Synthesis and Stereochemistry of Insect Derived Spiroacetals with Branched Carbon Skeletons

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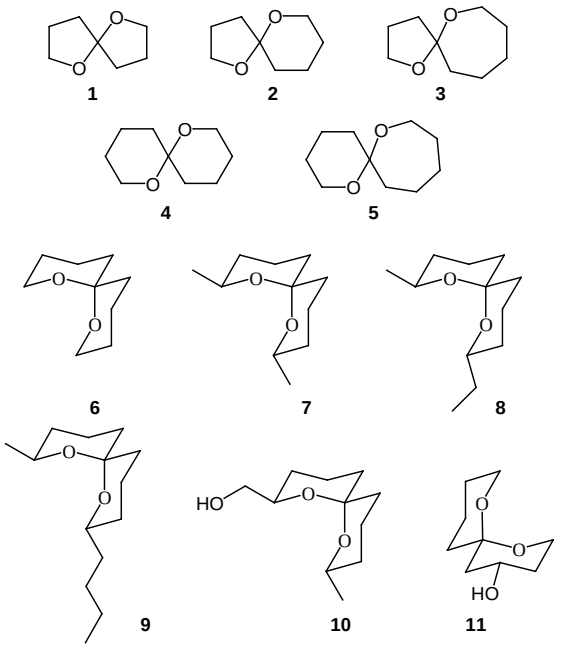
Abstract: About thirty constitutionally different spiroacetals have been characterised from insects but only three have branched carbon skeletons. Two are based on the 1,7-dioxaspiro[5.5]undecane system and are certain stereoisomers of the 2,4,8-trimethyl derivative, from the aposematic shield bug, *Cantao parentum* (White), and a 2,2,8-trimethyl derivative from the rove beetle, *Ontholestes murinus* (L). The 1,6-dioxaspiro[4.5]decane system is represented by a stereoisomer of the 2,3,7-trimethyl derivative in the *Cantao* species. The elucidation of their structures and stereochemistry by spectroscopy, synthesis and enantioselective gas chromatography is described.

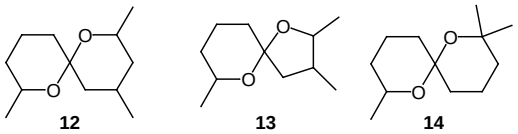
Key words: branched spiroacetals, *Cantao parentum*, *Ontholestes murinus*, enantioselective gas chromatography, enantioselective synthesis

Introduction

Spiroacetals are widely distributed in nature[1] and relatively simple spiroacetals are important components of glandular secretions of higher insects,[2] and have been principally described from the orders Coleoptera (beetles), Diptera (flies)[3] and Hymenoptera (bees and wasps). This group of about thirty different structures,[2] not including stereoisomers, represents volatile, less polar constituents of insect secretions and some of these spiroacetals are utilised for intra-specific or inter-specific communication. Five spiroacetal systems have been identified from insects − 1,6-dioxaspiro[4.4]nonanes, 1,6-dioxaspiro[4.5]decanes, 1,6-dioxaspiro[4.6]undecanes, 1,7-dioxaspiro[5.5]undecanes and 1,7-dioxaspiro[5.6]dodecanes (**1**−**5**),and the characterised members are very predominantly odd-numbered in carbon, e.g. **6** and **7.** Even-numbered variants are occasionally present, e.g. **8** and **9**, but at a comparatively low level. Functionalisation appears to be restricted to hydroxylation, e.g. **10** and **11** which at low level accompany the parent spiroacetals.[2]

Spiroacetals were, until recently, unknown from Hemiptera (an order which includes insects commonly known as bugs), and the lower insect orders. In addition, no spiroacetal with a branched carbon chain had been reported from the insect kingdom, and hence our recent brief reports[4−6] substantially extended our knowledge of the type, origin and possibly the evolutionary position of insect generated spiroacetals, as well as helped in confirming a diversified biosynthetic capability for certain insect species. We now describe our studies which led to the identification of a number of stereoisomers of the 2,4,8-trimethyl-1,7-dioxaspiro [5.5]undecane system **12,** and an isomer of the 2,3,7-trimethyl-1,6-dioxaspiro[4.5]decane system **13** from the aposematic shield bug, *Cantao parentum* (White), and a 2,2,8-trimethyl-1,7-dioxaspiro[5.5]undecane **14** from the rove beetle, *Ontholestes murinus* (L), in addition to a number of previously characterised spiroacetals.



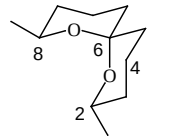


Results and Discussion

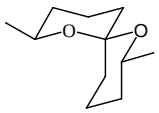
(a) Spiroacetals from the Aposematic Shield Bug, *Cantao parentum* (White)

During the course of a general investigation of the scent-gland chemistry of true bugs, attention was directed to the shield bug *Cantao parentum* (White) (Hemiptera: Scutelleridae), the only Australian representative of the four member *Cantao* genus.[7] *C. parentum* specimens are generally located in aggregations around a berry cluster of *Mallotus philippensis* (Lam.) (Euphorbiaceae), a rainforest tree of Australasia commonly known as the 'Red Kamala'. These aposematic insects, resplendent in an orange shield with contrasting black spots, are not regarded as a pest of any commercial crop. Adult bugs possess an unusual dorsal abdominal gland (DAG) system,[8,9] the flap component of which can be rapidly opened and closed, exposing the inner glandular surface from which volatiles are released. The DAG morphology is similar to that described from *Tectocoris diophthalmus* (Hemiptera: Scutelleridae), the cotton harlequin bug of Queensland.[9] GC-MS examinations of the dichloromethane extract of excised DAG's of both male or female bugs were conducted and a representative gas chromatograph is shown in Figure 1. The eight components of interest are labelled **(*A*)**–**(*H*)**, with increasing retention time. The elucidation of their structure and stereochemistry now follows, and it emerges that all eight are spiroacetals.

The mass spectrum of **(*A*)** indicated an apparent molecular weight of 184, a loss of methyl (*m*/*z* 169) and a spiroacetal-like fragmentation pattern.[2,10] This spectrum matched very closely that of authentic (*E*,*E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane[11] and retention time comparisons and co-injection studies with an authentic sample,[12] utilising a cyclodextrin-based phase, confirmed this structure and established the (2*S*,6*R*,8*S*)-configuration for **15**. This is the stereochemistry uniformly found for this component from insect sources.[2] Component **(*B*)** was initially suspected to be the (*E*,*Z*)-diastereomer **16,** which often accompanies the (*E*,*E*)-diastereomer in insects,[2,3] but retention time comparisons with the authentic (*E*,*E*), (*E*,*Z*) and (*Z*,*Z*)-diastereomers of 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane[13,14] disproved this.



(*E*,*E*)-(2*S*,6*R*,8*S*)-**15**



(*E*,*Z*)-**16**

The EIMS of **(*B*)** however, resembled those for the above diastereomers in that the same ions were present but with noticeably different relative intensities of some ions. These similarities suggested that if **(*B*)** were a dimethyl-1,7-dioxaspiro[5.5]undecane, the methyl groups were located in different rings, as otherwise additional ions, 14 amu greater than those actually observed, would have been observed[2] (see Figure 2). Comparisons of the EIMS with those for other known spiroacetals with M = 184, of different ring sizes, were also not encouraging.[4] These facts led us to the view that **(*B*)** was possibly a 2,10-dimethyl-1,7-dioxaspiro[5.5]undecane (see **18**, **19**, **21** in Scheme 1) which harmonises with our structural deductions for other components, e.g. **(*C*)** and **(*D*)**. This possibility was investigated by the synthesis of members of this system, as shown below in Scheme 1. Firstly, hydroxyenone **17**[5] was transformed to a mixture of spiroacetals **18** and **19**, but the retention times of both were considerably longer than that for the natural component **(*B*)**. Hydrazone **20**,[5] (described later in Scheme 7) was then alkylated with racemic 3-(tetrahydropyran-2′-yl)-1-iodobutane and further processed as shown in Scheme 1 to provide **21** along with a mixture of **18** and **19** as well. Necessarily **21** is the (2*S*,6*S*,10*R*) isomer and again was shown by direct GC-MS comparisons to differ from the natural component **(*B*)**. A diagnostic ion in the EIMS of each of **18**, **19** and **21**

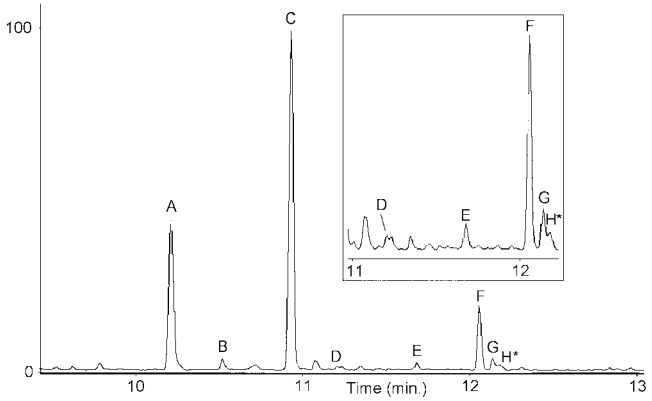
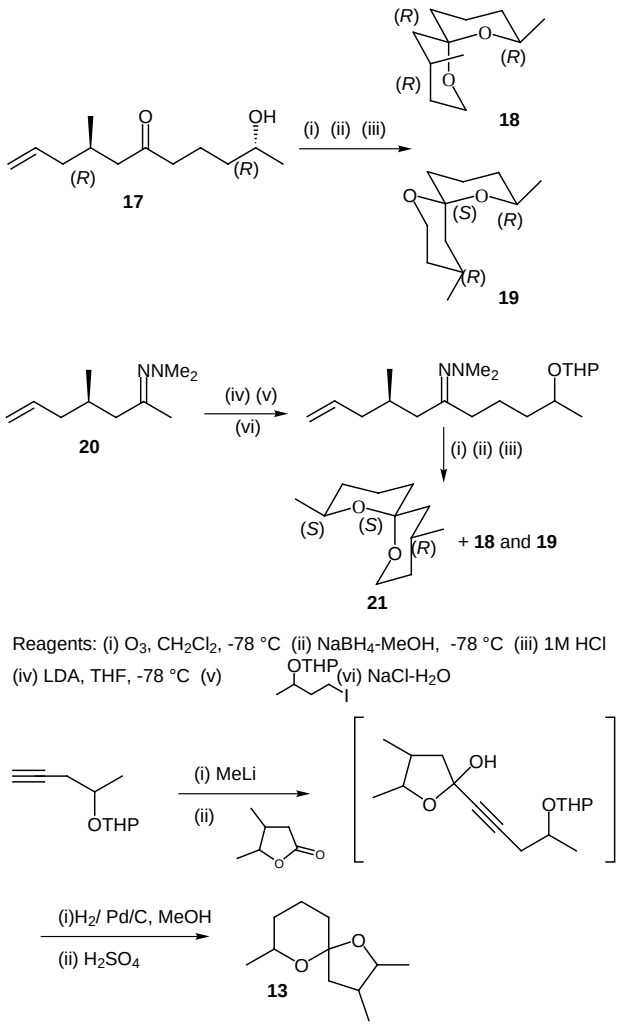


Figure 1 Gas chromatograph of dorsal abdominal gland extract from male *Cantao parentum* (White). *Column and conditions*: 30-m DB5 capillary column (J&W). Temperature programmed, 40 °C, 2 min then 10 °C/min to 270 °C. (*Compound H co-elutes with anisaldehyde on this column)

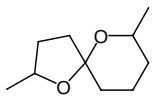
is *m*/*z* 139, attributable to the methylated analogue (β on the *exo*-cyclic double bond) of the *m*/*z* 125 ion from **7**, (see Figure 2). Such an ion is not present in the EIMS of component **(*B*)**, and consequently **(*B*)** is not an isomer of 2,10-dimethyl-1,7-dioxaspiro[5.5]undecane. Similar arguments apply to the 2,11-dimethyl system, which can also be excluded. Furthermore, on the basis of the mass spectral ions shown in Figure 2, an isomer of the 2,9-dimethyl-1,7-dioxaspiro[5.5]undecane system would be expected to exhibit an ion with *m*/*z* 154. No such ion is present in the EIMS of **(*B*)**.



Scheme 1

Subsequently, careful scrutiny of very low-level components of shorter retention times (9 min) led to the identification of an isomer of 2,7-dimethyl-1,6-dioxaspiro[4.5]decane, **22**,[15] by chromatographic and mass spectral comparisons with an authentic sample (from the collections of Dr. J.A. Lewis and Dr. E.N. Lawson). Curiously, this appears to be the first time this spiroacetal system has been identified from a natural source. General considerations of the EIMS of such spiroacetals,[10,16] and comparisons with that of component **(*B*)** raised the possibility that the latter could be an isomer of either the 2,3,7- or 2,4,7-trimethyl-1,6-dioxaspiro[4.5]decane systems. No member of these structural classes has been identified from a natural source. For purposes of comparisons, a mixture of stereoisomers of the 2,3,7-trimethyl system **13** was acquired as shown in Scheme 1. One of these isomers corresponded with component **(*B*)** by GC-MS and co-elution studies on both DB5 and cyclodextrin-based columns. The mass spectra of this isomer matches that of **(*B*)**. Further synthesis of the 2,3,7-trimethyl system **13** are now being conducted to establish the relative and absolute stereochemistry of this novel, carbon-branched spiroacetal system and will be described at a later date.

The mass spectra of components **(*C*)**−**(*H*)** indicated an apparent molecular weight of 198 for all, but of these, only the spectrum of **(*E*)** exhibited both M − CH_3 (*m*/*z* 183) and M − CH_2CH_3 (*m*/*z* 169) ions, suggesting that **(*E*)** was a diastereomer of the previously encountered[2] and synthesised[14] 2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane. Appropriate comparisons with an authentic sample of known chirality[14] confirmed that **(*E*)** was the (*E*,*E*)-diastereomer with the (2*S*,6*R*,8*S*) configuration **23.**



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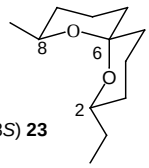


(2*S*,6*R*,8*S*) **23**

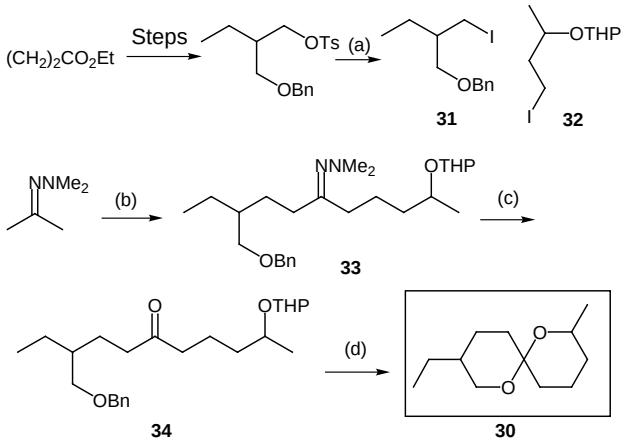
Components **(*C*)**, **(*D*)**, **(*F*)**, **(*G*)** and **(*H*)** were then considered, and it was observed that their mass spectra (with apparent M^+ of 198) exhibited more or less the same ions and these were consistent with a spiroacetal arrangement.[2] However, the relative intensities of common ions were often very different. Components **(*C*)** and **(*D*)** have very similar mass spectra which differ markedly from the mass spectra of **(*F*)** and **(*G*)** and **(*H*)**. In **(*C*)**−**(*H*)** (excepting ***(E)***) side-chain loss seems to be restricted to M − CH_3, as all exhibit *m*/*z* 183. Attention was initially directed to the major gland component **(*C*)** and GC-HRMS established the molecular formula $C_{12}H_{22}O_2$ (calcd. for $C_{12}H_2O_2$, 198.1618; obsvd, 198.1629).

Component **(*C*)**, in addition to the weak M − CH_3 ion (*m*/*z* 183), incorporated characteristic fragments[2,10] at *m*/*z* 112 and 115, which indicated the presence of a methylated tetrahydropyran or an oxepane as a partial structure. The fragments *m*/*z* 126 and 129 pointed to a homologous structure for the alternate ring, and the difference of 3 amu in the two sets of fragments demonstrated that methylene groups were adjacent to the spiro centre. This is emphasised by the structures of the ions anticipated[2] from the candidate spiroacetals below, (Figure 2) and on this basis, trimethylspiroacetals **25** and **26** but not **24**, would be

structural possibilities. Spiroacetal **24** would not exhibit a fragment at *m*/*z* 112, which is a prominent ion in component **(*C*)**.

Comparisons of mass spectra and retention times with those of known spiroacetals **27**–**29**[17] eliminated these as structures for ***(C)*** and left no feasible options based on an unbranched carbon skeleton. The absence of an observable ion at *m*/*z* 169 (M − 29) indicated the absence of an ethyl group α to oxygen, although location β to oxygen could not be unequivocally dismissed, on the basis of the mass spectra of compounds related to the talaromycins.[18] Consequently, we synthesised the ethyl substituted spiroacetal system **30**, as a diastereomeric mixture, by the route shown in Scheme 2. Two diastereomers were formed in almost equal amounts (spiro carbon shifts of δ = 95.76 and 95.29) but there were significant differences between their EIMS and that of the natural component **(*C*)**. Very weak (M − 29) ions (*m*/*z* 169) were observed in the EIMS of both synthesised isomers, but were lacking from the spectrum of component **(*C*)**.

We then returned to candidate structures **25** and **26**, whose important likely mass spectral fragmentations were summarised in Figure 2. With respect to the 2,3,8-trimethyl-1,7-dioxaspiro[5.5]undecane system **25**, we were synthesising 2,3,8-trialkyl derivatives for other purposes,[19] and were able to utilise (*R*)-citronellene (**35**) to acquire a suite of trimethylspiroacetals of constitution **25** in two ways.



Reagents and conditions: (a) NaI/acetone; (b) i. BuLi/THF, −78 °C, ii. iodide **31,** iii. LDA/THF, −78 °C, (iv) iodide **32**; (c) SiO_2/EtOAc/hexane/H_2O; (d) i. H_2/Pd-C/EtOH, ii. TsOH/MeOH

Scheme 2

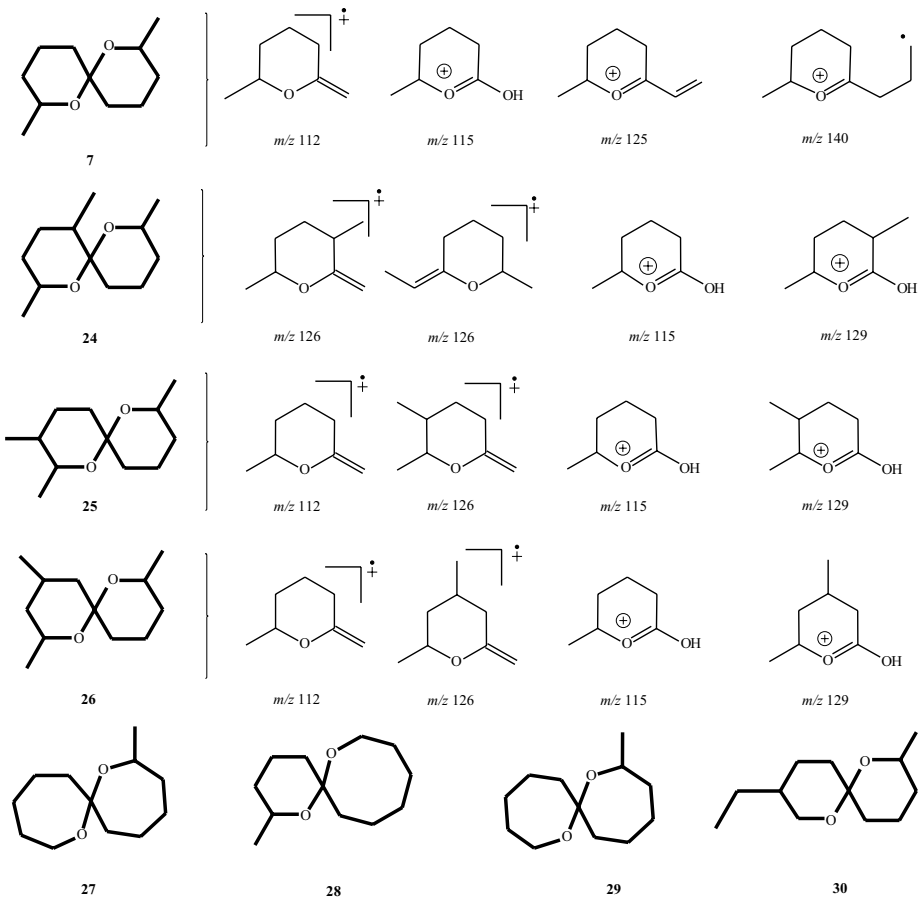
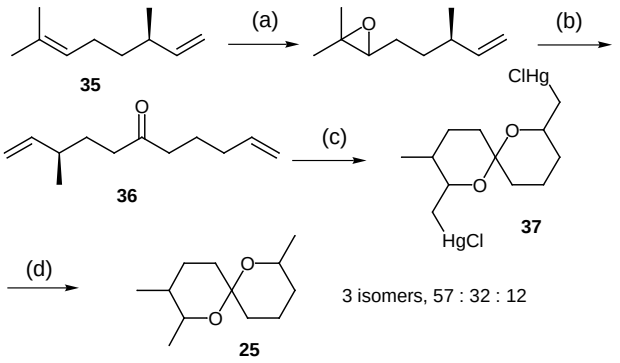


Figure 2 Some spiroacetal systems and likely important mass spectral fragment ions

Hydroxymercuration-cyclisation of dienone **36**, under (acidic) reversible conditions,[14] followed by reduction with $NaBH_4$ in the normal way, furnished three spiroacetals, as shown below (Scheme 3).



