Epoxy-5-methoxy-1,7-dioxaspiro-[5.5]undecane (23).** A solution of [3*S**,4*S**,5*S**,6*S**]-alcohol **9** (336 mg, 1.80 mmol) in dry tetrahydrofuran (10 mL), under an argon atmosphere, was cooled to 0 °C in an ice/water bath. Sodium hydride (46 mg, 1.80 mmol) was added, and the resultant suspension allowed to stir at 0 °C for 1.5 h. Methyl iodide (280 mg, 1.90 mmol) was added, the reaction mixture was allowed to warm to room temperature and stirred for 3 h. After quenching with sodium dihydrogen phosphate solution (10% w/v), the mixture was extracted with ethyl acetate, and the combined extracts were washed with water and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a pale yellow solid that was purified by flash chromatography using hexanes−ethyl acetate (6:4) as eluent to afford methyl ether **23** (314 mg, 87%) as colorless needles: mp 57−58 °C; IR (Nujol) 1253 [CO (epoxide)], 1190, 1173, 1115, 1083, 1038 (CO), 880 [CO (epoxide)] cm^{-1}; ^1H NMR ($CDCl_3$) 1.37 (1 H, ddd, $J_{11ax,11eq}$ = 13.7 Hz, $J_{11ax,\ 10ax}$ = 13.7 Hz, $J_{11ax,10eq}$ = 4.7 Hz, 11ax-H), 1.49−1.78 (4 H, m, 9-, 10-CH_2), 1.94 (1 H, dt, $J_{11eq,11ax}$ = 13.7 Hz, $J_{11eq,10}$ = 3.2 Hz, 11eq-H), 3.27 (1 H, d, $J_{5,4}$ = 4.6 Hz, 5-H), 3.28 (1 H, d, $J_{3,4}$ = 4.2 Hz, 3-H), 3.48 (1 H, dd, $J_{4,3}$ = 4.2, $J_{4,5}$ = 4.6 Hz, 4-H), 3.54 (3 H, s, Me), 3.58 (1 H, ddd, $J_{8ax,8eq}$ = 11.2 Hz, $J_{8ax,9ax}$ = 11.2 Hz, $J_{8ax,9eq}$ = 3.6 Hz, 8ax-H), 3.64−3.69 (1 H, m, 8eq-H), 3.84 (1 H, d, $J_{2eq,2ax}$ = 13.2 Hz, 2eq-H), 4.01 (1 H, d, $J_{2ax,2eq}$ = 13.2 Hz, 2ax-H); ^{13}C NMR ($CDCl_3$) 17.9, 24.7, 29.7 (CH_2, C-9, C-10 and C-11), 48.2 (CH, C-4), 49.7 (CH, C-3), 56.9 (CH_3, Me), 57.2 (CH_2, C-2), 61.5 (CH_2, C-8), 74.9 (CH, C-5), 94.5 (C, C-6); MS (CI, NH_3) *m*/*z* 201 (M + H, 100). Anal. Calcd for $C_{10}H_{26}O_4$: C, 59.99; H, 8.05. Found: C, 59.97, H, 8.20.

[3*S,4*S**,5*S**,6*S**]-5-Benzyloxy-3,4-epoxy-1,7-dioxaspiro-[5.5]undecane (24).** A solution of [3*S**,4*S**,5*S**,6*S**]-alcohol **9** (307 mg, 1.7 mmol) in dry tetrahydrofuran (10 mL) under an argon atmosphere was cooled to 0 °C in an ice/water bath. Sodium hydride (46 mg, 1.9 mmol) was added, and the resultant suspension was allowed to stir at 0 °C for 1 h. Benzyl bromide (310 mg, 1.8 mmol) was added, the reaction mixture was allowed to warm to room temperature and stirred for 24 h. After quenching with sodium dihydrogen phosphate solution (10% w/v), the mixture was extracted with ethyl acetate, and the combined extracts were washed with water and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a pale yellow oil that was purified by flash chromatography using hexanes−ethyl acetate (6:4) as eluent to afford benzyl ether **24** (423 mg, 93%) as colorless needles: mp 73.5−74 °C; IR (Nujol) 1254, 1197 (Ar−OCH_2), 1042 [CO (epoxide)], 995 (CO), 886 [CO (epoxide)] cm^{-1}; ^1H NMR ($CDCl_3$) 1.36 (1 H, ddd, $J_{11ax,11eq}$ = 13.7 Hz, $J_{11ax,10ax}$ = 13.7 Hz, $J_{11ax,10eq}$ = 4.6 Hz, 11ax-H), 1.47−1.78 (4 H, m, 9-, 10-CH_2), 2.02−2.06 (1 H, m, 11eq-H), 3.24 (1 H, d, $J_{3,4}$ = 4.2 Hz, 3-H), 3.35 (1 H, dd, $J_{4,3}$ = 4.2 Hz, $J_{4,5}$ = 4.2 Hz, 4-H), 3.38 (1 H, d, $J_{5,4}$ = 4.2 Hz, 5-H), 3.52−3.63 (2 H, m, 8-CH_2), 3.81 (1 H, d, $J_{2eq,2ax}$ = 13.2 Hz, 2eq-H), 4.01 (1 H, d, $J_{2ax,2eq}$ = 13.2 Hz, 2ax-H), 4.64 (1 H, d, $J_{A,B}$ = 12.2 Hz, OCH_AH_B-Ar), 4.85 (1 H, d, $J_{B,A}$ = 12.2 Hz, OCH_BH_A-Ar), 7.25−7.39 (5 H, m, Ar-H); ^{13}C NMR ($CDCl_3$) 17.9, 24.6, 29.8 (CH_2, C-9, C-10, C-11), 48.3 (CH, C-4), 49.7 (CH, C-3), 57.1 (CH_2, C-2), 61.3 (CH_2, C-8), 70.7 (CH, C-5), 72.0 (CH_2, OCH_2−Ar), 94.6 (C, C-6), 127.4, 127.6 (CH, Ar-C), 137.6 (C, Ar-C); MS (CI, NH_3) *m*/*z* 294 (M + NH_4, 12). Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.29. Found: C, 69.59, H, 7.50.