Reagents and conditions: (a) *m*-CPBA/CH_2Cl_2; (b) i. HIO_4/H_2O, ii. $CH_2=CH(CH_2)_2CH_2MgBr/H_3O^+$, iii. Swern (or TPAP), (c) i. $Hg(OAc)_2/H_3O^+$/THF, ii. NaCl; (d) $NaBH_4/H_2O$/THF/NaOH/TBEAc

Scheme 3

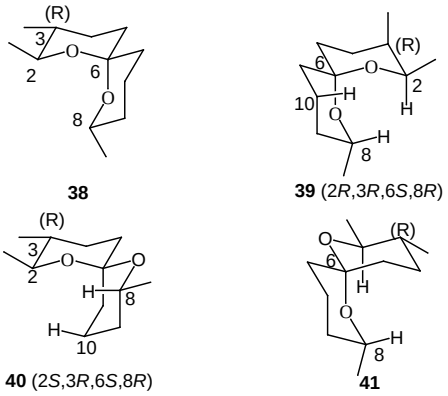


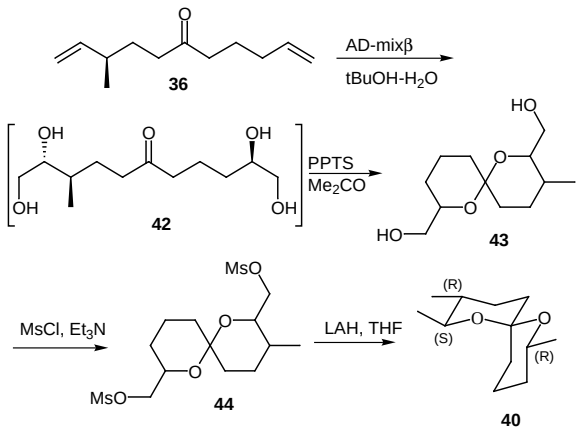
Figure 3 Structure of likely diastereomers of 2,3,8-trimethyl-1,7-dioxaspiro[5.5]undecane formed under equilibrating ring-closing conditions

Previous experience and MM2-calculations suggested that the diastereomers shown in Figure 3 were likely to be prominent under equilibrating conditions. The EIMS of the (two) major isomers were very similar with weak M^+ (*m*/*z* 198), discernible methyl loss (*m*/*z* 183), and intense ions at *m*/*z* 154 (loss of CH_3CHO), with the base peak at *m*/*z* 112. The EIMS of the minor isomer was quite different, with the base peak at *m*/*z* 115, and significant ions at *m*/*z* 154, 129, 128, 112, 111. The major isomers were separated (HPLC) and their NMR spectra interpreted, with emphasis on the following criteria: (i) H-2 is distinguishable from H-8 on the basis of one fewer *vic*-H coupling (CH_3 at C-3) (ii) H-2 and H-8, when experiencing 1,3-*diaxial* interaction with oxygen, will resonate at lower field than when 1,3- with a C−C bond[12,20] (iii) NOE's between H-2 and H-8 would be anticipated in **38** and **39**, but not in **40** and **41**. The isomer of shortest GC-retention time was demonstrated to be **40**. The signal at δ = 3.26 (d of quartets, *J* = 6.32 and 9.72 Hz) assignable only to H-2 on the basis of the coupling pattern, requires the CH_3 group at C-3 to be *equatorial*, H-2 to be *axial* and with a 1,3-*diaxial* relation with the C_6-C_{11} bond. On the other hand, H-8 (δ = 3.64, *J* = 2.2, 6.4, 11.3 Hz) is 1,3-*diaxial* with respect to the C_6-O_1 bond, because of its more deshielded position. There is no NOE between H-2 and H-8, consistent with the isomer **40**. In addition there is only one *axial*-proton (coupling pattern) below δ = 1.5 (neglecting H-2 and H-8), and this is H-10_{ax} (δ = 1.85, q of t, *J* = 13.2 and 4.0Hz) again consistent with **40**, in which there is only one *axial* C-O bond (C_6-O_1) in the molecule.

The second eluting trimethylspiroacetal provides interesting spectroscopic contrasts. The high field signal (δ = 10.71) for the CH_3 group at C-3 requires this group to be *axial* (also experiences a *synclinal* type of (γ-shielding from O-1) and this is confirmed by the resonance for H-2 (δ = 3.86, d of q, *J* = 6.64 and 2.5Hz), lacking *axial-axial* H-coupling. This chemical shift (δ = 3.86) indicates a 1,3-*diaxial* interaction of H-2 with the C_6-O_7 bond, and similarly for H-8 (δ = 3.65, d of q of d, *J* = 2.1, 6.4 and 11.2 Hz) with respect to the C_6-O_1 bond. These observations require structure **39**, and now there are two *axial* protons below δ = 1.5, indicating the presence of two *axial* C-O bonds.[12,20] These signals at δ = 2.08 (t of t, *J* = 13.5 and 4.6 Hz) and δ = 1.86 (q of t, *J* = 13.2 and 4.1 Hz) correspond to H-4*ax* and H-10*ax* respectively. As anticipated for **39**, there is a definite NOE between H-2 and H-8. Each of the above spiroacetals, **39** and **40,** were of approximately 71% ee (enantioselective GC) with $[\alpha]_D^{23}$ of +48.7 and −39.3 respectively. (calculated values for 100% ee, are +68.6 and −55.4, respectively). For spiroacetals **39** the (2*R*,3*R*,6*S*,8*R*) enantiomer eluted first from the β-cyclodextrin column, whereas for **40**, the (2*S*,3*R*,6*S*,8*R*) enantiomer eluted second.

A second approach to isomers of system **25** utilised AD-technology which we had previously employed as a key step in stereocontrolled spiroacetal construction. It appeared that use of the (*R*)-configured dienone **36** would be appropriate,[23] and treatment of **36** with AD-Mix β was predicted to form the tetrol with a stereochemistry that would harmonise with the existing (*R*)-centre, to eventually form the desired all-*equatorial*, doubly anomerically stabilised spiroacetal **38**. Treatment of dienone **36** in this way, (see Scheme 4) followed by cyclisation of the uncharacterised tetrol **42** (originally assumed to have the depicted stereochemistry) afforded in moderate yield, a single compound exhibiting ^1H and ^{13}C NMR spectra consistent with a bis(hydroxymethyl) spiroacetal, **43**. Mesylation, followed by hydride reduction, produced a single compound (GC) exhibiting EIMS appropriate for a 2,3,8-trimethyl-1,7-dioxaspiro[5.5] undecane, and this was **anticipated** to be **38**.

To our surprise, the product was identical (GC and GC-MS) with the previously characterised **40**, and sharing its absolute configuration (enantioselective GC). The unan-



Scheme 4

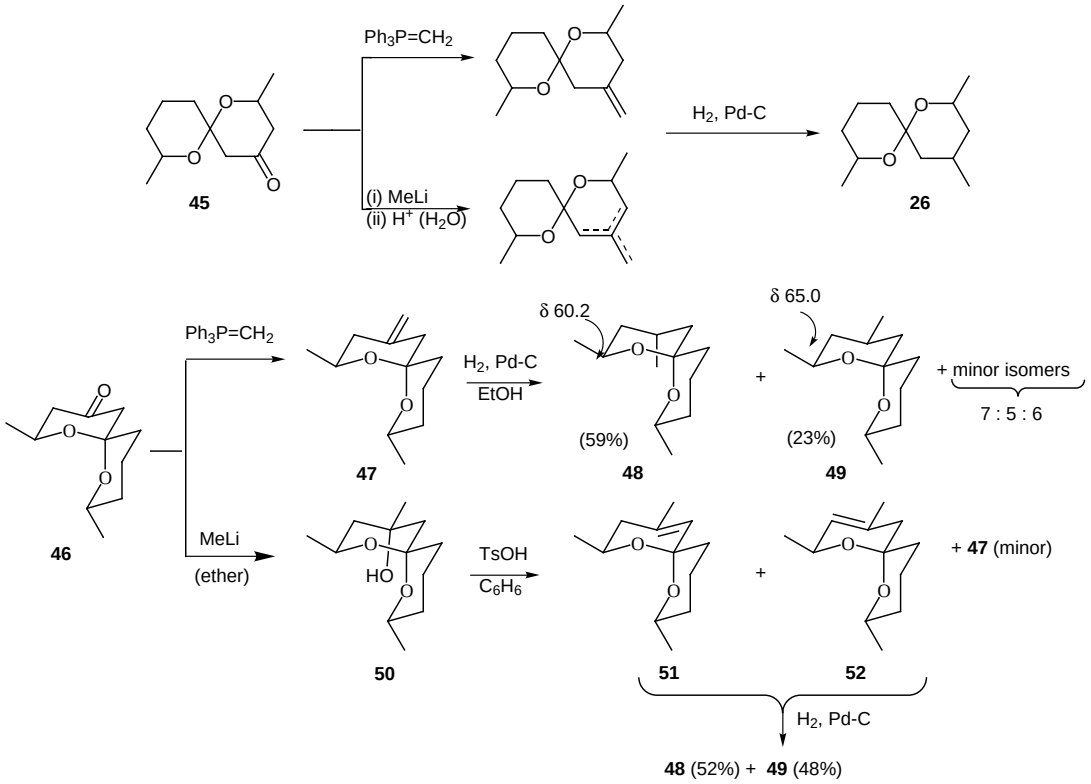
ticipated result is now being further investigated with respect to the influence of the (*R*)- centre at C-3 in **36** on the course of the AD-reaction.

The availability of these isomers of 2,3,8-trimethyl-1,7-dioxaspiro[5.5]undecanes and their mass spectral and chromatographic behaviour, allowed us to conclude that no isomer of this system is present in the *Cantao* secretion. We then turned our attention to the other system considered to be consistent with the mass spectral data of 2,4,8-trimethyl-1,7-dioxaspiro[5.5]undecane (**26**).

We had already described[24] the spiroketone system **45**, and access to a diastereomeric mixture of **26** appeared possible by either Wittig olefination-reduction or by addition of methyllithium, followed by dehydration and reduction (Scheme 5).

In practice, methylenation of (*E*,*E*)-ketone **46** provided very predominantly (~83%) one olefin isomer deduced to be the (*E*,*E*)-isomer **47** on the basis of NMR comparisons, particularly with (*E*,*E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**7**) (Scheme 5). Hydrogenation (5% Pd/C, 95% EtOH) provided five isomers (GC-MS) of **26** in the ratio 23:59:7:5:6 in order of elution, with the first two eluting well ahead of the last three isomers. Given the likely facial selectivity of hydrogen delivery, the isomer with a newly formed *axial* methyl group **48** would predominate, with the first eluting isomer (23%) then being the all-*equatorial* isomer **49**. NMR analyses confirm this. In particular, the chemical shift of C-2 (δ = 60.2 in the major isomer, 65 in the next most abundant) reflects the 1,3-shielding effect at C-2 by the *axial*-CH_3 at C-4 in the major isomer **48**. On the basis of elution order, the three minor isomers could incorporate a *Z*-configured tetrahydropyran ring, or remain (*E*,*E*)-configured but with either the C-2 or C-8 methyl group *axial*. These isomers were separated, by HPLC and identified along with their diastereomers as discussed later.

The alternative approach to spiroacetal system **26** commenced with addition of MeLi to the (*E*,*E*)-spiroketone **46** and this resulted in essentially a single tertiary alcohol **50**, as expected (Scheme 5). Dehydration with tosic acid in benzene afforded a mixture of three alkenes *ca* 2:46:52,



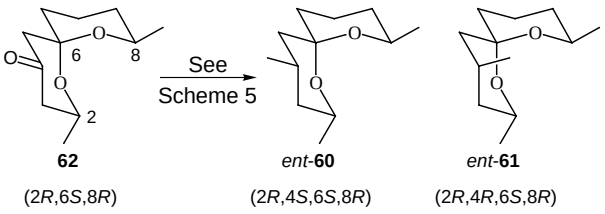
Scheme 5

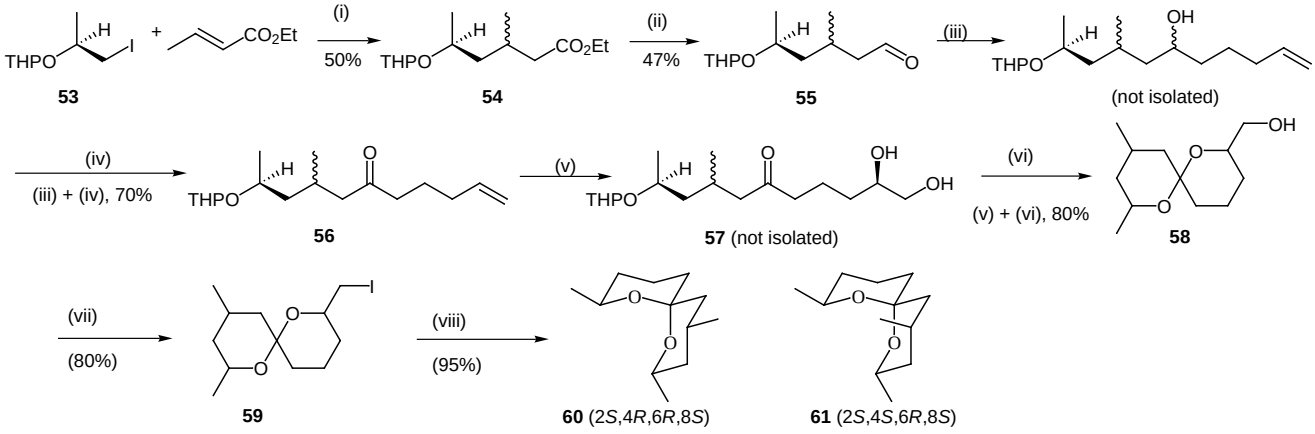
with the very minor isomer being the *exo*-methylene compound **47**, already acquired by Wittig methylenation of the (*E*,*E*)-spiroketone. The two major olefins, **51** and **52** were separated (HPLC) and individually characterised. Hydrogenation of this olefin mixture afforded a 48:52 mixture of the (*E*,*E*)-ring configured spiroacetals, with the *axial*-methyl compound **48** slightly predominating.

With authentic samples of the stereoisomeric racemic trimethylspiroacetals available, chromatographic comparisons established that the all-*equatorial* (*E*,*E*)-2,4,8-trimethyl-1,7-dioxaspiro[5.5]undecane **49** was the predominating natural compound (peak ***C***, Figure 1). In addition, the low intensity peak in the natural sample (peak ***D***), on the basis of retention time and matching mass spectrum, is assigned as spiroacetal **48**, with an *axial*-C-4 methyl group. (The very similar mass spectra are consistent with these C-4 epimers). The next question to be addressed was the absolute stereochemistry of the components. The observation that all five synthetic (racemic) diastereomers (**48**, **49** and three minor isomers) were nicely separated into their enantiomeric pairs on a β-cyclodextrin column, confirmed that enantioselective gas chromatography would provide the required information, once appropriate enantiomers were acquired. In addition, it was likely that the last three eluting isomers of the five component synthetic mixture corresponded with peaks **(F)**, ***(G)*** and ***(H)*** of the natural extract, and that the major natural component **C** was of high ee, when compared with the well-separated peaks for the enantiomers of the racemic all-*equatorial* (*E*,*E*)-isomer, **49**.

The synthesis of enantiomers of the 2,4,8-trimethyl spiroacetal system **12** was next undertaken, and several approaches were developed. The first commenced with the free-radical addition of the ethyl (*S*)-(+)-lactate derived iodide **53**[14] to ethyl crotonate (Scheme 6), to provide the protected hydroxy ester **54** in 50% yield, as a diastereomeric mixture. Reduction to the aldehyde **55** (DIBAL-H) followed by addition of pent-4-enylmagnesium bromide and then Dess−Martin oxidation (70%) furnished hydroxy enone **56**. Dihydroxylation of **56** with AD-Mix β[25] installs predominantly (*R*)-chirality at the newly created secondary alcohol centre. This monoprotected triol **57** was not isolated, but immediately deprotected and cyclized with 1 M HCl in aqueous methanol to afford the hydroxy spiroacetal **58**, as a 1:1 mixture of isomers [δ C_6(spirocentre) at 97.49 and 96.42] both of which were (*E*,*E*) ring configured and could be separated by flash chromatography. Reduction of the hydroxymethyl group was achieved by conversion to the iodomethyl derivative **59** (I_2/Ph_3P/imidazole), followed by reduction with Raney-Ni in basic ethanol.[26] The two resulting 2,4,8-tri-methyl spiroacetals were separated and purified (HPLC, hexane/H_2O, 100:1) to provide about equal amounts of the C-4 epimers. Initial use of the (*S*)-lactate based iodide therefore results in final acquisition of the (2*S*,4*R*,6*R*,8*S*)-all-*equatorial* isomer **60** and the (2*S*,4*S*,6*R*,8*S*) epimer **61**, as shown in Scheme 6. These isomers had $[\alpha]_D^{23}$ −66.4 ($CHCl_3$) and $[\alpha]_D^{23}$ −69 ($CHCl_3$), respectively.

The enantiomers of **60** and **61** were obtained from predominantly (2*R*,6*S*,8*R*)-2,8-dimethyl-1,7-dioxaspiro [5.5]undecan-4-one (**62**), following the sequence outlined in Scheme 5.

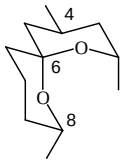




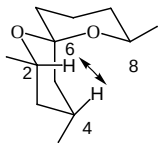
Reagents and conditions: (i) Bu_3SnH/AIBN/benzene, 48h, syringe pump; (ii) DIBAL-H/CH_2Cl_2, −78 °C; (iii) CH_2=CH$(CH_2)_2CH_2MgBr$/Et_2O, −50 °C; (iv) Dess−Martin oxidation; (v) AD mix-β (vi) 1 M HCl/MeOH/H_2O; (vii) I_2/Ph_3P/imidazole/toluene, 100 °C; (viii) Ra-Ni/EtOH/H_2O/1% NaOH

Scheme 6

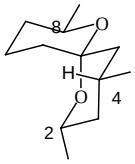
In addition to *ent*-**60** and *ent*-**61**, three minor isomers were also formed in this procedure, and HPLC led to almost complete separation of these closely eluting compounds. The first of these to be examined exhibited an EIMS that resembled that of the later eluting natural component (peak ***G***), although there were significant differences. The ^{1}H NMR signal at $\delta = 4.13$ ($J = 7.0, 3.5, 1.6$Hz) did not incorporate an *axial-axial* coupling, (normally 10−11 Hz in these systems), so that this proton, which must be either H-2 or H-8, must be *equatorial*. There was an NOE between the other low field signal ($\delta = 3.9$, J = 11.4, 6.4, 1.8 Hz) and **both** O−CH(**CH$_3$**) methyl groups, confirming that both C−O bonds were *axial*. The high field signal for C-4 ($\delta = 19.48$, DEPT) also required the C-2 methyl group to be *axial*. (γ-shielding of C-4 by *axial* C-2 methyl group). Consequently, this isomer is **63**, and because (*R*)-3-(tetrahydropyran-2′-yloxy)iodobutane was employed, **63** also represents its absolute configuration. The chemical shifts and coupling constants are fully in accord with this structure.



63
(2*S*,4*S*,6*S*,8*R*)



64
(2*S*,4*R*,6*R*,8*R*)



65
(2*S*,4*R*,6*S*,8*R*)

The two remaining spiroacetals from this sequence exhibited quite different EIMS in that the first eluting had a base peak *m*/*z* 115, and the second eluting at *m*/*z* 129, with a very weak *m*/*z* 115. In each of these isomers, the ^{1}H NMR chemical shifts for H-2 and H-8 were separated by ca 0.6−0.7 ppm, indicating that one of these protons experienced a 1,3-*diaxial* interaction with a C−O bond, and the other with a C−C bond, as outlined previously. In addition, the chemical shift data required the three methyl groups to be *equatorial* and thus structures **64** and **65** were arrived at. It is to be noted that these are epimeric at the spirocentre (C-6), and consistent with this, **64** and **65** equilibrated over time. A basis for distinction between structures **64** and **65** would be NOE's, as in **64**, an NOE between H-2 (lower field of the H-2, H-8 pair) and H-4 would be anticipated, whereas in **65**, an NOE between H-4 and H-8 (now at lower field than H-2) would be absent. Experiments demonstrated that these structural assignments were correct. In addition, structures **64** and **65** were acquired in another way, with more stereochemical control, by AD-technology, and this is described later in Scheme 8.

With the availability of **60,** *ent*- **60**, **61** and *ent*-**61**, and the racemates, elution and co-injection studies, using a β-cyclodextrin column, established that the major natural component (Figure 1, Peak ***C***) was (2*S*,4*R*,6*R*,8*S*)-2,4,8-trimethyl-1,7-dioxaspiro[5.5]undecane (**60**) with no detectable level of its enantiomer. Compound **60** represents the rare class of insect-derived branched carbon chain spiroacetals,[2] and is the first spiroacetal of any type from Hemiptera or lower insect orders. The compound is not sex-specific, and an aggregation role may be indicated by the presence of a single large colony in a host tree (*Mallotus philippensis* (Lam.) (Euphorbiacea)) at certain stages of insect development.

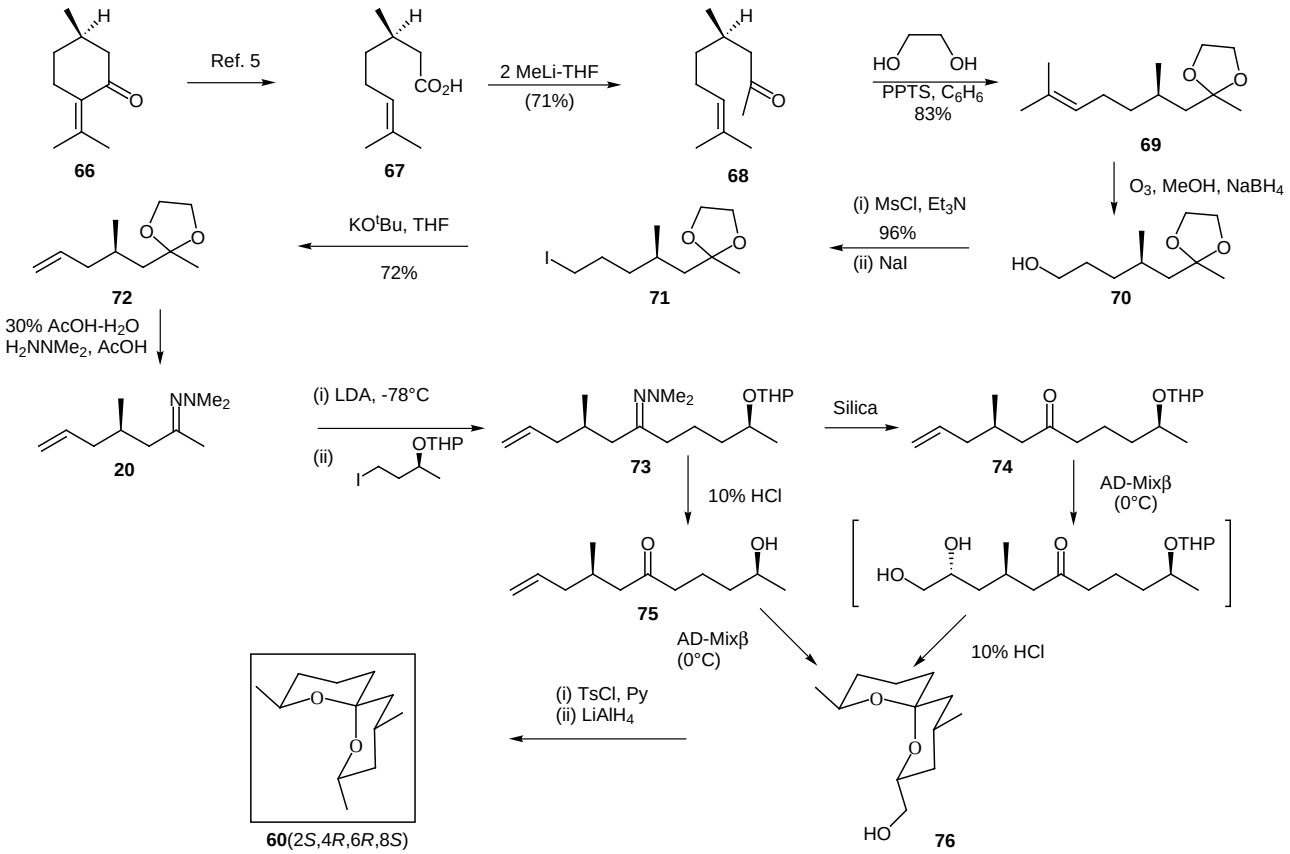
The synthesis of (2*S*,4*R*,6*R*,8*S*)-2,4,8-trimethyl-1,7-dioxaspiro[5.5]undecane (**60**, described above in Scheme 6, also led to the C-4 epimer **61**, because the free radical addition of the (*S*)-(+)-lactate derived iodide **53** to ethyl crotonate was not diastereoselective. Control of the absolute stereochemistry at C-4 would result from use of the chiral pool component, (*R*)-(+)-pulegone (**66**) or the derived (*R*)-(+)-citronellic acid (**67**),[5] with other methyl-bearing stereogenic centres resulting from alkylation and asymmetric induction procedures.

The methyl ketone **68**, derived from (*R*)-(+)-citronellic acid (**67**), was protected as the ethylene ketal **69** before ozonolysis and sodium borohydride reduction to alcohol **70**. Tosylation (or mesylation) and treatment with NaI yielded iodide **71**, which under eliminative conditions (KOBu-*t*) furnished alkene **72**.

Alkene **72** was deprotected, transformed to the *N*,*N*-dimethylhydrazone **20** and alkylated with (*S*)-3-(tetrahydropyran-2'-yloxy)-1-iodobutane[14,27] to provide hydrazone **73**. Selective deprotection using silica afforded the THP-ether **74**, whereas use of 10% aqueous HCl released hydroxyenone **75.** The absolute stereochemistry at the positions that would become C-4 and C-8 in the target spiroacetal **60**, were now installed. Further chirality introduction at C-2 was based on asymmetric dihydroxylation, and use of AD-Mix β with either **74** or **75** was predicted to provide the appropriate configuration for subsequent ring closure to the hydroxymethyl derivative **76**, which on tosylation and reduction provided **60** (ee ~ 99.5%) whose ^{1}H, ^{13}C NMR and mass spectra matched those already obtained (Scheme 7).

As indicated earlier, several minor components of the secretion appeared to be diastereomers of the major component **60** identified above, and variation in the procedures would permit acquisition of several of these. For example, alkylation of hydrazone **20** with (*R*)-3-(tetrahydropyran-2'-yloxy)-1-iodobutane[20,27] yielded **77** which also could be selectively or fully deprotected to furnish **78** and **17** respectively (Scheme 8). Treatment of either with AD-Mix-α followed by cyclisation provided predominantly the hydroxymethyl compound **79**, although use of **78** appeared to be more efficient. Reduction of **79**, via the tosylate, yielded *ent*-**61,** with $[\alpha]_D^{23}$ +71 and ee ~ 99.5%.

Intermediate **17** was also treated with AD-Mix β to provide predominantly **80** and then, by acid treatment, the hydroxymethyl isomers **81** and **82**, reduction of which afforded a mixture (ca 55:45) of two spiroacetals which are epimeric at the spirocentre. These spiroacetals proved to be identical with **64** and with **65** respectively, by comparisons of their NMR spectra and stereochemical analy-

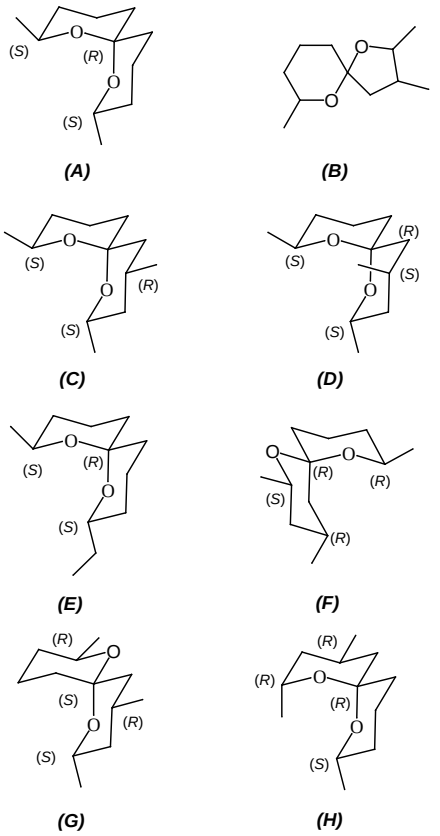


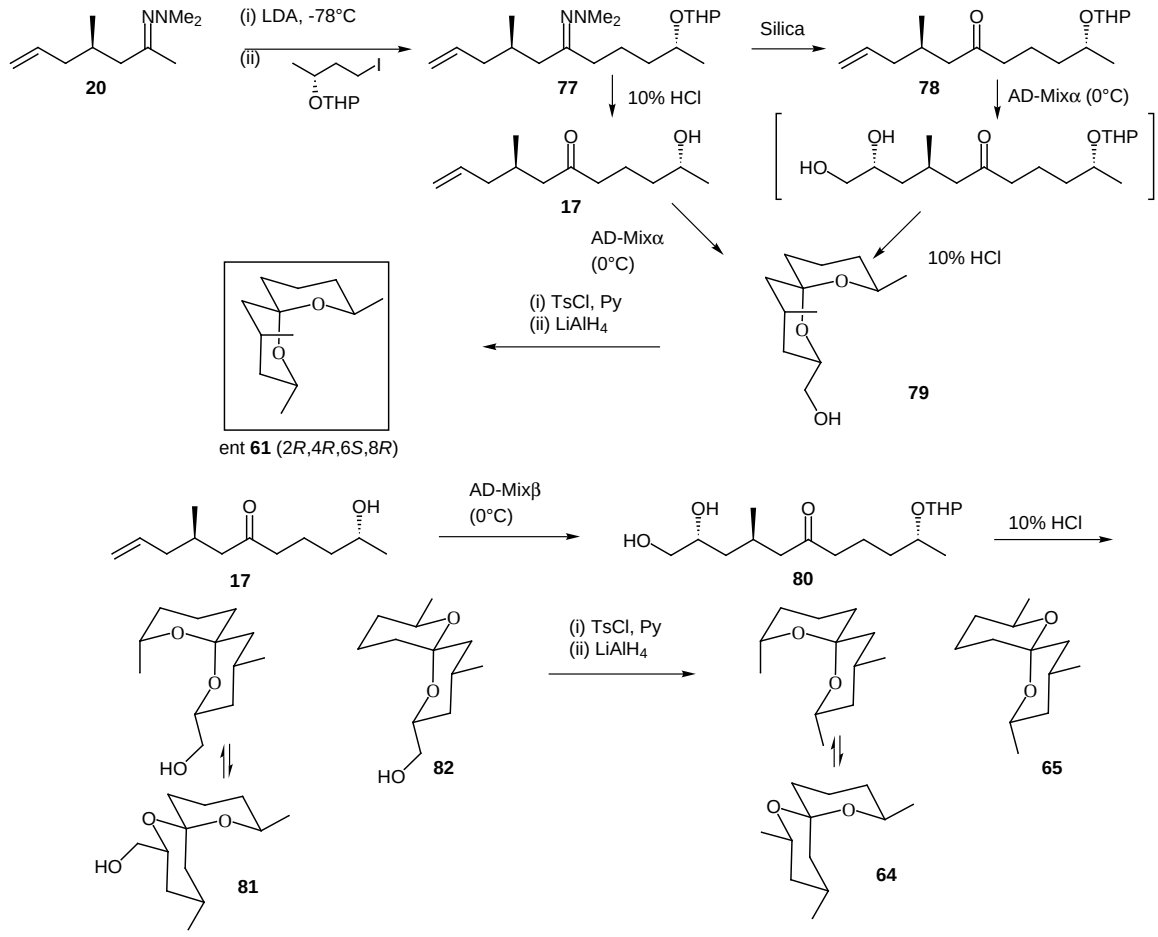
Scheme 7

ses on the β-cyclodextrin column. NMR analyses confirm that the conformation represented by **64** is the dominant one, and this is probably true for **81** also.

The availability of a variety of diastereomers of system **12** of known absolute configuration, permitted detailed examination of the chirality of the spiroacetal components in the *Cantao* sample. This work was conducted using a β-cyclodextrin column[28] in the GC-MS system so that the mass spectra of peaks considered to be enantiomers could be compared. Co-injection studies and observation of peak enhancements allowed a complete stereochemical profile to be drawn. The enantiomer pairs of the synthesised spiroacetals were well separated on the β-cyclodextrin column, and there is a strongly predominating chirality in each of the components **(*A*)**−**(*H*)**. Because of the low levels of the minor components, accurate estimates of ee's are difficult, but only in the case of **(*D*)** is its enantiomer observable. The absolute stereochemistry of the peaks **(*A*)**−**(*G*)** in order of elution on the DB-5 column (Figure 1) excepting **(*B*)**, are shown below. Component **(*H*)**, which elutes last on the non-polar DB-5 column, elutes prior to **F** and **(*G*)** on the cyclodextrin column.

Exposure of a dichloromethane extract of the *Cantao* secretion to aqueous HCl for two days at room temperature, caused peaks **(F)** and **(*G*)** to become nearly equal in intensity. This is expected for energetically closely balanced





Scheme 8

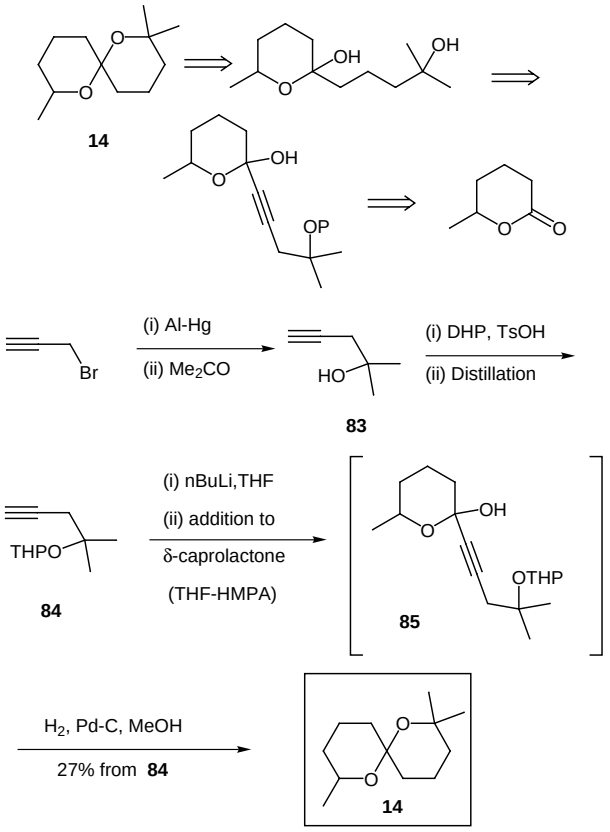
spiroacetals that are epimeric at the spirocentre, as **64** and **65** are, (see Scheme 8), and which structures are assigned to **(F)** and **(*G*)** respectively. The fact that the abundances of **(F)** and **(*G*)** in the natural sample are very different (ca 8:1) is not an unusual state of affairs with such epimeric spiroacetals in insects.[2,3,12]

Speculation on the biosynthesis of insect spiroacetals has been presented elsewhere,[2,29] and the origin of the component **(*B*)** and **(*C*)** may be associated with either propionate or even amino acid intervention. Because of the novelty of **(*B*)** and **(*C*)** and the latter's predominance in the secretion, such incorporation studies are planned.

(b) Spiroacetals from the Rove Beetle, *Ontholestes murinus* (L.)

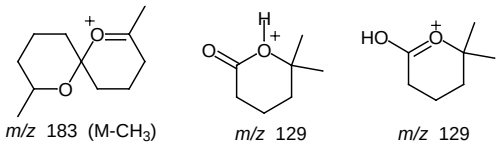
The rove beetle subtribe, Staphylinina, comprises about forty-five members in central Europe and all have evolved gland systems which are utilised in a very conspicuous defensive strategy. On molestation, abdominal elevation occurs with eversion of a pair of glands derived from the membrane between the sixth and seventh abdominal tergite. Simultaneously, a defensive secretion may exude and be directed towards the molestation by the manouverable abdominal tips. This defence strategy appears to have evolved to provide protection for the vulnerable abdominal area. Some studies of the volatile chemical constituents of certain rove beetle emissions have been reported and summarised in the report by Huth and Dettner.[30] These authors characterised forty-one volatile components from a range (13) of Staphylinids, and iridoid aldehydes and lactones, short-chain ketones, cyclic compounds and spiroacetals were identified. It is with the latter structural type that our present interest lies. In 1986, Dettner and Schwinger[31] described the defensive secretion of *Ontholestes murinus* (L) and this contained (along with other volatiles) (*E*,*E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**7**), of undetermined absolute stereochemistry. This spiroacetal was accompanied by another component of apparent molecular mass of 198 and a spiroacetal-like mass spectral fragmentation pattern. In the subsequent report,[30] this latter compound was described as a 2,2,8-trimethyl-1,7-dioxaspiro[5.5]undecane without further data. The suggested arrangement, with a *gem*-dimethyl group, was a most unusual feature in an insect derived spiroacetal,[2] and therefore verification by synthesis, and determination of the absolute stereochemistry, were of interest. Consequently, acquisition of **14** in both racemic and optically active forms was required.

The synthesis of system **14** has not been reported previously and the approach summarised below was based on the precedented addition[32] of alkynol derivatives to lactones followed by hydrogenation, and cyclisation was anticipated to provide system **14**. Reaction of acetone with propargyl bromide and aluminium-amalgam provided alkynol **83** in high yield, whereas use of zinc powder resulted in a much lower yield. The crude alcohol was protected as its THP ether **84** and then deprotonated to the lithiated alkyne, which was transferred via cannula into a solution of δ-caprolactone in THF/HMPA at −78 °C. The resulting crude ynol **85**, as a diastereomeric mixture, was hydrogenated in methanol to furnish the desired spiroacetal **14**, which was purified by flash chromatography and preparative gas chromatography. This sequence is summarised below in Scheme 9.

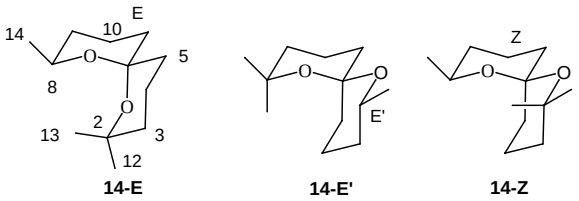


Scheme 9

Spiroacetal **14**, obtained as a single diastereomer, was characterised by ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry and also by enantioselective gas chromatography (see later). In the EIMS, there is, as expected, some similarity between **14** and **7** with both exhibiting characteristic ions at *m*/*z* 169, 115, 112, but **14** in addition, exhibits intense peaks at *m*/*z* 183 and 129, consistent with the *gem*-dimethyl grouping. These intense ions in the mass spectrum (see ref. 6 for a reproduced spectrum) are assigned the structures shown below.

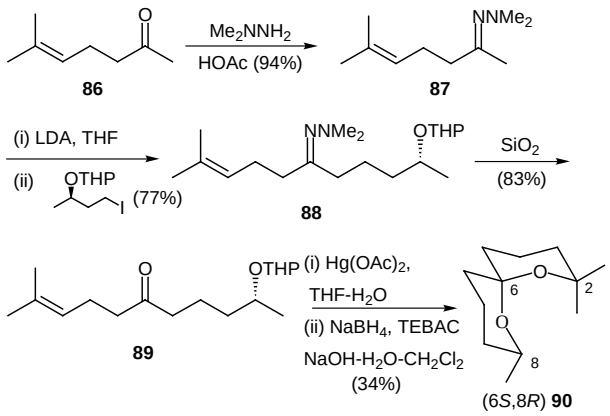


Interpretation of the ^{1}H and ^{13}C NMR spectra should be approached in terms of the three diastereomeric forms drawn below, the two *E*-forms **14**-*E* and **14**-E', with the former enjoying maximum anomeric stablisation), and the **14**-*Z* form.