[3*R,5*S**,6*S**]-3-Benzyloxy-5-methoxy-1,7-dioxaspiro-[5.5]undecane (3).** To a solution of [3*R**,5*S**,6*S**]-alcohol **25** (81 mg, 0.4 mmol) in dry tetrahydrofuran (10 mL) was added sodium hydride (19 mg, 0.8 mmol) and the resultant suspension stirred at room temperature for 0.25 h. Benzyl bromide (86 mg, 0.5 mmol) was added and the suspension allowed to stir for a further 3 h, until complete by TLC. The reaction was quenched with sodium dihydrogen phosphate solution and the mixture extracted with ethyl acetate. The combined extracts were washed with water and dried over magnesium sulfate. Removal of the solvent under reduced pressure gave a tan oil that was purified by flash chromatography using hexanes−ethyl acetate (7:3) as eluent to afford bis-ether **3** (106 mg, 91%) as a colorless oil: IR (film) 2983, 2870 (CH), 1126, 1062, 1046, 1009 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.40 (1 H, ddd, $J_{11ax,11eq}$ = 13.7 Hz, $J_{11ax,10ax}$ = 13.7 Hz, $J_{11ax,10eq}$ = 4.4 Hz, 11ax-H), 1.49−1.78 (4 H, m, 9-, 10-CH_2), 1.97 (1 H, ddd, $J_{4ax,4eq}$ = 14.4 Hz, $J_{4ax,5}$ = 4.2 Hz, $J_{4ax,3}$ = 4.2 Hz, 4ax-H), 2.04 (1 H, dddd, $J_{4eq,4ax}$ = 14.4 Hz, $J_{4eq,5}$ = 4.9 Hz, $J_{4eq,3}$ = 4.9 Hz, $J_{4eq,2eq}$ = 1.5 Hz, 4eq-H), 2.15 (1 H, dt, $J_{11eq,11ax}$ = 13.7 Hz, $J_{11eq,10}$ = 2.6 Hz, 11eq-H), 3.01 (1 H, dd, $J_{5,4eq}$ = 4.9 Hz, $J_{5,4ax}$ = 4.2 Hz, 5-H), 3.43 (3 H, s, OMe), 3.59−3.76 (5 H, m, 3-H, 2-, 8-CH_2), 4.57−4.60 (2 H, m, OCH_2-Ar), 7.25−7.36 (5 H, m, Ar-H); ^{13}C NMR ($CDCl_3$) 17.8, 25.1 (CH_2, C-9, C-10) 28.6 (CH, C-4), 31.8 (CH_2, C-11), 57.4 (CH_3, OMe), 61.0 (CH_2, C-8), 62.5 (CH_2, C-2), 70.1 (CH, C-3), 70.2 (CH_2, O-CH_2-Ar), 78.4 (CH, C-5), 96.9 (C, C-6), 127.1, 127.3, 127.5, 128.1 (CH, Ar-C), 138.6 (C, Ar-C); MS (CI, NH_3) *m*/*z* 293 (M + H, 20). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.96, H, 7.95.