The spectral data (Table) are confidently interpreted in terms of **14**-E. The ^{13}C NMR spectrum was assigned with the aid of 2D spectra (HSQC, COSY, NOESY) and the DEPT spectrum. The methyl groups resonate at δ = 21.55 (C-14), 25.36 (C-13) and 32.78 (C-12) with C-10 (δ = 19.22) and C-4 (δ = 15.82) being at higher field as a result of the two-fold γ-shielding effects of oxygen, but with C4 additionally shielded by the *axially*-orientated C13 methyl group. With these assignments settled, the ^{1}H NMR spectrum was interpreted using the correlated spectra, chemical shifts and signal multiplicities. The tabulated assignments as shown in the Table. The chemical shift of H-8 requires this proton (δ = 3.87) to have a 1,3-diaxial relationship with oxygen, not present in **14**-*Z*. Distinction between **14**-*E* and **14**-*E*' follows, for example, from aspects of the 2D-NOESY spectrum, with the strong NOE effect between H-13 and H-8 expected for **14**-*E*. Spatial proximity between these proton groups is much reduced in **14**-*E*'. The synthesised **14**-*E* exhibited gas chromatographic and EIMS behaviour identical with those of the insect derived material.

Attention was then directed to determination of the absolute stereochemistry. An expeditious route commenced with commercially available 6-methylhept-5-en-2-one (**86**), which was converted to its *N*,*N*-dimethylhydrazone **87**. Kinetic deprotonation and alkylation with the THP-protected (*R*)-3-hydroxy-1-iodobutane[33] provided hydrazone **88** which was converted to protected hydroxyenone **89** by flash chromatography on silica. Hydroxymercuration-cyclisation of **89** with $Hg(OAc)_2$ in 1:1 THF/H_2O, followed by biphasic reduction with $NaBH_4$, provided the (6*S*,8*R*) enantiomer of **14**-*E*, i.e. **90**, in 34% yield from the enone, with $[\alpha]_D^{22}$ +46.2 (*c* = 7.09, $CHCl_3$). Enantioselective gas chromatography showed that the ee exceeded 98%, and MS and NMR data matched those for the racemate **14**-*E*. The sequence is shown in Scheme 10.



Scheme 10

The enantiomers of (racemic) **14**-*E* were very well separated using a β-cyclodextrin stationary phase in the GC-MS system, and the synthesised (6*S*,8*R*) isomer **90**, eluted earlier than its antipode. Further comparisons with the extracts of *O. murinus* established that the natural spiroacetal was the (6*R*,8*S*) isomer of >95% ee. A lower than anticipated level of the natural spiroacetal resulted in this less precise measure of the ee. With the availability from previous work[14] of stereoisomers of (*E*,*E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**7**), similar analyses indicated that the (2*S*,6*R*,8*S*) isomer **15** (>98% ee) was present, as found previously for this spiroacetal in insects. However, in another rove beetle, *O. tesselatus*,[30] the (*E*,*E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane exhibited comparable levels of the enantiomers − a hitherto unobserved situation.

Conclusion

The structures and stereochemistry of several spiroacetals with branched carbon skeletons from insect sources have been determined by spectroscopy, synthesis and enantioselective gas chromatography. These enrich the landscape of insect-derived spiroacetals, and pose interesting questions of function, and biosynthetic diversity.

^{1}H and ^{13}C NMR spectra were recorded with Bruker AC200, AMX-400 or DRX-500 spectrometers, using either $CDCl_3$ or benzene-d_6 as solvents. Chemical shifts (δ) are given in ppm, and coupling constants (J) in hertz. The signal for the residual $CHCl_3$ (in $CDCl_3$) was adopted as a secondary standard for ^{1}H NMR spectra (δ 7.24), and the centre of the $CDCl_3$ triplet (δ 77.00) for ^{13}C NMR spectra. Low resolution mass spectral data refer to GC-MS data with a Hewlett-Packard 5970 B mass selective detector, and enantioselective gas chromotagraphy/mass spectrometry to a Shimadzu GC-MS system equipped with a β-cyclodextrin column. High resolution mass spectra were recorded on a Kratos MS-25RFA spectrometer. Preparative gas chromatography was conducted with a Shimadzu gas chromatograph, Model GC-9A, equipped with OV101 and C-20M columns. Optical rotations were measured with a Perkin Elemer 241 MC polarimeter. The extracts from the two species were obtained as previously described.[4–6]

Table ^{13}C and ^{1}H NMR Data for Spiroacetal *14-E*

C	δ_C	δ_H	multiplicity, *J* (Hz)
2	71.96		
3	32.97	1.63 1.10	m m
4	15.82	1.83 1.45	H_{ax}, qt, *J*=13.5, 4.0 H_{eq}, m
5	37.10	1.65 1.35	H_{eq}, *J*=13.5 H_{ax} m
6	96.24		
8	65.66	3.87	dqd, *J*=11.3, 6.4, 2.1
9	36.43	1.50 1.10	m m
10	19.22	1.99 1.40	H_{ax}, qt, *J*=13.5, 3.5 H_{eq}, dtt, *J*=13.5, 3.5
11	37.25	1.63 1.33	H_{eq}, brd *J*=13.5; H_{ax}, m
12	32.78	1.14	s
13	25.36	1.30	s
14	21.54	1.05	d, *J*=6.4

2,10-Dimethyl-1,7-dioxaspiro[5.5]undecanes 18, 19, 21

Hydroxyenone **17** and hydrazone **20** are described later in the context of Schemes 7, 8, and spiroacetals **18**, **19** and **21** will be discussed elsewhere.

9-Ethyl-2-methyl-1,7-dioxaspiro[5.5]undecane (30) Commencing with Iodide 31

2-(Benzyloxymethyl)-1-iodobutane (**31**): The known 2-(benzyloxymethyl)butan-1-ol[34] (4.06 g, 20 mmol) was dissolved in pyridine (15 mL) at 0 °C and tosyl chloride (8g, 42 mmol) was added in portions over 15 min after which time the mixture was stirred at 0 °C for a further 30 min, and left overnight at 20 °C. The pyridine was removed under reduced pressure, and the residue was dissolved in Et_2O/H_2O (80 mL/80 mL). The H_2O layer was further extracted with Et_2O (40 mL) and the combined Et_2O solutions were washed with H_2O (2 × 50 mL), aq sat. Na_2CO_3 (2 × 50 mL), brine (2 × 50 mL), dried ($MgSO_4$) and then concentrated to give a pale yellow oil (7.8 g), which was directly chromatographed on silica (cyclohexane/EtOAc, 12:1) to give the pure tosylate (6.34 g, 87%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.83 (t, 3 H, *J* = 7.6 Hz, CH_2CH_3), 1.36 (m, 2 H, CH_2CH_3), 1.81 (m, 1 H), 3.36 (m, 2 H, CH_2OBn), 4.07

(d, 2 H, J = 5.2 Hz, CH_2OTs), 4.36 (s, 2 H, CH_2Ph), 2.36 (s, 3 H), 7.26 (m, 7 H), 7.76 (d, 2 H, d, J = 8.3 Hz).

^{13}C NMR: (50 MHz, $CDCl_3$): δ = 11.0, 20.3, 21.4, 40.0, 68.8, 70.1, 72.8, 127.2 (2 C), 127.3, 127.6 (2 C), 128.0 (2 C), 129.6 (2 C), 132.7, 138.0, 144.4.

This tosylate (3.52 g, 15 mmol), NaI (6.1 g, 41 mmol) and anhyd acetone (30 mL) were then refluxed with stirring for 2.5 h, after which the mixture was concentrated and then partitioned with Et_2O/H_2O (50 mL/50 mL). The H_2O layer was further extracted with Et_2O (30 mL), and the combined Et_2O extracts were washed with aq NaS_2O_3 (30 mL), aq sat. Na_2CO_3 (30 mL) and brine (30 mL) before drying ($MgSO_4$). Concentration provided a yellow oil (2.93 g) which was chromatographed on silica (cyclohexane/EtOAc, 50:1) to provide **31** as a pale yellow slightly unstable oil (2.68 g, 87%).

^{1}H NMR: (200 MHz, $CDCl_3$): δ = 0.90 (t, 3 H, J = 7.0 Hz, CH_2CH_3) 1.38 (m, 3 H, $CHCH_2$), 3.76 (m, 4 H), 4.52 (s, 2 H, PhCH_2), 7.34 (s, 5 H, C_6H_5).

^{13}C NMR: (50 MHz, $CDCl_3$): δ = 11.1, 12.5, 24.2, 41.1, 72.3, 73.2, 127.5 (3 C), 128.2 (2 C), 138.2.

GC-MS: m/z (%) = 304 (M^+, 4.3), 177 (M − I, 1.6), 159 (1.5), 121 (3), 92 (20), 91 (100), 65 (13.9), 55 (4.1).

This iodide was used directly in the alkylation sequence described below.

2-(Tetrahydropyran-2'-yloxy)-9-(benzyloxymethyl)undecan-6-one (34)

To a stirred solution of acetone-*N*,*N*-dimethylhydrazone (400 mg, 4 mmol) in anhyd THF (5 mL) at −78 °C was added BuLi (2.5 mL of 1.6 M in hexane) and after a further hour, a solution of the above iodide **31**, (608 mg, 2 mmol) in THF (2 mL) was added. The mixture warmed to r.t. and after 3 h, the solvent was removed (reduced pressure) and the residue was taken up in Et_2O/pentane (1:1). This solution was filtered through neutral alumina, dried ($MgSO_4$) and concentrated to give the pale yellow monoalkylation product (560 mg), which was used without further purification.

^{1}H NMR: (200 MHz, $CDCl_3$): δ = 0.87 (t, 3 H, J = 7.0 Hz, CH_3CH$_2$), 1.40−1.58 (m, 5 H, CH_2CHCH_2), 1.92 (2, 3 H), 2.19 (t, 2 H, J = 7.0 Hz), 2.40 [s, 6 H, $N(CH_3)_2$], 3.36, (d, 2 H, J = 4.2 Hz, OCH_2CH), 4.46 (s, 2 H, PhCH_2), 7.30 (s, 5 H, C_6H_5).

^{13}C NMR: (50 MHz, $CDCl_3$): δ = 11.2, 16.4, 23.6, 28.1, 36.4, 39.6, 47.0 (2 C), 72.5, 73.0, 127.3, 127.4 (2 C), 128.4 (2 C), 138.7, 167.8 (C=N).

GC-MS: m/z (%) = 276 (M^+, 25), 232 (2.1), 186 (9.1), 185 (68), 169 (6.2), 113 (23), 100 (92), 92 (14), 91 (91), 70 (29), 65 (25).

The above mono-alkylated hydrazone (388 mg, 1.4 mmol) in anhyd THF (1 mL) was added to a cooled solution (−78 °C) of LDA in anhyd THF (3 mL) generated from diisopropylamine (287 mg, 2.8 mmol) and BuLi (1.8 mL of 1.6 M hexane solution). After stirring the mixture for 1 h at −78 °C, 3-(tetrahydropyran-2'-yloxy)butyl iodide (32; 398 mg, 1.4 mmol) in anhyd THF (1 mL) was added at this temperature, and then allowed to stir for 24 h at r.t. The solution was concentrated under reduced pressure, taken up in Et_2O/pentane (1:1), filtered through neutral alumina, dried ($MgSO_4$) and again concentrated to give the dialkylation product (520 mg, 68%, GC analysis).

GC-MS: m/z (%) = 432 (M^+, 19), 388 (2.5), 348 (12), 347 (52), 342 (6), 341 (23), 331 (21), 286 (5), 257 (40), 91 (100).

The dialkylated hydrazone **33**, (300 mg) was dissolved in EtOAc/acetone/H_2O (4:4:1), silica gel (2 g) was added and the mixture stirred for 12 h at r.t.. The filtered solution was then chromatographed (silica gel, cycloxhexane/EtOAc, 3:1) to provide a yellow oil (200 mg, 73%) of the ketone **34** as a diastereomeric mixture.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (t, 6 H, J = 7.2 Hz, 2 CH_3), 1.15 and 1.22 (2 d, 6 H, J = 6.0 Hz, 2 CH_3), 1.20−1.85 (m, 30 H), 2.36−2.40 (2 t, 4 H, J = 7.0 Hz), 3.32−3.34 (2 d, 4 H, J = 5.0 Hz), 3.40−3.57 (m, 2 H), 4.46 (s, 4 H, PhCH_2), 4.61−4.67 (2 t, 2 H, J = 4.6 Hz), 7.31 (s, 10 H, 2 C_6H_5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.0, 18.9, 19.6, 19.9, 21.4, 25.1, 25.13, 25.3, 25.4, 31.0, 33.8, 35.9, 36.7, 39.2, 40.1, 40.2, 42.5, 62.4, 62.6, 70.6, 72.6, 72.9, 73.6, 95.6, 98.6, 127.3, 128.1, 138.4, 211.2.

GC-MS: m/z (%) = 289 (8.9), 288 (2.4), 246 (1.6), 199 (30), 197 (17), 125 (14), 91 (100).

The above ketone (200 mg) was dissolved in EtOH (6 mL, 95%) and Pd-C (~30 mg) was added before hydrogenation (1.5 atm) for 2.5 h. The mixture was then filtered, concentrated and added to MeOH (3 mL) containing TsOH (50 mg) and stirred for 1 h to provide the desired 9-ethyl-2-methyl-1,7-dioxaspiro[5.5]undecane (**30**) (82 mg, 81%) as a mixture of two closely eluting diastereomers of approximately equal proportions. The EI-MS of these isomers were very similar. No attempt was made to separate these diastereomers as their chromatographic behaviour and EI-MS confirmed their absence from the natural secretion.

^{1}H NMR: (200 MHz, $CDCl_3$): δ = (for isomeric mixture): 0.81−2.10 [m with app. quartets (0.83) and doublets (~1.08), 19 H], 3.1−4.2 (m, 3 H).

^{13}C NMR: (50 MHz, $CDCl_3$): δ = 11.1, 12.1, 18.8, 18.9, 21.7 (2 C), 22.5, 22.6, 24.9, 25.2, 31.4, 32.6 (2 C), 34.1, 34.8 (2 C), 35.7, 37.0, 63.0, 65.0 (2 C), 65.3. 95.3, 95.8.

GC-MS: (isomer 1): m/z (%) = 198 (11.8), 197 (1.8), 183. (2.4), 168 (1.3), 155 (2.0), 154 (8.3), 139 (4.6), 129 (4.8), 126 (4.8), 125 (1.6), 115 (100), 114 (34), 112 (92.9), 111 (40.6), 99 (7.6), 98 (8.4), 97 (61.0), 84 (23.1), 83 (62.4), 73 (16.3), 71 (17.4), 70 (16.1). (The GC-MS data for isomer 2 was extremely similar).

HRMS: Calcd for $C_{12}H_{22}O_2$ 198.1618. Obsvd 198.1619.

Dienone 36

(*R*)-(−)Citronellene (**35**; 10g, 72 mmol) was dissolved in CH_2Cl_2 (200 mL) and cooled to 0 °C. To this stirred solution was added *m*-CPBA (70%, 17 g, 72 mmol) in portions over 2 h. The mixture was then filtered, washed with aq sat. $NaHCO_3$ solution (50 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to yield the crude epoxide (isomeric mixture) as a yellow oil (9.9 g, 89%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.97 (d, 3 H, J = 6.6 Hz), 1.21 (s, 3 H), 1.26 (s, 3 H), 1.29−1.66 (m, 4 H), 2.10 (m, 1 H), 2.67 (dd, 1 H, J = 6.3, 5.1 Hz), 4.85−4.98 (m, 2 H), 5.54−5.73 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.6, 18.6, 20.1, 20.4, 24.8, 26.5, 26.7, 33.0, 33.2, 37.5, 37.7, 58.3, 64.4, 64.5, 112.9, 113.1, 144.0, 144.1.

GC-MS: m/z (%) = 139 (0.8) (M − CH_3), 125 (0.5), 111 (1.2), 95 (5.3), 81 (100).

The crude epoxide mixture was dissolved in Et_2O (200 mL), and HIO_4 (16.4 g, 72 mmol) was added in portions at r.t. to the stirred solution. After 2 h, the mixture was filtered, washed with aq satd $NaHCO_3$ solution (3 × 50 mL), and brine (20 mL), then separated and dried ($MgSO_4$). The volume of this organic phase was carefully reduced to about 50 mL, and GC-MS showed that the desired aldehyde had formed. This solution was immediately used in the next step.

GC-MS: m/z (%) = 97 (6, M − CH_3), 94 (5), 83 (14), 79 (20), 68 (67), 67 (57), 55 (100).

A three-necked flask equipped with a reflux condenser and a rubber septum was charged with Mg (3.46 g, 0.144 mol) and anhyd Et_2O (5 mL). Dibromoethane (260 μL, 3 mmol, 2%) was added by a syringe and the contents gently stirred until refluxing had ceased. 5-

Bromopent-1-ene (1 drop) was added and then a further amount (8.5 mL, 72 mmol) as a solution in Et_2O (20 mL), at such a rate so as to maintain a steady reflux. After addition was complete, the reaction was stirred for a further 15 min with slight warming. The previously generated solution of the aldehyde was cannulated into the reaction flask at 0 °C and stirred overnight at r.t. The reaction was quenched (10% HCl, 100 mL) and then extracted with Et_2O (3 × 100 mL). The solvent was removed and the residue dissolved in CH_2Cl_2 (150 mL), after a small sample of the secondary alcohol, resulting from the Grignard addition, was characterised.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.97 (d, 3 H, *J* = 7 Hz), 1.12−1.68 (m, 9 H), 2.03 (m, 3 H), 3.50−3.60 (br s, 1 H), 4.87−5.01 (m, 4 H), 5.56−5.85 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.3, 24.9, 32.5, 33.7, 35.1, 36.9, 37.8, 72.0, 112.8, 114.6, 138.7, 144.4.

The solution of the alcohol in CH_2Cl_2 was treated with NMO (10 g, 85 mmol), TPAP (150 mg, 0.42 mmol, 0.5%) and 3Å molecular sieves (4.1 g). After stirring for 2 h, the mixture was passed through a small plug of silica and the solvent was removed in vacuo. Flash chromatography (hexane) yielded dienone **36** as a slightly yellowish oil (9.6 g, 75% from citronellene); $[\alpha]_D^{25}$ −6.53 (*c* = 2.5, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.96 (d, 3 H, *J* = 6.8 Hz), 1.18−1.70 (m, 5 H), 1.96−2.10 (m, 3 H), 2.35 (td, 3 H, *J* = 7.6, 3.4 Hz), 4.87−5.01 (m, 4 H), 5.49−5.82 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.3, 22.8, 30.1, 37.5, 40.5, 41.9, 113.4, 115.1, 138.0, 143.8, 190.2.

GC-MS: *m*/*z* (%) = 165 (1.5) (M^+ − 15), 151 (0.8), 139 (1), 126 (9), 111 (12), 97 (25), 83 (29), 69 (61), 55 (99), 41 (100).

HRMS: *m*/*z* Calcd. for $C_{12}H_{20}O$ 180.1514. Found 180.1515.

Oxymercuration-Cyclisation of Dienone 36

Dienone **36** (1 g, 5.6 mmol) was dissolved in anhyd THF (30 ml) along with 1% $HClO_4$-H_2O (30 mL) and $Hg(OAc)_2$ (3.76 g, 11.8 mmol). The flask was light-protected (Al foil) and stirred overnight, before removal of the THF. The aqueous layer was extracted with CH_2Cl_2 (4 × 30 mL), and this solvent was removed to yield a semi-solid (2.95 g, 74%), of the bis(2,8-acetoxymercuriomethyl)-3-methyl-1,7-dioxaspiro[5.5]undecane. This crude bis-acetate (1.69 g, 2.3 mmol) was dissolved in THF (10 ml) and aq sat. NaCl (10 mL) was added, and the mixture stirred. THF was removed and the white precipitate of the chloromercuric derivative **37** was collected and dried in vacuo (1.32 g, 86%); mp 105−107 °C.

Anal. calcd for $C_{12}H_{20}Cl_2Hg_2O_2$: C 21.5, H 3.0. Found C 21.9, H 3.2.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.75 (d, 3 H, *J* = 7 Hz), 0.86 (d, 3 H, *J* = 6.5 Hz), 0.81−1.74 (m, 31 H), 1.92 (m, 2 H), 2.11 (tt, 1 H, *J* = 13.5, 4.5 Hz), 2.15−2.41 (m, 2 H), 3.18 (td, 1 H, *J* = 10.0, 4.0 Hz), 3.50 (tdd, 1 H, *J* = 11.0, 4.0, 2.5 Hz) 3.63 (dddd, 1 H, *J* = 11.5, 9.0, 4.5, 2.5 Hz), 3.71 (ddd, 1 H, *J* = 11.0, 5.0, 2.5 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 10.6, 18.2, 19.3, 19.4, 26.9, 28.0, 29.5, 30.1, 32.4, 34.3, 34.4, 34.6, 34.62, 36.0, 36.30, 37.5, 37.7, 39.5, 69.5, 69.7, 70.6, 74.9, 97.3, 97.7.

Reduction of the Bis(mercurymethyl)spiroacetal 37

The bis(mercurymethyl)spiroacetal (as the acetate 450 mg, 63 mmol) was dissolved in THF (6 mL) and 0.025 M aq NaOH (6 mL) was added followed by Et_3BnNCl (215 mg, 0.94 mmol). $NaBH_4$ (48 mg, 1.26 mmol) was added and the mixture stirred for 1 h. After filtering through Celite, the aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined Et_2O extracts were dried ($MgSO_4$) and the solvent carefully removed to leave an oil. This was chromatographed (silica gel, pentane) to provide the desired product (diastereomeric mixture) (103 mg, 83%).

HRMS: *m*/*z* Calcd for $C_{12}H_{22}O_2$ 198.1619. Obsvd 198.1612.

GC analysis revealed three diastereomers (57:32:12) of system 25 and the two major ones were separated by HPLC (6% EtOAc in hexane, silica gel).

Isomer 1 40

$[\alpha]_D^{25}$ −69.4 (*c* = 0.09, $CHCl_3$). Chiral GC (β-cyclodextrin) 71% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.80 (d, 3 H, *J* = 6.6 Hz), 1.10, (d, 3 H, *J* = 6.4 Hz), 1.12 (d, 3 H, *J* = 6.3 Hz), 1.09−1.24 (m, 2 H), 1.32−1.61 (m, 8 H), 1.85 (qt, 1 H, *J* = 12.7, 3.9 Hz), 3.26 (dq, 1 H, *J* = 9.7, 6.3 Hz), 3.64, (dqd, 1 H, *J* = 12.7, 6.3, 1.9 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.4 (CH_3), 18.9 (CH_2), 19.3 (CH_3), 21.7 (CH_3) 27.7 (CH_2), 32.7 (CH_2), 34.9 (CH_2) 36.0 (CH_2) 36.7 (CH), 64.9 (CH), 70.6 (CH), 95.8 (C).

2D-NOESY: No cross peak between δ = 3.64 and 3.26.

GC-MS: *m*/*z* (%) = 198 (2.6), 183 (0.8), 154 (24), 139 (2.5), 126 (22), 115 (22), 112 (100), 97 (24), 83 (34), 69 (30), 55 (44), 43 (55).

Isomer 2, 39

$[\alpha]_D^{25}$ +48.7 (*c* = 4.3, $CHCl_3$). Chiral GC (β-cyclodextrin) 71% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (d, 3 H, *J* = 7 Hz), 1.04 (d, 3 H, *J* = 6.7 Hz), 1.10 (d, 3 H, *J* = 6.3 Hz), 1.08−1.18 (m, 1 H), 1.28−1.37 (m, 3 H), 1.45−1.58 (m, 5 H), 1.85 (tt, 1 H, *J* = 13.2, 4.1 Hz), 2.08 (tt, 1 H, *J* = 13.5, 4.6 Hz), 3.65 (dqd, 1 H, *J* = 11.2, 6.4, 2.1 Hz), 3.86 (dq, 1 H, *J* = 6.6, 2.5 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8 (CH_3), 18.7 (CH_3), 19.0 (CH_2), 21.9 (CH_3), 26.4 (CH_2), 29.9 (CH_2) 31.2 (CH), 32.8 (CH_2), 32.8 (CH_2), 35.0 (CH_2), 65.1 (CH), 66.3 (CH), 96.2 (C).

2D-NOESY: Cross peak between δ = 3.86 and 3.65.

GC-MS: *m*/*z* (%) = 198 (1.9), 183 (0.8), 154 (25), 139 (2.3), 126 (14), 115 (16), 112 (100), 97 (23), 83 (32), 69 (23), 55 (39), 43 (48).

Dienone 36 with AD-Mix β

To a flask containing *tert*-butyl alcohol (20 mL) and H_2O (20 mL) was added AD-Mix β (10.5 g) and methanesulfonamide (0.57 g, 6 mmol). The thick orange mixture was cooled (0 °C) and then dienone **36** (1 g, 5.5 mmol) was added in one portion and the reaction was left to stir for 23 h at 0 °C (cold-room). Na_2SO_3 (6 g) was added and the mixture was stirred at r.t. for 1 h. After filtration, the solvent was removed in vacuo (bath temperature, 80 °C) and acetone (~ 50 mL) and PPTS (50 mg) was added to the residue, presumably containing the tetrol in some form. This mixture was refluxed overnight, filtered and the solvent removed to yield an oil (1.13 g, 89%). This was chromatographed (cyclohexane/EtOAc, 30:70) to provide the 2,8-bis(hydroxymethyl)-3-methyl-1,7-dioxaspiro[5.5]undecane (**43**).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (d, 3H, *J* = 6.2 Hz), 1.23-1.66 (m, 10 H), 1.85 (qt. 1 H, *J* = 13.4, 4.1 Hz), 2.0−2.1 (br s, 2 H), 3.33 (m, 1 H,), 3.45−3.59 (m, 3 H), 3.66−3.73 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.3 (CH_3), 18.4, 26.3, 27.4 (CH_2), 30.8 (CH), 35.0, 35.7 (CH_2), 63.8, 66.1 (CH_2), 69.7, 75.0 (CH), 95.8 (C).

For further characterisation, this was transformed to mesylate **44** in the normal way with methanesulfonyl chloride in CH_2Cl_2 and Et_3N, to provide a viscous oil which was purified by flash chromatography (cyclohexane/EtOAc, 70:30) (73 mg, 29%); $[\alpha]_D^{25}$ −23.4 (*c* = 0.135, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (d, 3 H, *J* = 6 Hz), 1.22−1.64 (m, 10 H), 1.86 (qt, 1 H, *J* = 13.2, 4.1 Hz), 3.00 (s, 3 H), 3.01 (s, 3 H), 3.48 (ddd, 1 H, *J* = 9.6, 5.4, 2.1 Hz), 3.86 (ddd, 1 H, *J* = 11.8, 6, 4, 2.1 Hz), 4.11−4.18 (ddd, 2 H, 10.9, 6, 4 Hz) 4.21−4.36 (ddd, 2 H, *J* = 11.2, 5.4, 2.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.3 (CH_3), 18.2, 26.2, 27.3 (CH_2), 30.5 (CH), 34.5, 35.2 (CH_2), 37.5 (CH_3), 37.6 (CH_3) 67.6 (CH), 71.0 (CH_2), 72.5 (CH_2), 73.2 (CH), 96.4 (C).

Anal. calcd for $C_{14}H_{26}O_8S_2$: C 43.5, H 6.8. Found C 43.8, H 6.9.

(2*S*,3*R*,6*S*,8*R*)-2,3,6-Trimethyl-1,7-dioxaspiro[5.5]undecane (40)

The above bis-mesylate (20 mg, 0.05 mml) was dissolved in anhyd THF (10 mL) and treated with $LiAlH_4$ in the usual way to provide the 2,3,8-trimethyl-1,7-dioxaspiro[5.5]undecane. Comparisons of mass spectra and retention times confirm this isomer is identical to the first eluting isomer formed by the procedure in Scheme 3, which was demonstrated to be **40**.

2,8-Dimethyl-4-methylene-1,7-dioxaspiro[5.5]undecane (47)

Methyltriphenylphosphonium iodide (2.58 g, 6.4 mmol) was added portionwise to a stirred solution of BuLi (4 ml, 1.6 M solution in hexanes, 6.4 mmol) in anhyd THF (20 mL). The resulting mixture was stirred at r.t. for 4 h, during which time a yellow solid formed. Predominantly (*E*,*E*)-spiroketone **46** (1 g, 5.05 mmol) in anhyd THF (5 mL) was added over a period of 5 min, during which time a white solid formed. The stirred mixture was refluxed overnight. After removal by filtration, the solid was washed with Et_2O (2 × 20 mL) and the combined filtrate and washings were washed with H_2O, dried (Na_2SO_4) and concentrated. Purification by flash column chromatography (CH_2Cl_2/hexane, 1:4) yielded 0.47 g (52%) of the alkene **47**, accompanied by a low level (~10%) of a second isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (d, 3 H, *J* = 6.3 Hz, CH_3), 1.14 (m, 1 H, H-9*ax*), 1.15 (d, 3 H, *J* = 6.5 Hz, CH_3), 1.37 (ddd, 1 H, *J* = 14.0, 12.0, 5.0 Hz, H-11*ax*) 1.52 (m, 2 H, H-9*eq*, H-10*eq*), 1.62 (dm, 1 H, *J* = 14.0 Hz, H-11*eq*), 1.81−1.93 (m, 2 H, H-10*ax*, H-3*ax*), 2.10 (dm, 1 H, *J* = 14.0 Hz, H-5*eq*), 2.15−2.25 (m, 2 H, H-5*ax*, H-3*eq*), 3.62 (m, 2 H, H-2,8), 4.72 (m, 2 H, CH_2=).

^{13}C NMR: (100 MHz, $CDCl_3$): δ = 19.0 (C-10), 21.5, 21.7 (2 CH_3) 32.4 (C-9), 34.7 (C-11), 41.5 (C-3) 44.3 (C-5), 65.4, 65.6 (C-2,8), 97.0 (C-6), 109.6 (CH_2=), 142.1 (C-4). (this isomer is *E*,*E*-ring configured).

GC-MS: *m*/*z* (%) = 196 (12), 152 (26), 151 (12), 138 (10), 137 (76), 124 (16), 115 (100), 109 (24), 97 (73), 95 (12), 85 (22), 82 (28), 81 (14), 79 (10), 73 (20), 69 (92), 67 (46).

HRMS: *m*/*z* Calcd for $C_{12}H_{20}O_2$ 196.1462. Obsvd 196.1468.

2,4,8-Trimethyl-1,7-dioxaspiro[5.5]undecanes (48) and (49)

A solution of **47** (0.47 g, 2.4 mmol) in EtOH (10 mL) with 10% Pd/C catalyst (200 mg) was stirred under a H_2 atmosphere at r.t. for 2.5 h. After removal of the catalyst by filtration, the mixture was diluted with H_2O (100 mL) and extracted with pentane. The combined pentane extracts were evaporated and the residue purified by HPLC (Et_2O/hexane 1:100) yielding 336 mg (78%). The major isomers were separated (HPLC, 2.5% EtOAc/hexane) and fully characterised.

Spiroacetal 48

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.04−1.6 (m, including 3 × CH_3 at 1.12, 18 H, d, *J* = 6.4, 1.15 Hz, d, *J* = 6.4 and 1.19 Hz, d, *J* = 7.3 Hz), 1.89 (app qt, 1 H, *J* = 13.3, 4.0 Hz, H-10a), 1.96 (m, 1 H, H-4e), 3.72 (m, 1 H, H-8), 3.88, (m, 1 H, H-2).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.1 (C-10), 20.7, 21.9, 22.0 (3 × CH_3), 25.4 (C-4), 32.5 (C-9), 35.4 (C-11), 38.6 (C-3), 40.1 (C-5), 60.2 (C-2), 65.2 (C-8), 97.5 (C-6).

EIMS: *m*/*z* = 198 (8), 154 (8), 139 (19), 129 (70), 128 (35), 126 (45), 115 (78), 114 (21), 112 (62), 111 (49), 98 (9), 97 (43), 87 (20), 83 (50), 69 (100), 55 (64).

HRMS: *m*/*z* Calcd for $C_{12}H_{22}O_2$ 198.1618. Obsvd 198.1612

Spiroacetal 49

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.78 (app q, 1 H, *J* = 12.1 Hz, H-3a), 0.67 (d, 3 H, *J* = 6.7 Hz, CH_3 at C-4), 0.95 (t, 1 H, *J* = 12.6 Hz, H-5a), 1.09 (d, 3 H, *J* = 6.4 Hz, CH_3), 1.12 (d, 3 H, *J* = 6.2 Hz, CH_3), 1.15 (m, 1 H, H-9a), 1.35 (td, 1 H, *J* = 13.3, 4.6 Hz, H-11a), 1.47−1.52 (m, 5 H, H-10e, H-9e, H-11e, H-3e, H-5e), 1.86 (tt, 1 H, *J* = 13.3, 3.5 Hz, H-10a), 2.00 (m, 1 H, H-4a), 3.67 (m, 2-H, H-2,8).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.0 (C-10), 21.7, 21.9, 22.0 (3 × CH_3) 25.1 (C-4), 32.8 (C-9), 35.1 (C-11), 41.6 (C-3), 43.9 (C-5), 65.0, 65.1, (C-2,C8), 96.5 (C-6).

EIMS: *m*/*z* = 198 (10), 154 (8), 139 (17), 129 (100), 128 (42), 126 (53), 115 (96), 114 (15), 112 (74), 111 (51), 98 (10), 97 (34), 83 (17), 69 (33), 55(31).

HRMS: *m*/*z* Calcd for $C_{12}H_{22}O_2$, 198.1618. Obsvd 198.1617.

Alternative Approach to Diastereomers of 2,4,8-Trimethyl-1,7-dioxaspiro[5.5]undecane (26)

Addition of MeLi in Et_2O at −78 °C to racemic spiroketone **46** followed by a standard workup provided essentially a single alcohol **50**.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.10 (d, 3 H, *J* = 6.5 Hz, CH_3), 1.12 (s, 3 H, CH_3-4), 1.17 (d, 3 H, *J* = 6.5 Hz, CH_3), 1.20−1.96 (m, 10 H), 3.72 (m, 1 H, H-2 or H-8), 3.90 (m, 1 H, H-8 or H-2), 4.69 (1 H, OH).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.5 (C-10), 21.2, 21.8 (CH_3 2,8), 29.9 (CH_3-4), 32.2, 34.6 (C-3,9), 45.6, 45.7 (C-5,11), 61.6 (C-2), 66.1 (C-8), 68.3 (C-4), 98.3 (C-6).

GC-MS: *m*/*z* (%) = 214 (M^+, 4), 155 (22), 145 (34), 142 (11), 127 (24), 115 (16), 114 (11), 112 (10), 103 (15), 97 (18), 85 (42), 84 (21), 83 (10), 69 (18), 58 (5).

HRMS: *m*/*z* Calcd for $C_{12}O_3H_{22}$ 214.1568. Obsvd 214.1572.

Elimination of H_2O (catalytic TsOH acid in benzene) afforded three alkenes, with the minor one being the exo-methylene derivative **47** described above. Separation was achieved by HPLC using 3% Et_2O/hexane.

2,4,8-Trimethyl-1,7-dioxaspiro[5.5]undec-3-ene (52)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.10 (d, 3 H, *J* = 6.5 Hz, CH_3), 1.19 (d, 3 H, *J* = 7.0 Hz, CH_3), 1.41−1.99 (m, 6 H, H-9,10,11), 1.64 (br s, 3 H, CH_3-4), 1.85 and 2.05 (br d, 1 H each, *J* = 13.0 Hz, 2 × H-5), 3.77 (m, 1 H, H-8), 4.10 (br m, 1 H, H-2), 5.32 (m, 1 H, H-3).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.2 (C-10), 21.0, 21.9, 22.8 (CH_3-2,4,8), 32.6, 34.7, 40.6 (C-9,11,5), 63.7 (C-8), 66.1 (C-2), 96.0 (C-6), 123.7 (C-3), 129.2 (C-4).

GC-MS *m*/*z* (%): = 196 (M^+, 17), 153 (12), 140 (10), 139 (93), 138 (24), 137 (19), 127 (11), 112 (18), 107 (43), 97 (29), 85 (22), 83 (20), 82 (33), 81 (15), 69 (100).

HRMS: *m*/*z* Calcd for $C_{12}H_{20}O_2$, 196.1462. Obsvd 196.1456.

2,4,8-Trimethyl-1,7-dioxaspiro[5.5]undec-4-ene (51)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.12 and 1.23 (d, 2 × 3 H, *J* = 6.5 Hz, CH_3-2, CH_3-8), 1.41−1.95 (m, 8 H), 1.66 (br s, 3 H, C-4 CH_3), 3.86 (m, 1 H, H-8), 3.99 (m, 1 H, H-2), 5.32 (br s, 1 H, H-5).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.9 (C-10), 21.1, 22.2, 22.8 (CH_3-2,4,8), 32.5, 34.6, 37.3 (CH_2-3,9,11), 63.0 (C-8), 65.8 (C-2), 94.9 (C-6), 124.9 (C-5), 136.1 (C-4).

GC-MS: *m*/*z* (%) = 196 (M^+, 6), 181 (6), 152 (8), 137 (16), 127 (100), 124 (68), 109 (30), 81 (14), 80 (30), 79 (17), 55 (15).

HRMS: *m*/*z* Calcd for $C_{12}H_{20}O_2$ 196.1462. Obsvd 196.1455.

Hydrogenation of this olefin mixture in the normal way provided a 48:52 mixture of the target spiroacetals **48** and **49** respectively.

Enantiomers of 48, 49 and Minor Isomers (Scheme 6).

Ethyl 3-Methyl-5-(tetrahydropyran-2′-yloxy)hexanoate (54)

A solution of Bu_3SnH (80 g, 30 mmol) in benzene (30 mL) was added over a period of 48 h to a solution of 53 (8.1 g, 30 mmol) and AIBN (100 mg) in a mixture of ethyl crotonate (34.2 g, 300 mmol) and benzene (50 mL). After completion of the addition, the solvent was removed in vacuo and the residue was purified by flash chromatography (Et_2O/hexane, 1:20) to provide **54**, 4.2g (50%). This mixture of four diastereomers was characterised only by its ^1H and ^{13}C NMR spectra before reduction to aldehyde **55**.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.9−1.2 (m, 9 H, CH_3), 1.3−2.6 (m, ~11 H), 3.45−3.55 (m, 1 H), 3.8−4.2 (m, 4 H), 4.75−4.85 (br s, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = with overlapping signals between 13.7−49.0, 59.8−72.9 (12 C, C−O), 95.3, 95.5, 98.8, 99.4 (C-2'), 172.2−172.5 (4 C, C=O).

3-Methyl-5-(tetrahydropyran-2'-yloxy)hexanal (55)

A solution of Dibal-H in CH_2Cl_2 (12 mmol, 12 mL of a 1 M solution) was added slowly to a solution of ester **54** (3 g, 12 mmol) in CH_2Cl_2 (100 mL) at −78 °C. After 30 min, none of the starting material could be detected by TLC, and the reaction was quenched by adding H_2O (10 mL). After addition of 1 M HCl until the mixture became clear, the organic layer was separated and the aqueous phase was extracted with Et_2O. The combined Et_2O extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was purified by flash column chromatography (Et_2O/hexane, 1:20) to yield **55** (1.3 g, 47%) as an isomeric mixture, characterised by its NMR spectra.

^1H NMR (100 MHz, $CDCl_3$): δ = 0.7−1.00 (series of doublets, 6 H, CH_3), 1.2−2.3 (m, ~11 H), 3.2−3.9 (m, 3 H), 4.55−4.65 (br s, 1 H), 9.3−9.45 (narrow triplets, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$, DEPT): δ = with higher field signals from 19.2−51.29, 61.7 (CH_2O), 61.8, 62.5, 62.6, 68.2 (CHO), 68.6, 72.1, 72.6, 95.5 (C-2'), 95.9, 98.4, 99.2, 200.5

8-Methyl-6-oxo-10-(tetrahydropyran-2'-yloxy)dec-1-ene (56)

A solution of pent-4-enylmagnesium bromide [prepared from Mg turnings (120 mg, 5 mmol) and 1-bromopent-4-ene (745 mg, 5 mmol) in Et_2O] was added at −50 °C to a solution of **55** (1.12 g, 5 mmol) in Et_2O. After stirring for 20 min, the mixture was quenched by addition of H_2O (10 mL), and then was carefully acidified with 1 M HCl. The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined Et_2O extracts were washed with brine, dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was directly oxidized without any further purification. The crude alcohol was dissolved in CH_2Cl_2 (100 mL) and after addition of molecular sieves 4Å (2 g) and PDC (2 g), the mixture was vigorously stirred until no alcohol could be detected (TLC). The mixture was diluted with Et_2O (100 mL) and filtered through silica gel (50 g) and the silica gel thoroughly washed with Et_2O. The combined Et_2O extracts were evaporated in vacuo. The residue was purified by flash chromatography (Et_2O/hexane 1:10) to provide the ketone **56** (1.0 g, 70%), again as a mixture of isomers.

^1H NMR (200 MHz, $CDCl_3$): δ = 0.9−1.15 (doublets, 6 H, CH_3), 1.4−2.4 (m with prominent signals at 1.35, 1.7, 2.0 and 2.05−2.15, 17 H), 3.5 (br s, 1 H), 3.8−4.1 (m, 2 H), 4.75−4.85 (m, 1 H), 5.05−5.15 (m, 2 H), 5.7−5.85 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.5, 19.8, 19.94, 19.9, 20.1, 20.2, 20.3, 20.4, 20.5, 20.6, 22.2, 22.8, 23.01, 23.03, 23.07, 23.1, 25.95 (2 C), 25.98, 26.0, 26.2, 26.23, 26.26, 26.3, 31.59, 31.6, 31.7 (2 C), 33.4, 33.45, 33.5, 41.2, 42.2, 42.28, 42.3, 44.4, 44.8, 44.9, 45.20, 49.6, 50.2, 50.5, 50.8, 62.0 (C−O), 62.1, 62.6, 62.7, 68.6, 68.9, 72.6, 72.8, 95.6 (OCHO), 96.0, 98.7, 99.31, 115.06 (CH_2) 115.08, 115.11, 115.14, 138.39 (CH=CH_2), 138.4, 138.5, 208.2 (C=O), 208.4 208.6.