[3*R,5*S**,6*S**]-5-Benzyloxy-3-methoxy-1,7-dioxaspiro-[5.5]undecane (4).** To a solution of [3*R**,5*S**,6*S**]-alcohol **29** (189 mg, 0.67 mmol) in dry tetrahydrofuran (10 mL) was added sodium hydride (24 mg, 1.0 mmol) and the resultant suspension stirred at room temperature for 0.25 h. Methyl iodide (100 mg, 0.7 mmol) was added and the suspension allowed to stir for a further 2 h, until complete by TLC. The reaction was quenched with sodium dihydrogen phosphate solution, the mixture was extracted with ethyl acetate, and the combined extracts were washed with water and dried over magnesium sulfate. Removal of the solvent under reduced pressure gave a tan oil that was purified by flash chromatography using hexanes−ethyl acetate (7:3) as eluent to afford bis-ether **4** (181

mg, 92%) as a colorless oil: IR (film) 2934, 2869 (CH), 1127, 1097, 1046, 1010 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) 1.30 (1 H, ddd, $J_{11ax,11eq} = 13.5$ Hz, $J_{11ax,10ax} = 13.5$ Hz, $J_{11ax,10eq} = 4.3$ Hz, 11ax-H), 1.48−1.59 (3 H, 9-CH_2, 10-H or 10-H′), 1.73−1.81 (1 H, m, 10-H or 10-H′), 1.92 (1 H, ddd, $J_{4ax,4eq} = 14.6$ Hz, $J_{4ax,5} = 3.9$ Hz, $J_{4ax,3} = 3.9$ Hz, 4ax-H), 2.09 (1 H, dddd, $J_{4eq,4ax} = 14.6$ Hz, $J_{4eq,5} = 4.2$ Hz, $J_{4eq,3} = 4.2$ Hz, $J_{4eq,2eq} = 1.6$ Hz, 4eq-H), 2.19 (dt, $J_{11eq,11ax} = 13.5$ Hz, $J_{11eq,10} = 2.8$ Hz, 11eq-H), 3.18 (1 H, dd, $J_{5,4eq} = 4.2$ Hz, $J_{5,4ax} = 3.9$ Hz, 5-H), 3.25−3.28 (1 H, m, 3-H), 3.36 (3 H, s, OMe), 3.62−3.75 (4 H, m, 2-, 8-CH_2), 4.53 (1 H, d, $J_{A,B} = 12.9$ Hz, OC$H_A$$H_B$-Ar), 4.69 (1 H, d, $J_{A,B} = 12.9$ Hz, OC$H_A$$H_B$-Ar), 7.25−7.37 (5 H, m, Ar-H); ^{13}C NMR ($CDCl_3$) 17.9, 25.1, 25.4, 29.6 (CH_2, C-4, C-9, C-10, C-11), 56.4 (CH_3, OMe), 60.9 (CH_2, C-8), 61.7 (CH_2, C-2), 71.3 (CH_2, OCH_2-Ar), 72.9 (CH, C-3), 75.2 (CH, C-5), 96.9 (C, C-6), 127.3, 127.9, 128.0 (CH, Ar-C), 138.5 (C, Ar-C); MS (CI, NH_3) *m*/*z* 293 (M + H, 30). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.72, H, 8.39.

Biological Testing of Spiroacetals 3 and 4. Spiroacetals **3** and **4** were screened for herbicidal activity in glasshouses at ZENECA Research Station at Jealotts Hill, Berkshire, UK. Those showing herbicidal activity progressed to screens in which they were applied both pre- and postemergence to four weeds. Weeds included in the tests were: *A. fatua, S. viridis, A. retroflexus, and C. album*. Agral 90 at 0.1% v/v was added to each spray sample. There was one replicate per treatment. The experimental herbicides were applied as simple formulations pre- and postemergence at a rate of 2000 g ha^{-1}. Preemergence units contained seeds of the test species sown into sandy loam soil (1.0−1.5% organic matter). Postemergence treatments were applied at the 1.5−2.5 leaf growth stage of the test species. Applications were made using a laboratory sprayer with a track-mounted moving nozzle, using a spray volume equivelent to 1000 L ha^{-1}. Postemergence treatments were assessed 13 days after treatment, and preemergence treatments were assessed 20 days after treatment. Both of the herbicide solutions formed satisfactory spray solutions, with no settling-out, and there was no deposit on the spray nozzle prefilter. Following chemical application, the treated plants were removed to the glasshouses and grown on. Conditions were sunny and warm. The results are summarized in Tables 1 and 2.

Acknowledgment. We thank The Australian Research Council and The University of Sydney for Financial Support. We also thank ZENECA, UK, for the herbicide testing.

Supporting Information Available: ^1H NMR spectra for compounds **12, 17, 19, 26−28, 3−32** (400 MHz), and **33** (200 MHz), mass spectral fragmentation data for compounds **3, 4, 7, 9−21,** and **23−33**, and experimental procedures for **19−21** and **25−32** (16 pages)**.** This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO971172Q