8,10-Dimethyl-1,7-dioxaspiro[5.5]undec-2-ylmethanol (58)

The above ketone **56** (700 mg, 2.5 mmol) was added to a solution of AD-Mix-β (4.2 g) in *tert*-butyl alcohol (15 mL) and H_2O (15 mL) at 0 °C and maintained at this temperature for 15 h. The mixture was quenched by the addition of CH_2Cl_2 (20 mL), MeOH (5 mL), and HCl (5 mL of 1 M). After stirring for 30 min, the organic layer was separated and the aqueous phase was extracted with Et_2O. The combined Et_2O extracts were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo. The residue was purified by flash chromatography (Et_2O/hexane, 1:5), to provide a mixture (350 mg, 68%) of the two (*E*,*E*)-diastereomers of **58**. Further chromatography led to separation of the pure (2*S*,4*S*,6*R*,8*R*)-**58** (with an *axial* C-4 methyl group) and a less pure sample of the (2*S*,4*R*,6*R*,8*R*)-**58** (with an *equatorial* C-4 methyl group).

^1H NMR (200 MHz, $CDCl_3$) (2*S*,4*S*,6*R*,8*R*)-**58**: δ = 1.1−1.42 [m, 13 H including CH_3 doublets at 1.14 (*J* = 6.6 Hz) and 1.16 (*J* =7.3 Hz)], 1.55 (d of m, 1 H, *J* = 13.0 Hz) 1.68 (dd, 1 H, *J* = 7, 5.5 Hz), 1.79 (br m, 1 H), 1.97 (1 H, qt, *J* = 13.5, 4.2 Hz), 3.44 (m, 2 H), 3.7 (m, 1 H), 3.9 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.7, 21.3, 22.1, 25.7, 26.7, 36.2, 38.5, 40.3, 60.4, 66.5, 70.4, 97.5.

HRMS: *m*/*z* Calcd for $C_{12}O_3H_{22}$, 214.1567. Obsvd 214.1517.

^{13}C NMR (50 MHz, $CDCl_3$): (2*S*,4*R*,6*R*,8*R*)-**58**: δ = 18.7, 22.2, 21.9, 25.4, 26.9, 35.8, 41.7, 44.1, 65.4, 66.4, 70.2, 96.4.

2-Iodomethyl-8,10-dimethyl-1,7-dioxaspiro[5.5]undecane (59)

I_2 (305 mg, 1.2 mmol) was added to a hot (100 °C) toluene solution (50 mL) of spiroacetal **58** (250 mg, 1.2 mmol), Ph_3P (309 mg, 1.2 mmol) and imidazole (220 mg, 3 mmol). After stirring for 20 min at this temperature, no starting material was detectable (TLC) and the reaction was quenched with H_2O (20 mL). The organic layer was separated and the aqueous phase was extracted with Et_2O. The combined Et_2O extracts were washed with $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and the solvent evaporated in vacuo. The residue was subjected to flash chromatography (Et_2O/hexane, 1:20) to provide **59** (300 mg, 80%) as a diastereomeric mixture that was not separated.

^1H NMR (200 MHz, $CDCl_3$) of isomer mixture: δ = 0.8−1.0 (m, 4 H, with CH_3 doublet), 1.25−2.45 (m, 15 H, with superimposed CH_3 doublet at 1.28), 2.78−3.03 (m, 2 H, CH_2I), 3.59−3.75 (m, 1 H) and 4.08−4.31 (m, 1 H).

^{13}C NMR (50 MHz, C_6D_6): δ = 9.8, 10.4, 19.1 (2 C), 21.6, 21.9, 22.1, 22.2, 25.1, 25.9, 31.1, 31.2, 35.3, 35.9, 38.7, 40.1, 41.9, 44.1, 60.8, 65.5, 69.3, 70.5, 97.1, 98.0. (24 ^{13}C signals resolved).

GC-MS (one isomer): *m*/*z* (%) = 324 (M^+, 2.7), 280 (3.4), 241 (21.8), 240 (7.7), 238 (11.5), (196), (9.2), 169 (12.4), 139 (11.4), 129 (100), 128 (50), 126 (25.9), 113 (35.6), 111 (53.6), 98 (11), 83(24.9). The other diasteromer exhibited a very similar mass spectrum.

(2*S*,4*R*,6*R*,8*S*)-2,4,8-Trimethyl-1,7-dioxaspiro[5.5]undecane (60) and the (2*S*,4*S*,6*R*,8*S*)-epimer 61

The above iodide mixture **59** (200 mg, 0.62 mmol) was added to a suspension of Raney-Nickel in EtOH/H_2O (10 mL, 20:1) containing NaOH, (40 mg, 1 mmol). After stirring for 3 d, no starting material could be detected (GC) and the reaction mixture was diluted with brine (80 ml) and pentane. The combined pentane extracts were washed again with brine ($MgSO_4$) and the solvent was evaporated at 40 °C. The residue was purified by HPLC (hexane/Et_2O, 100:1) and yielded 45 mg of **60** and 48 mg of **61** (overall yield 76%). These isomers had NMR and mass spectral data matching those listed for

the racemates, **49** and **48** with $[\alpha]_D^{23}$ −66.4 ($CHCl_3$) and −69.0 ($CHCl_3$), respectively.

Alternative Synthesis of 60 and Some Diastereomers from (*R*)-(+)-Pulegone

Methyl ketone **68**: MeLi (200 mL of 1.4 M solution in Et_2O) was added to anhyd THF (250 mL) under N_2 and cooled to −78 °C. Citronellic acid {**67**, $[\alpha]_D^{25}$ +9.3) prepared from technical grade (*R*)-(+)-pulegone (24.5 g, 144 mmol)} was gradually added as a solution in anhyd THF (250 mL) while maintaining the temperature at −78 °C. After stirring for 1 h at −78 °C, the reaction was permitted to warm to r.t. for 30 min, after which GC monitoring indicated complete reaction. An excess of aq sat. NH_4Cl was added and allowed to stir for a further 30 min. The aqueous phase was separated and extracted three times with Et_2O. The combined Et_2O extracts were washed with aq sat. $NaHCO_3$ and the washings were extracted once with Et_2O. The combined organic layers were washed with brine, and dried ($MgSO_4$). Removal of solvent in vacuo afforded the crude ketone **68** which was purified by flash chromatography on silica gel, using 20:1 hexane/Et_2O as solvent to afford 16.85 g (71%); $[\alpha]_D^{25}$ +14.4 (*c* = 3.45, $CHCl_3$)

^{1}H NMR: (400 MHz, $CDCl_3$): δ = 0.87 (d, 3 H, *J* = 6.6 Hz), 1.11−1.34 (m, 2 H), 1.56 (br s, 3 H), 1.64 (br d, 3 H, *J* = 1.2 Hz), 1.86−2.03 (m, 3 H), 2.08 (br s, 3 H), 2.18 (dd, 1 H, *J* = 15.8, 8.2 Hz), 2.37 (dd, 1 H, *J* = 15.7, 5.6 Hz), 5.05 (tm, 1 H, *J* = 7.1Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.5, 19.6, 25.4, 25.6, 28.9, 30.3, 36.9, 51.1, 124.2, 131.4, 209.0.

GC-MS : *m*/*z* (%) = 169 (0.4), 168 (3.2, M^+), 153 (1.3), 150 (1.5), 135 (6.5), 125 (2.5), 111 (4.2), 110 (17.3), 109 (4.5), 98 (4.4), 95 (42), 85 (18), 69 (27), 67 (16), 55 (15), 43 (100) 41 (56).

HRMS: *m*/*z* Calcd for $C_{11}H_{20}O$ 168.1514. Obsvd 168.1522.

Protected Enone 69

Ketone **68** (16.85 g, 100.3 mmol), was dissolved in distilled benzene (300 mL) and anhyd ethylene glycol (17 mL, 300 mmol) to which anhyd PPTS (3.8 g, 15 mmol) was added. The reaction was refluxed under a Dean−Stark trap overnight. GC monitoring showed ≈85% reaction, so the flask was cooled, 3Å molecular sieves were added, and the mixture stirred overnight. No further reaction could be induced, so the reaction was quenched with aq sat. $NaHCO_3$, the aqueous layer separated, and extracted with Et_2O. The benzene layer was evaporated in vacuo, and the resulting oil taken up in Et_2O. This was washed with aq sat. $NaHCO_3$ and the combined Et_2O layers were washed with brine, dried ($MgSO_4$) and the solvent removed in vacuo to provide the crude acetal **69** (20.13 g, 83% allowing for 12% contamination with starting material). This was not purified, but used directly in the subsequent ozonolysis, and the data below were obtained on a small sample purified by flash chromatography using 50:1 hexane/Et_2O as solvent; $[\alpha]_D^{25}$ +2.3 (*c* = 3.341, $CHCl_3$).

^{1}H NMR (400 MHz,$CDCl_3$): δ = 0.93 (d, 3 H, *J* = 6.6 Hz), 1.28 (s, 3 H), 1.10−1.19 (m, 1 H), 1.33−1.46 (m, 2 H), 1.57 (br s, 3 H), 1.59−1.67 (m, 2 H), 1.65 (br d, 3 H, *J* = 1.1 Hz) 1.86−2.02 (m, 2 H), 3.87−3.93 (m, 4 H), 5.07 (tm, 1 H, *J* = 7.1 Hz).

^{13}C NMR (100 MHz $CDCl_3$): δ = 17.6, 20.8, 24.0, 25.4, 25.6, 28.7, 38.1, 45.5, 64.2, 64.4, 110.5, 124.8, 131.0.

GC-MS: *m*/*z* (%) = 213 (0.1), 212 (0.5, M^+), 197 (3.3), 151 (1.1), 150 (7.7), 142 (1.0), 136 (1.5), 135 (14), 129 (5.9), 121 (1.9), 109 (5.8), 107 (2.4), 95 (8.8), 87 (100), 85 (11), 69 (14), 55 (11), 43 (80), 41 (52).

HRMS: *m*/*z* Calcd for $C_{13}H_{24}O_2$ 212.1776. Obsvd 212.1775.

Anal. calcd for $C_{13}H_{24}O_2$: C 73.5, H 11.4. Found C 73.2, H 11.2.

Protected Ketol 70

Crude enone **69** (20.13 g, 95 mmol) was dissolved in distilled MeOH (300 mL) and cooled to −78 °C. Ozone was bubbled through the solution, which turned pale blue after ≈ 2h. While maintaining the temperature at −40 °C, solid $NaBH_4$ (7.6 g, 200 mmol) was added, then the solution was warmed to r.t. A solution of 30% H_2O_2 (100 mL, 800 mmol) and H_2O (250 mL), containing NaOH (32 g, 800 mmol) was then added and stirred for 1 h. Over this time a gelatinous precipitate was formed. The supernatant layer was decanted, and the precipitate washed with Et_2O. The mixture was extracted 5 times with Et_2O, and the MeOH rich extracts were concentrated in vacuo. The resulting oil was partitioned between Et_2O and H_2O and the combined Et_2O layers dried ($MgSO_4$). Removal of solvent in vacuo afforded crude alcohol **70**. Purification by flash chromatography using 1:1 hexane/Et_2O provided 14.66 g (82%); $[\alpha]_D^{25}$ +1.8 (*c* = 3.79, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, 3 H, *J* = 6.5 Hz), 1.11−1.2 (m, 1 H), 1.27 (s, 3 H), 1.35−1.66 (m, 6 H), 1.81 (br s, 1 H), 3.56 (br t, 2 H, *J* = 6.5 Hz), 3.84−3.91(m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 24.0, 28.6, 30.0, 33.8, 45.4, 63.0, 64.2, 64.3, 110.4.

GC-MS : *m*/*z* (%) = 188 (0.0, M^+) 174 (1.1), 173 (9.7, M-15), 155 (0.1), 142 (0.1), 130 (0.1), 129 (1.0), 127 (0.5), 113 (1.9), 99 (5.6), 88 (4.6), 69 (47), 55 (5.1), 43 (49), 41 (13).

HRMS: *m*/*z* Calcd for $C_9H_{17}O_3$ (M − 15) 173.1178. Obsvd 173.1177.

Protected Iodo Ketone 71

Alcohol **70** (14.66 g, 78 mmol) was dried over 3Å molecular sieves and then cannulated from the sieves into a reaction flask containing anhyd CH_2Cl_2 (900 mL) under N_2. Anhyd Et_3N (60 mL, 468 mmol) was added via a syringe, and then distilled MsCl (12 mL, 156 mmol) was added dropwise, also via a syringe. The reaction was exothermic and after ≈6 mL of MsCl had been added, the solvent began to refux and the reaction was cooled in ice for the remainder of the addition, after which GC monitoring showed complete reaction had occurred. After the addition of an excess of aq sat. $NaHCO_3$ solution and stirring for several hours, the organic layer was separated and the solvent removed in vacuo. The resulting oil was taken up in Et_2O and washed with aq sat. $NaHCO_3$. The combined aqueous layers were extracted 3 times with Et_2O, and the combined Et_2O layers were washed with brine, dried ($MgSO_4$), and the solvent removed in vacuo to provide crude but quite clean mesylate (20.09g, 96%). The following data were obtained from a small sample purified by flash chromatography using 2:1 hexane/Et_2O as solvent; $[\alpha]_D^{25}$ +3.45 (*c* = 3.044, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, 3 H, *J* = 6.6 Hz), 1.17−1.27 [m, 4 H, incl. 1.27 (3 H,s)], 1.41−1.51 (m, 2 H), 1.58−1.81 (m, 4 H), 2.96 (s, 3 H), 3.84−3.92 (m, 4 H), 4.17 (t, 2 H, *J* = 6.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 24.1, 26.5, 28.4, 33.3, 37.3, 45.3, 64.2, 64.3, 70.3, 110.1.

GC-MS : *m*/*z* (%) = 266 (0.1 M^+), 253 (0.6), 252 (1.1), 251 (8.7, M-15), 115 (0.9), 129 (0.7), 113 (3.6), 111 (0.8), 109 (1.3), 99 (5.8), 88 (4.1), 87 (100), 83 (3.2), 79 (9.2), 69 (7.1), 59 (2.4), 55 (6.2), 43 (40), 41 (13).

HRMS: *m*/*z* Calcd for $C_{10}H_{19}O_5S$ (M − 15) 251.0953. Obsvd 251.0955.

The above mesylate (20.09 g, 75 mmol) as a solution in anhyd THF was dried with 3Å molecular sieves overnight. Dried and re-ground NaI (40 g, 225 mmol) was dissolved in anhyd THF (900 mL) under N_2. The starting material was cannulated into the reaction mixture and allowed to stir for 25 h, when GC monitoring indicated the reaction was virtually complete. An excess of aq satd $NaHCO_3$ solution was added, then stirred for 30 min. Et_2O was added to assist the

layers to separate, and the organic layer was concentrated to an oil. This was re-partitioned between aq satd $NaHCO_3$ solution and Et_2O, and the aqueous layer extracted three times with Et_2O. The aqueous layer from the reaction was likewise extracted, and the combined Et_2O extracts were washed with brine and aq 1% $Na_2S_2O_3$. After drying ($MgSO_4$) followed by removal of solvent in vacuo, the crude iodide **71** was purified via flash chromatography on silica gel using 50:1 hexane/Et_2O as solvent affording 19.21g (85%) of the product; $[\alpha]_D^{25}$ +6.3 (*c* = 3.049, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (d, 3 H, *J* = 6.6 Hz), 1.18−1.31 [m, 4 H, incl. 1.29 (s, 3 H)], 1.42-1.50 (m, 2 H), 1.57−1.69 (m, 2 H), 1.72−1.90 (m, 2 H), 3.15 (br t, 2 H, *J* = 6.9 Hz), 3.86−3.94 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.2, 21.0, 24.1, 28.2, 31.1, 38.7, 45.4, 64.3, 64.4, 110.3.

GC-MS : *m*/*z* (%) = 298 (0.0, M^+), 285 (0.1), 284 (0.9), 283 (7.9, M − 15), 197 (1.0), 171 (0.1), 155 (2.7) 128 (0.7), 127 (2.7), 113 (2.6), 99 (2.7), 88 (4.9), 87 (100), 69 (6.0), 67 (1.8), 59 (1.7), 55 (5.4), 43 (50), 41 (19).

HRMS: *m*/*z* Calcd for $C_9H_{16}O_2I$ (M − 15) 283.0195. Obsvd 283.0195.

Anal. Calcd for $C_{10}H_{19}IO_2$: C 40.3, H 6.4. Found C 40.5, H 6.3.

Protected enone 72

Iodide **71** (9.6g, 32mmol) as a solution in anhyd THF was dried overnight with 3Å molecular sieves. Fresh *t*-BuOK (10 g) was dissolved in anhyd THF (500 mL) under N_2 and the iodide solution was added by cannula. Precipitate was observed to form even before the addition was complete, and GC monitoring after 30 min indicated the reaction was complete. A minor amount of displacement (≈3%) of the iodide formed the *t*-Bu ether. Aq sat. $NaHCO_3$, aq sat. NaCl and a little 1% $Na_2S_2O_3$ were added to quench the reaction which was allowed to stir for 15 min. The organic layer was separated and concentrated in vacuo. The resulting oil was partitioned between aq sat. $NaHCO_3$ and Et_2O, and the aqueous layer extracted three times with Et_2O. The combined Et_2O extracts were diluted with 20% pentane, washed with brine, dried ($MgSO_4$), and the solvent removed in vacuo to provide the crude alkene **72** (6.29 g). This reaction was repeated on the same scale and the products from both were combined for flash chromatography using 50:1 petroleum ether/Et_2O to afford 7.91g (72%) of **72**; $[\alpha]_D^{25}$ −1.0 (*c* = 14.29, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (d, 3 H, *J* = 6.7 Hz), 1.29 (s, 3 H), 1.40−1.45 (m, 1 H), 1.64−1.77 (m, 2 H), 1.87−1.95 (m, 1 H), 2.06−2.13 (m, 1 H), 3.86−3.94 (m, 4 H), 4.95 (t, 1 H, *J* = 1.3 Hz), 4.97−5.00 (m, 1 H) 5.69−5.79 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 24.1, 28.8, 42.3, 44.7, 64.2, 64.7, 110.4, 115.9, 137.4.

GC-MS: *m*/*z* (%) = 170 (0.0, M^+), 156 (0.6), 155 (5.5, M − 15), 114 (0.9), 113 (6.3), 108 (1.1), 99 (6.6), 97 (1.7), 95 (1.3), 88 (5.1), 87 (100), 69 (3.9), 67 (3.3), 59 (9.4), 55 (4.4), 43 (57), 41 (21), 39 (10).

HRMS: *m*/*z* calcd for $C_9H_{15}O_2$ (M − 15) 155.1072. Obsvd 155.1074.

Anal. Calcd for $C_{10}H_{18}O_2$: C 70.5, H 10.7. Found C 70.1, H 10.6.

Protected Hydroxyenone 74

Alkene **72** (3.0 g, 17.6 mmol) was stirred in 30% AcOH (8 mL) at 80 °C for 5 h and then cooled, before the addition of aq sat. Na_2CO_3 (10 mL) and then Et_2O (20 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined Et_2O extracts were washed with brine (3 × 15 ml), separated, dried ($MgSO_4$) and concentrated in vacuo to provide the crude enone (2.2 g, 100%) which was converted without purification to the hydrazone as follows. The enone (2.2 g, 17.5 mmol) was added to a solution of *N*,*N*-dimethylhydrazine (3.2 g, 53 mmol) in absolute EtOH (12 mL), followed by AcOH (0.5 mL). The mixture was refluxed for 3 h, after which time the starting material had been consumed (GC). After removal of excess hydrazine and solvent, the residual oil was distilled (80−84 °C/15 Torr) to provide the hydrazone **20** (2.3 g, 78%) as a mixture of two isomers. [Alternatively, the mixture was extracted with Et_2O (20 mL) which was washed with aq $NaHCO_3$ solution (2 × 15 mL) and then H_2O (3 × 15 mL) before drying ($MgSO_4$) and concentration]. Chromatography on neutral alumina (pentane/Et_2O, 1:1) provided the hydrazone **20** as two isomers (21:79) of >97% purity (GC). The major isomer of **20** (*syn-anti* around C=N) was characterised by its GC-MS, ^{1}H and ^{13}C NMR data, before being alkylated.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.76 (d, 3 H, *J* = 6.4 Hz), 1.84 (s, 3 H, CH_3), 1.77−2.26 (m, 5 H), 2.32 [s, 6 H, N $(CH_3)_2$], 4.85 (m, 1 H), 4.93 (m, 1 H), 5.66 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.7 18.9, 30.7, 41.1, 45.7, 46.9, (2 C) 116.1, 136.7, 166.9.

GC-MS: *m*/*z* (%) = 168 (6, M^+) 125 (10), 100 (50), 59 (12), 58 (96), 56 (28), 45 (24), 44 (100).

Alkylated Hydrazone 73

To a stirred solution of *i*-Pr_2NH (1.2 g, 12 mmol) in anhyd THF (40 mL), was added BuLi (7.4 mL of 1.6 M solution in hexane, 12 mmol) dropwise at −40 °C, and the mixture was stirred for 2 h at this temperature. After cooling to −78 °C, a solution of hydrazone **20** (1 g, 6 mmol) in anhyd THF (6 mL) was added dropwise, followed by stirring at −78 °C for 3 h. A solution of (3*S*)-3-(tetrahydropyran-2'-yl)butyl iodide (1.7 g, 6 mmol) in anhyd THF (5 mL) was then added dropwise and the mixture allowed to warm to r.t. and stirred (12 h). Et_2O (50 mL) and H_2O (50 mL) were added and the aqueous layer was then re-extracted with Et_2O (3 × 20 mL). The combined Et_2O extracts were washed with brine (3 × 30 mL), separated, dried ($MgSO_4$) and concentrated in vacuo to provide the crude alkylation product **73** (1.8 g, 93%), again as an isomeric mixture (ca 42:58), which provided concordant ^{1}H and ^{13}C NMR spectra and GC-MS data.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.81 (d, 6 H, *J* = 6.1 Hz), 1.05 (d, 3 H, *J* = 6 Hz), 1.17 (d, 3 H, *J* = 6.2 Hz), 1.46−2.47 (m, 22 H), 2.34 (s, 12 H), 3.42 (m, 2 H), 3.66−3.86 (m, 4 H), 4.57 (br s, 1 H), 4.64 (br s, 1 H), 4.90 (m, 2 H), 4.97 (m, 2 H), 5.70 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.1, 19.2, 19.7, 21.6, 22.3, 22.8, 25.4, 25.5, 29.75, 29.8, 30.8, 30.84, 31.7, 36.6, 37.5, 41.3, 42.56, 42.6, 47.5, 62.5, 62.8, 70.5, 73.64 95.5, 98.9, 116.1, 116.2, 136.9, 136.94, 171.6, 171.7.

GC-MS (one isomer): *m*/*z* (%) = 324 (M^+, 10), 239 (64), 223 (42), 196 (34), 180 (25), 171 (56), 128 (45), 125 (52).

Protected Hydroxyenone 74

Hydrazone **73** (1 g, 3.08 mmol) was chromatographed on silica gel (EtOAc/hexane, 1:10 → 10:1) to provide the ketone **74** (0.71 g, 82%), as a diastereomeric mixture.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.83 (d, 6 H, *J* = 6 Hz, CH_3), 1.04, 1.16 (each d, 3 H, *J* = 6 Hz, CH_3), 1.35−2.45 (m, 34 H, both isomers), 3.35−3.9 (m, 6 H), 4.5−4.7 (m, 2 H), 4.9−5.0 (m, 2 H), 5.55−5.70 (m, 1 H).

^{13}C NMR: (50 MHz, $CDCl_3$): δ = 19.0, 19.6, 19.7, 19.8, 20.0, 21.5, 25.4, 25.5, 28.8, 29.6, 31.1, 36.0, 36.8, 41.1, 43.26, 43.3, 49.3, 62.5, 62.8, 70.7, 73.8, 95.7, 98.8, 116.3, 116.4, 136.6, 210.6, 210.8.

GC-MS: *m*/*z* (%): = 197 (4.3), 181 (19.6), 169 (1.1), 165 (2.4), 163 (4.3), 139 (16.7), 125 (5.6), 112 (15.6), 97 (21.3), 85 (100), 81 (65). (one diastereomer only).

HRMS: *m*/*z* Calcd for $C_{17}O_3H_{30}$ 282.2195. Obsvd 282.2178.

Hydroxy Ketone 75

Cond HCl (2 drops) was added to the hydrazone **73** (0.4 g, 1.23 mmol) in MeOH (15 mL) and the mixture was stirred for 4 h. Aq concd Na_2CO_3 was added until neutrality and then the solvent was removed in vacuo, and the residue was extracted with Et_2O (3 × 20 mL). The combined Et_2O extracts were dried ($MgSO_4$), concentrated in vacuo and chromatographed (silica gel, EtOAc/hexane, 1:7 → 1:1) to provide the hydroxy ketone **75** (0.2 g, 82%); $[\alpha]_D^{25}$ +3.9 (*c* = 1.56, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.82 (d, 3 H, *J* = 6.1 Hz), 1.11 (d, 3 H, *J* = 6.5 Hz), 1.33−2.38 (m, 11 H), 3.69 (m, 1 H), 4.90 (m, 1 H), 4.96 (m, 1 H), 5.67 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.6, 19.7, 23.4, 28.8, 38.6, 41.1, 43.1, 49.3, 67.4, 116.4, 136.6, 211.1.

GC-MS: *m*/*z* (%) = 183 (44), 145 (42), 142 (46), 139 (37), 127 (76), 123 (42), 115 (95), 99 (26), 81 (48), 69 (20), 65 (26), 43 (100).

HRMS: *m*/*z* Calcd for $C_{12}H_{22}O_2$ 198.1619. Obsvd 198.1622.

HRMS: *m*/*z* Calcd for $C_{12}H_{20}O$ (M − H_2O) 180.1513. Obsvd 180.1514.

Spiroacetal 76

The AD-Mix β reagent (1.8 g) was added to a stirred solution of *t*-BuOH/H_2O (10 mL/10 mL) at r.t., and this yellowish solution was cooled to 0 °C whereupon a yellowish solid precipitated. Alkene **75** (200 mg, 1 mmol) was added and the mixture was stirred at 0 °C for 3 d. Solid Na_2SO_3 (1.5 g) was added and the system was allowed to warm to r.t. and stirred (1 h). EtOAc (10 mL) was added and the aqueous layer was re-extracted with EtOAc (3 × 10 mL). The combined EtOAc fraction was dried ($MgSO_4$), concentrated in vacuo and chromatographed on silica gel (EtOAc/hexane, 1:10 → 1:1) to provide the spiroacetal **76** (165 mg, 76%). (An additional quantity of **76** was obtained from a similar sequence with protected hydroxyenone **74** in 63% yield); $[\alpha]_D^{25}$ −71.3 (*c* = 1.13, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (d, 3 H, *J* = 6.6 Hz), 1.10 (d, 3 H, *J* = 6.3 Hz), 1.23−2.06 (m, 11 H), 3.47−3.77 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0, 21.9, 22.0, 24.5, 32.5, 34.8, 35.1, 44.2, 65.4, 66.3, 69.6, 96.5.

GC-MS: *m*/*z* (%) = 214 (M^+, 6), 183 (58), 145 (36), 144 (42), 142 (42), 139 (34), 127 (70), 123 (20), 115 (93), 112 (20), 111 (54), 97 (48), 85 (31), 84 (48), 69 (93), 43 (100).

HRMS: *m*/*z* Calcd for $C_{12}H_{22}O_3$ 214.1569. Obsvd 214.1569.

(2*S*,4*R*,6*R*,8*S*)-2,4,8-Trimethyl-1,7-dioxaspiro[5.5]undecane (60)

The spiroacetal alcohol **76** (165 mg, 77 mmol) in anhyd pyridine (2 mL) (at −15 °C) was treated with tosyl chloride (294 mg, 154 mmol). After completion of the addition, the mixture was stirred for 3 h, and the temperature allowed to rise to 5 °C. Ice-water was added and the mixture was extracted with Et_2O (3 × 10 mL). The combined Et_2O extracts were washed with aq $CuSO_4$ solution, H_2O, aq sat. $NaHCO_3$ and brine, separated, dried ($MgSO_4$) and concentrated in vacuo. Preparative scale TLC (silica gel, hexane/EtOAc, 5:1) gave an oil (0.75 g, 88%). This tosylate was characterised by its ^{1}H and ^{13}C NMR spectra, before being reduced; $[\alpha]_D^{25}$ −27.4 (*c* = 0.66, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.81 (d, 3 H, *J* = 6.6 Hz), 1.04 (d, 3 H, *J* = 6.3 Hz), 1.22−2.00 (m, 11 H), 2.40 (s, 3 H), 3.58 (ddq, 1 H, *J* = 11.0, 6.0, 2.0 Hz), 3.76 (dddd, 1 H, *J* = 11.0, 6.0, 4.0, 2.0 Hz), 3.95 (d, 1 H, *J* = 6 Hz), 3.94 (d, 1 H, *J* = 4 Hz), 7.30 (d, 2 H, *J* = 8.5 Hz), 7.77 (d, 2 H, *J* = 8.5 Hz).

^{13}C NMR: (50 MHz, $CDCl_3$): δ = 18.7, 21.6, 21.8, 21.9, 24.5, 32.5, 34.7, 35.1, 43.7, 65.4, 66.9, 72.9, 96.6, 127.9 (2C), 129.7 (2 C), 133.2, 144.6.

This tosylate (81 mg, 0.22 mmol) was dissolved in anhyd Et_2O (1.5 mL) at 0 °C and under N_2, $LiAlH_4$ (50 mg, 1.32 mmol) was added. The mixture was stirred at r.t. for 24 h. The excess of $LiAlH_4$ was destroyed by the addition of H_2O (0.2 mL) and aq 15% NaOH. The mixture was then stirred for 10 min and filtered through Celite. The filter cake was washed three times with Et_2O, and the combined Et_2O extracts were dried ($MgSO_4$), concentrated at reduced pressure and then chromatographed on silica gel (hexane/EtOAc) to provide the spiroacetal **60** (21.3 mg, 49%). This material was >99% ee and provided physical and spectroscopic data in agreement with those listed above.

Spiroacetal *ent*-61 (Scheme 8)

Hydrazone **20** (Scheme 7) was alkylated with (*R*)-3-(tetrahydropyran-2'-yl)butyl iodide in the manner described above for the (*S*)-iodide. The hydrazone was selectively removed by chromatography on silica gel with hexane/Et_2O to afford the protected hydroxyenone **78** in 85% yield.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.82, (d, 6 H, *J* = 6 Hz), 1.02, 1.15 (d, each 3 H, *J* = 6 Hz), 1.39−2.12 (m, 26 H), 2.27−2.37 (m, 8 H), 3.37−3.78 (m, 6 H), 4.54 and 4.60 (m, each 1 H), 4.88 and 4.95 (m, each 2 H), 5.56−5.73 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.0, 21.5, 19.6, 19.73, 19.7, 20.0, 25.4, 25.4, 28.8, 31.1, 31.12, 35.9, 36.7, 41.1, 43.2, 43.3, 49.2, 62.5, 62.8, 70.6, 73.5, 95.6, 98.8, 116.3, 116.3, 136.5, 136.6, 210.6, 210.8.

GC-MS: *m*/*z* (%) = 197 (3.3), 181 (17), 139 (12), 112 (15), 97 (16), 85 (100), 83 (12), 69 (52).

Treatment of hydrazone **77** with 10% HCl in the way described above, afforded instead the fully deprotected hydroxyenone **17**; $[\alpha]_D^{23}$ −5.0 (*c* = 2.93, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.82 (d, 3 H, *J* = 6 Hz), 1.11 (d, 3 H, *J* = 6 Hz), 1.32−2.38 (m, 11 H), 3.68 (m, 1 H), 4.88, 4.96 (each m, 1 H), 5.64 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.6, 19.7, 23.3, 28.8, 38.5, 41.1, 43.1, 49.2, 67.3, 116.4, 136.5.

GC-MS: *m*/*z* (%) = 180 (M − H_2O, 2.6), 130 (14), 112 (50), 111 (16), 97 (44), 84 (10), 83 (34), 73 (12), 71 (20), 69 (94), 68 (36).

HRMS: *m*/*z* Calcd for $C_{12}H_{22}O_2$ 198.1619. Obsvd 198.1619.

Reaction of 78 with AD-Mix α

Commercial AD-Mix α (4.2 g) was dissolved in *t*-BuOH/H_2O (15 mL/15 mL) and formed a green-yellow solution which was cooled to 0 °C. Olefin **78** (0.564 g, 2 mmol) was added at 0 °C to this system and the mixture was stirred for 3 d at this temperature. After TLC indicated complete consumption of starting olefin, Na_2SO_3 (4.5 g) was added and the system was allowed to warm to r.t. EtOAc (3 × 50 mL) was added and the combined organic layers were washed with H_2O, separated, dried ($MgSO_4$) and concentrated in vacuo to give the crude product (0.75 g, 84%), which consisted of two isomers (TLC). This crude mixture was dissolved in MeOH (5 mL) and several drops of concd HCl were added. After stirring for about 20 min, the system was neutralized with NaOH/MeOH solution and concentrated to remove the MeOH. The residue was partitioned between H_2O/Et_2O (20:20) and the H_2O layer was re-extracted with Et_2O (3 × 20 mL). The combined Et_2O layers were washed with H_2O (30 mL), dried ($MgSO_4$) and concentrated in vacuo and chromatographed on silica gel (Et_2O/hexane, 0:10 → 1:10) to give predominantly the spiroalcohol **79** (0.23 g, 54%) together with a mixture of two spiroacetals (0.07 g, 16%) shown later to be **81** and **82**. In a similar way, hydroxyenone **17** (0.15 g, 0.75 mmol) was treated with AD-Mix α (1.4 g) in *t*-BuOH/H_2O (5:5 mL) for 3 d at 0 °C and worked up as for the reaction of **78**. Again a mixture of **79** (36 mg, 22%) and **81** + **82** (~35 mg, 22%) were obtained.

79

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.06 (d, 3 H, *J* = 6 Hz), 1.16 (d, 3 H, *J* = 6 Hz), 1.21−2.26 (m, 11 H), 3.47 (ddd, 1 H, *J* = 9.0, 7.0, 4.6 Hz), 3.56 (ddd, 1 H, *J* = 9.0, 7.8, 3.4 Hz), 3.69 (ddq, 1 H, *J* = 11.0, 6.0, 1.6 Hz), 3.78−3.91 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.0, 20.6, 21.9, 24.8, 32.2, (2 C), 35.2, 40.5, 65.0, 65.4, 66.5, 97.3.

GC-MS : *m*/*z* (%) = 214 (M^+, 5), 183 (50), 145 (37), 144 (30), 142 (30), 139 (28), 127 (66), 123 (14), 115 (94), 113 (16), 112 (25), 111 (57), 99 (12), 98 (10), 97 (40), 85 (32).

HRMS: *m*/*z* Calcd for $C_{12}H_{22}O_3$ 214.1563. Obsvd 214.1569.

Tosylate of 79

Alcohol **79** was converted to the tosylate in the manner described above, and was characterised only by ^{1}H and ^{13}C NMR spectroscopy prior to its reduction.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.05 (d, 3 H, *J* = 6.0 Hz), 1.12 (d, 3 H, *J* = 7.0 Hz), 1.18−2.94 (m, 11 H), 2.41 (s, 3 H), 3.63 (ddq, 1 H, *J* = 11.0, 6.0, 2.0 Hz), 3.86−4.01 (m, 1 H), 3.95 (br s, 2 H), 7.30 and 7.77 (d, each 2 H, *J* = 8 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.8, 20.5, 21.6, 21.9, 24.7, 32.3, 32.32, 35.0, 40.1, 62.6, 65.5, 73.2, 97.5, 127.9 (2 C), 129.8 (2 C), 133.2, 144.6.

ent-**61**

The above tosylate (150 mg, 0.4 mmol) was dissolved in anhyd Et_2O (5 mL) and $LiAlH_4$ (200 mg) was added in several portions at 0 °C to the stirred and N_2-protected solution. The mixture was allowed to warm to 20 °C and stirred overnight, before the dropwise addition of H_2O to destroy any excess $LiAlH_4$. After stirring for 0.5 h at 20 °C, the mixture was filtered through Celite and the Et_2O solution was dried ($MgSO_4$), concentrated and chromatographed on silica gel (pentane/Et_2O, 10:0 → 10:1) to provide (2*R*,4*R*,6*S*,8*R*)-2,4,8-trimethyl-1,7-dioxaspiro[5.5]undecane (*ent*-**61**) (62 mg, 77%); $[\alpha]_D^{23}$ +71 (*c* = 1.86, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.09, 1.12 (d, each 3 H, *J* = 6.5 Hz) 1.17 (d, 3 H, *J* = 7.3 Hz), 1.33−1.94 (m, 11 H), 3.63 (ddq, 1 H, *J* = 11.0, 6.0, 2.0 Hz), 3.85 (ddq, 1 H, *J* = 10.0, 6.0, 3.0 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.1, 20.8, 21.9, 22.0, 25.5, 32.5, 35.5, 38.6, 40.1, 60.2, 65.2, 97.5.

GC-MS: *m*/*z* (%) = 198 (M, 5), 183 (2.1) 139 (14), 129 (56), 128 (25), 126 (32), 115 (66), 114 (16), 112 (50), 111 (46), 97 (36), 87 (14), 84 (13), 83 (36), 71 (12), 70 (13), 69 (86).

HRMS: *m*/*z* Calcd for $C_{12}H_{22}O_2$, 198.1619, obsvd. 198.1620.

(2*S*,4*R*,6*R*,8*R*)- and (2*S*,4*R*,6*S*,8*R*)-2,4,8-Trimethyl-1,7-dioxaspiro[5.5]undecanes 64 and 65

Protected hydroxyenone **78** (0.564 g, 2 mmol) was treated with AD-Mix β at 0 °C for 3 d in *t*-BuOH/H_2O in the normal way and worked up to provide (0.31 g, 72%) of a mixture of **81** and **82** (55:45), along with a small amount (50 mg, 12%) of another product, probably **79**, although this was not pursued. Hydroxyenone **17** (0.4 g, 2 mmol) was also reacted with AD-Mix β (0.42 g) in *t*-BuOH/H_2O (15 mL/15 mL) and worked up after 3 d at 0 °C to provide a mixture of **81** and **82** (0.12 g, 28%) with a very minor amount (~9%) of a third isomer, again presumably **79**. To enable characterisation, the major isomers of this alcohol, **81** and **82** were separated by HPLC (45% EtOAc/hexane) and independently characterised, although under normal GC conditions, they were barely resolved.

Spiroalcohol 81

$[\alpha]_D^{23}$ −53 (*c* = 1.92 $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (d, 3 H, *J* = 6.6 Hz, CH_3), 1.16 (d, 3 H, *J* = 6.0 Hz, CH_3), 1.45−2.16 (m, 11 H), 3.46 (dd, 1 H, *J* = 11.0 Hz), 3.54−3.70 (m, 2 H), 4.09 (dddd, 1 H, *J* = 11.0, 5.6, 3.3, 2.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.3 (CH_2), 21.9, 22.2 (CH_3), 24.2 (CH), 32.2, 35.4, 35.7, 38.2 (CH_2) 66.0 (CH_2) 68.9, 70.5 (CH), 97.8 (C).

GC-MS: *m*/*z* (%) = 214 (M, 0.7), 199 (1), 183 (14), 147 (25), 145 (7), 142 (8), 139 (9) 127 (10), 115 (100), 111 (13), 97 (4), 84 (11), 81 (14), 69 (52).

HRMS: *m*/*z* Calcd for $C_{12}O_3H_{22}$ 214.1568. Obsvd 214.1569.

Spiroalcohol 82

$[\alpha]_D^{23}$ +29.7 (*c* = 1.12, $CHCl_3$).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.88, (d, 3 H, *J* = 6.5 Hz, CH_3), 1.12 (d, 3 H, *J* = 6.2 Hz, CH_3), 1.50−2.22 (m, 11 H), 3.56 (v br s, 3 H), 4.13 (ddq, 1 H, *J* = 11.6, 2.5 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.3 (CH_2), 22.15, 22.2 (CH_3), 26.6 (CH), 28.2, 33.0, 35.2, 45.2 (CH_2), 66.3 (CH_2), 66.8, 72.9 (CH), 98.2 (C).

GC-MS: *m*/*z* (%) = 214 (M^+, 5), 184 (4), 183 (33), 165 (2), 147 (5), 146 (6), 145 (40), 144 (28), 139 (21), 127 (100), 123 (11), 115 (22), 113 (11), 111 (13), 99 (16), 97 (14), 95 (5), 85 (33), 81 (99), 73 (67), 69 (59).

HRMS: *m*/*z* Calcd for $C_{12}O_3H_{22}$ 214.1568. Obsvd 214.1570.

A mixture of alcohols **81** and **82** (0.27 g) was converted to the tosylates (0.45 g, 97%) in the manner described above and these were characterised (as a mixture) by NMR spectroscopy before their reduction.

Tosylates of the Mixture 81 + 82

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.84 and 0.86 (d, each 3 H, *J* = 6.5 Hz), 1.06 and 1.13 (d, each 3 H, *J* = 6.5 Hz), 1.48−2.08 (m, 22 H), 2.40 (s, 6 H), 3.62 (m, 2 H), 3.94 (m, 4 H), 4.14 (m, 2 H), 7.27 and 7.31 (each m, 4 H_{arom}).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.1, 18.6, (CH_2), 21.64, 21.6 (CH_3-Ar), 21.7, 22.0, 22.04, 22.1 (4 × CH_3) 24.1, 26.6 (CH) 28.1, 31.9, 32.9, 35.4, 35.5, 35.6, 38.6, 44.7 (CH_2), 66.3, 67.7, 68.9, 70.1 (CH), 72.7, 72.8 (CH_2), 97.8, 98.1 (C), 127.9 (2 C), 128.1 (2 C), 129.7 (2 C), 129.8 (2 C), 133.0, 133.1, 144.7 (2 C).

This tosylate mixture (0.4 g) was treated with $LiAlH_4$ in the normal way and worked up to provide a mixture of **64** and **65** (0.17 g, 79%), which could be separated by HPLC (hexane/Et_2O, 100/5), with **65** eluting prior to **64**, although the opposite order of elution was observed with a non-polar column under GC conditions. NMR spectra of these freshly separated isomers (epimeric at the spiro-centre) could be obtained for both $CDCl_3$ and benzene-d_6 solutions. Storage for extended periods in the former solvent resulted in a mixture of **64** and **65** as a result of epimerisation. Stereoisomers **64** and **65** were also obtained as minor isomers from processing (2*R*,6*S*,8*R*)-ketone **62** according to Scheme 5. Minor spiroacetal **63** was also obtained from this procedure.

(2*S*,4*R*,6*R*,8*R*)-2,4,8-Trimethyl-1,7-dioxaspiro[5.5]undecane (64)

$[\alpha]_D^{23}$ −42 (*c* = 1.74, $CHCl_3$).

^{1}H NMR (400 MHz, benzene-d_6): δ = 0.74 (dd, 1 H, *J* = 12.6, 11.7 Hz, H-5*ax*), 0.81 (d, 3 H, *J* = 6.4 Hz, CH_3-4), 1.12 (ddd, 1 H, *J* = 8.8, 4.1, 2.1 HZ, H-11*eq*), 1.16 (d, 3 H, *J* = 6.2 Hz, CH_3-8), 1.18 (d, 3 H, *J* = 6.2 Hz, CH_3-2), 1.28−1.36 (m, 3 H, H-10*ax*, H-11*ax* and H-5*eq*), 1.39 (dm, 1 H, *J* = 12.9 Hz, H-3*ax*), 1.53 (m, 1 H, H-9*eq*), 1.62 (m, 1 H, H-10*eq*), 1.71 (ddd, 1 H, *J* = 12.6, 12.3, 4.1 Hz, H-9*ax*), 1.86 (m, 1 H, H-4), 1.97 (ddd, 1 H, *J* = 13.2, 3.5, 1.8 Hz, H-3*eq*), 3.48 (ddq, 1 H, *J* = 9.4, 6.3, 3.2 Hz, H-8), 4.24 (ddq, 1 H, *J* = 12.6, 6.2, 2.3 Hz, H-2).

^{1}H NMR (200 MHz, $CDCl_3$) This spectrum is less well resolved but the important features are: δ = 0.85 (d, 3 H, *J* = 6.5 Hz, CH_3-4), 1.12

and 1.17 (d, each 3 H, J = 6.0 Hz, CH_3-2) and CH_3-8), 1.5−1.9 (m, 5 H), 2.13 (ddd, 1 H, J = 14.0, 3.6, 1.8 Hz), 3.60 (ddq, 1 H, J = 10.0, 6.0, 2.8 Hz), 4.11 (ddq, 1 H, 9.0, 6.0, 2.4 Hz) (other ring protons appear in the region 0.70−1.35).

^{13}C NMR (100 MHz, benzene-d_6): δ = 19.2 (C-10), 22.1 (CH_3-8 or CH_3-2), 22.1 (CH_3-8 or CH_3-2), 22.4 (CH_3-4), 25.2 (C-4), 32.6 (C-11), 36.4 (C-9), 39.2 (C-3), 42.3 (C-5), 65.9 (C-2), 68.5 (C-8), 97.4 (C-6).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 19.5 (C-10), 21.8 (CH_3-4), 21.9 (CH_3-8 or CH_3-2), 22.2 (CH_3-8 or CH_3-2), 24.6 (C-4), 32.3, 36.1, 37.8 and 42.0 (C-3,5,9,11), 66.1 (C-2), 68.7 (C-8), 97.8 (C-6).

GC-MS : *m*/*z* (%) = 198 (M, 2.3), 183 (2.6), 155 (1), 154 (3), 139 (8), 129 (16), 128 (10), 126 (14), 116 (7), 115 (100), 112 (17), 111 (16), 97 (41), 83 (10), 73 (13), 69 (59).

HRMS: *m*/*z* Calcd for $C_{12}O_2H_{22}$ 198.1619. Obsvd 198.1614.

(2*S*,4*R*,6*S*,8*R*)-2,4,8-Trimethyl-1,7-dioxaspiro[5.5]undecane (65)

$[\alpha]_D^{23}$ +16.5 (*c* = 0.89, $CHCl_3$) (this value is approximate only).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.87 (d, 3 H, J = 6.0 Hz, CH_3-4), 1.11 and 1.17 (d, 6 H, J = 6.0 Hz, CH_3-2 and CH_3-8), 1.49−1.65 (m, 10 H), 2.12−2.20 (m, 1 H, H-11), 3.52 (ddq, 1 H, J = 11.0, 6.0, 2.0 Hz, H-2), 4.15 (ddq, 1 H, J = 11.0, 5.0, 2.0 Hz, H-8).

^{1}H NMR (400 MHz, benzene-d_6) containing some isomer **64**: δ = 0.69 (dd, 1 H, J = 12.6, 11.0 Hz), 0.73 (d, 3 H, J = 6.4 Hz, CH_3-4), 1.02 (dt, 1 H J = 13.8, 3.8 Hz), 1.16 (d, 6 H, J = 6.4, CH_3-2 and CH_3-8), 1.20 (dm, 1 H, J = 10.8 Hz), 1.28−1.45 (m, 4 H), 1.61−1.75 (m, 3 H), 1.97 (dm, 1 H, J = 13.2 Hz), 3.25 (ddq, 1 H, J = 12.0, 6.2, 2.3 Hz, H-2), 4.36 (ddq, 1 H, J = 12.6, 6.2, 2.3 Hz, H-8).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.3 (C-10), 22.0 (CH_3-4), 22.2 (CH_3-8 and CH_3-2), 27.1 (C-4), 28.3, 33.2, 41.6, 45.0 (C-3,5,9,11), 66.4 (C-8), 68.2 (C-2) 97.9 (C-6).

^{13}C NMR (100 MHz, benzene-d_6-containing some isomer **64**): δ = 19.0 (C-10), 22.36. 22.4, 22.43 (CH_3-8,2 4), 27.3 (C-4), 28.5, 33.3, 41.9, 45.0 (C-11,9,5,3), 66.1 (C-8), 68.7 (C-2), 97.7 (C-6).

GC-MS: *m*/*z* (%) = 198 (M, 7), 183 (2), 154 (2), 139 (7), 130 (7), 129 (100), 128 (37), 126 (8), 115 (18), 114 (6), 113 (6), 112 (22), 111 (47), 99 (2), 98 (4), 97 (13), 87 (26), 85 (5), 84 (9), 83 (46), 70 (9), 69 (65).

HRMS: *m*/*z* Calcd for $C_{12}O_2H_{22}$ 198.1619. Obsvd 198.1620.

(2*S*,4*S*,6*S*,8*R*)-2,4,8-Trimethyl-1,7-dioxaspiro[5.5]undecane (63)

With respect to **63** (component ***H*** in the natural secretion is the enantiomer of **63**) the following characterisation was made; $[\alpha]_D^{23}$ +14.5 (c = 0.9, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87, (d, 3 H, J = 6.8 Hz, CH_3-4), 1.05 (dd, 1 H, J = 13.3, 12.2 Hz, H-5*ax*), 1.06 (d, 3 H, J = 6.4 Hz, CH_3-8), 1.13 (m, 1 H, H-9*ax*), 1.32 (td, 1 H, J = 13.8,13.2, 4.9, H-11*ax*), 1.35 (m, 1 H, H-3a), 1.35 (d, 3 H, J = 6.8, CH_3-2), 1.45−1.57 (m, 3 H, H-10*eq*, H-9*eq* and H-11*eq*), 1.48 (dm, 1 H, J = 12.9 Hz, H-3*eq*), 1.68 (ddd, 1 H, J = 13.2, 3.8, 2.0 Hz, H-5*eq*), 1.84 (ddddd, 1 H, J = 13.2, 13.2, 13.2, 4.7, 3.9 Hz, H-10*ax*), 2.16 (m, 1 H, H-2), 3.92 (ddq, 1 H, J = 11.4, 6.4, 1.8 Hz, H-8), 4.13 (ddq, 1 H, J = 7.7, 7.7, 3.5 Hz, H-2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2 (C-10), 19.5 (C-4), 20.8 (CH_3-2), 21.6 (CH_3-8), 22.2 (CH_3-4), 32.8 (C-9), 36.7 (C-11), 38.9 (C-3), 45.2 (C-5), 65.9 (C-8), 69.4 (C-2), 96.8 (C-6).

GC-MS: *m*/*z* (%) = 198 (M^+, 4), 183 (3.5), 154 (3), 139 (15), 129 (59), 128 (30), 126 (21), 115 (21), 112 (31), 111 (40), 99 (4), 97 (19), 87 (17), 84 (10), 83 (36), 71 (11), 69 (70), 56 (12), 55 (55), 41 (100).

HRMS: *m*/*z* Calcd for $C_{12}O_2H_{22}$ 198.1619. Obsvd 198.1618.

Alkynol 83

Under N_2, $HgCl_2$ (250 mg, 0.92 mmol) was added to a stirred suspension of Al (2.5 g, 93 mmol) in anhyd THF (30 mL), followed by a solution of propargyl bromide (12 g, 100 mmol) in anhyd THF (15 mL). After completion of the addition, the mixture was stirred at 40−45 °C for 30 min. After cooling to 0 °C, a solution of acetone (6.8 g, 120 mmol) in anhyd THF (15 mL) was added and the resulting mixture was stirred at 40−45 °C for 30 min. The mixture was poured into ice-water (100 mL) and aq sat. NH_4Cl (100 mL) and then extracted with Et_2O (3 × 50 mL). The combined Et_2O extracts were washed with brine dried ($MgSO_4$), and concentrated under reduced pressure to provide the crude alcohol **83** (12.7 g).

IR (neat): ν = 3409s, 3309s, 2974s, 2931s, 2118m cm^{-1}.

This product was used in the next step without further purification.

Alkynol THP Ether 84

The above alcohol (9.2g, 94 mmol) and *p*-toluenesulfonic acid monohydrate (200 mg, 1 mmol) were stirred in CH_2Cl_2 (250 mL) at 0 °C under N_2, and dihydropyran (12 g, 150 mmol) was added slowly over 15 min. The mixture was quenched with aq sat. $NaHCO_3$, and the aqueous layer was washed with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give crude ether **84** (14.5 g). Distillation afforded the THP ether **84** (10.5 g, 57% based on propargyl bromide).

IR (neat): ν = 3311m, 2940s, 2869s, 2119m cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30 (s, 3 H), 1.32 (s, 3 H), 1.97 (t, 1 H, J = 2.7 Hz), 1.47 (m, 4 H), 1.65 (m, 1 H), 2.40 (dd, 2 H), 3.37−3.48 (m, 2 H), 3.88−3.99(m, 2 H), 4.92 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.6, 25.4, 26.0, 26.1, 32.1, 32.2, 63.2, 69.9, 75.5, 81.7, 94.1.

GC-MS: *m*/*z* (%) = 143 ($M^+ - C_3H_3$, 1.7), 101 (M^+ − OTHP, 6.5), 85 (100), 81 (57.5), 79 (30.9), 67 (16.4), 57 (18.9), 56 (18.2), 55 (15.6).

Anal. calcd for $C_{11}H_{18}O_2$: C 72.5, H 10.0. Found C 72.47, H 10.33.

Alkynol Lactol 85

Ether **84** (0.54 g, 3.0 mmol) was dissolved in THF (20 mL) and cooled to −78 °C before BuLi (1.9 mL, 1.6 M in hexane, 3 mmol) was added dropwise via syringe, and the resultant solution was stirred for 30 min. In a separate flask, δ-caprolactone (0.34 g, 3 mmol) was dissolved in THF (20 mL) and HMPA (freshly distilled, 100 μL), and cooled to −78 °C. Lithiated **84** in the first flask was then cannulated into the lactone solution by slow dropwise addition. The reaction was stirred at −78 to −60 °C for 4 h, and then H_2O (60 mL) was added. The resulting mixture was allowed to warm to r.t. and extracted with hexane (3 × 60 mL). The hexane layers were washed with aq sat. $NaHCO_3$ and dried (K_2CO_3). Removal of the solvent afforded the crude addition product **85** (1.28 g). This material was used directly in the next step without further purification.

Spiroacetal 14-*E*

Lactol **85** (0.43 g) was dissolved in anhyd MeOH (20 mL), and 5% Pd/C (50 mg) was added. The mixture was then shaken (Parr hydrogenator) under H_2 (3 bar) for 4 h, and filtered through a pad of Celite. After removal of the solvent, the residue was extracted with Et_2O (3 × 50 mL), washed with brine, and dried ($MgSO_4$). Concentration under reduced pressure provided 0.46 g of material, which was purified by flash chromatography on silica gel (hexane/Et_2O, 30:1) to afford the trimethylspiroacetal **14**-*E* (54 mg, 27% from **84**). The ^{1}H and ^{13}C NMR data are shown in the Table.

GC/MS: *m*/*z* (%) = 198 (M^+, 7.8), 140 (17.5), 129 (55.2), 128 (38.4), 125 (20.8), 115 (34.0), 112 (60.3), 111 (62.5), 99 (19.8), 97

(23.9), 83 (49.5), 69 (71.9), 56 (23.2), 55 (77.2), 43 (100), 42 (43.0), 41 (86.3), 39 (35.6). (for plotted spectrum, see Ref. 6)

HRMS: *m*/*z* Calcd for $C_{12}H_{22}O_2$ 198.1619. Obsvd 198.1616.

Hydrazone 87

6-Methylhept-5-en-2-one (**86**) (4.2 g, 25 mmol) was added dropwise to a mixture of stirred dimethylhydrazine (4.6 g, 76 mmol) and glacial AcOH (0.5 g, 8 mmol). After completion of the addition, the mixture was stirred for 3 h at r.t. Et_2O was added and the Et_2O layer was washed with aq satd $NaHCO_3$ solution, H_2O and dried ($MgSO_4$). Concentration under reduced pressure and purification by flash chromatography on neutral alumina (hexane/Et_2O, 1:1) afforded the *N*,*N*-dimethylhydrazone **87** (5.26 g, 94%) as a pale yellow oil.

^{1}H NMR (200 MHz, $CDCl_3$) (two isomers): δ = 1.6 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3), 1.91 (s, 3 H, CH_3), 1.94 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 2.42 (s, 6 H, CH_3), 2.20−2.22 (m, 4 H), 5.11 (m, 1 H).

^{13}C NMR (50 MHz, $CDCl_3$) (two isomers): δ = 16.1, 17.2, 25.2, 38.5, 46.5, 47.0, 122.8, 122.9, 131.5, 167.0, 168.9.

GC-MS (two isomers) isomer 1: *m*/*z* (%) = 168 (M^+, 5.4), 153 ($M^+ - CH_3$, 7.4), 126 (15.0), 112 (14.8), 99 (50.3), 96 (15.4), 82 (29.2), 67 (35.9), 58 (43.6), 56 (100.0). The second isomer provided a very similar spectrum. The spectral data agreed with those reported.[35]

Hydrazone 88

To a solution of LDA prepared from 0.91 M BuLi (4.4 mL) in Et_2O and (*i*-Pr)$_2$NH (0.56 mL) was added dropwise the hydrazone **87** (0.504 g, 3 mmol) in anhyd THF (3 mL) at −78 °C. The mixture was stirred for 1 h, then (*R*)-3-(tetrahydropyran-2'-yl)butyl iodide (0.71 g, 2.5 mmol) in anhyd THF (4 mL) was added and the mixture was stirred for 1 h at −78 °C, followed by warming to r.t., and stirred overnight. Aq sat. $NaHCO_3$ was added. After removal of the THF under reduced pressure, the residue was extracted with 1:1 hexane/Et_2O (3 × 50 mL). The combined organic extracts were washed with H_2O, 1% aq $Na_2S_2O_3$ solution and brine, before being dried ($MgSO_4$). Concentration under reduced pressure provided the crude hydrazone **88** (0.863 g) which was purified by flash chromatography on neutral alumina (hexane/Et_2O, 2:1) (0.748 g, 77%).

^{1}H NMR (200 MHz, $CDCl_3$) (isomer mixture): δ = 1.00 (d, CH_3, *J* = 6.1 Hz), 1.02 (d, CH_3, *J* = 6.1 Hz), 1.51 (s, 3 H), 1.58 (s, 3 H), 1.42−1.85 (m, 24 H), 2.11 (m, 4 H), 2.29 (s, 6 H), 2.30−2.38 (m, 8 H), 3.36−3.83 (m, 6 H), 4.54 (m, 1 H), 4.59 (m,1 H), 5.01 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 17.5, 17.6, 18.9, 19.6, 19.9, 21.3, 21.5, 22.2, 22.7, 25.3, 25.4, 25.5, 29.6, 31.0, 35.7, 35.8, 35.9, 36.4, 36.9, 37.4, 38.8, 46.8, 47.3, 62.4, 62.6, 70.4, 70.7, 73.3, 73.5, 95.5, 95.6, 98.3, 98.7, 123.2, 123.3, 131.7, 132.0, 171.8, 172.0.

GC-MS (isomer 1): *m*/*z* (%) = 324 (M^+, 5.2), 239 (41), 112 (19), 96 (22), 85 (71), 82 (41), 69 (25), 67 (36), 57 (24), 55 (38), 45 (56), 44 (65), 43 (52), 42 (34), 41 (100).

HRMS: *m*/*z* Calcd for $C_{19}H_{36}N_2O_2$ (M^+ + 1) 325.2850. Obsvd (M^+ + 1) 325.2844.

2-(Tetrahydropyran-2'-yloxy)-10-methylundec-9-en-6-one (89)

Hydrazone **88** (0.50 g, 1.5 mmol) was converted by flash chromatography (silica gel, hexane/Et_2O, 4:1) to ketone **89** (0.36 g, 83%).

^{1}H NMR (200 MHz, $CDCl_3$) (two isomers): δ = 1.07 (d, 3 H, *J* = 6.1 Hz), 1.19 (d, 3 H, *J* = 6.1 Hz), 1.56 (s, 3 H), 1.64 (s, 3 H), 1.44−1.71 (m, 24 H), 2.19−2.26 (m, 4 H), 2.26−2.43 (m, 8 H), 3.45 (m, 2 H), 3.67−3.88 (m, 4 H), 4.58 (m, 1 H), 4.66 (m, 1 H), 5.21 (m, 2 H).

^{13}C NMR (50 MHz, $CDCl_3$) (two isomers): δ = 17.2, 18.7, 19.4, 19.5, 19.7, 19.8, 21.2, 22.3, 25.2(2 C), 30.9(2 C), 34.3, 35.7, 36.5, 42.3, 42.4, 62.1, 62.3, 65.4, 70.3, 73.5, 95.3, 98.4, 122.6(2 C), 132.0, 132.1, 210.0, 210.2.

GC-MS (isomer 1): *m*/*z* (%) = 264 (0.2), 199 (1.6), 198 (M^+ − THP, 10.4), 181 (M^+ − OTHP, 12.3), 180 (6.7), 165 (16.9), 112 (20.7), 95 (8.5), 85 (100.0), 69 (57.2), 67 (22.2), 55 (37.4), 43 (34.6), 41(73.2).

Anal. calcd for $C_{17}H_{30}O_3$: C 72.3, H 10.7. Found C 72.0, H 10.9.

Spiroacetal 90

$Hg(OAc)_2$ (3.5 g, 10.9 mmol) was added to the above ketone **89** (1.0 g, 3.5 mmol) in THF/H_2O (75mL/75mL) and the mixture was stirred for 2 h. $BnEt_3NCl$ (10.0 g, 43.9 mmol) in aq 10% NaOH solution (75 mL) and CH_2Cl_2 (50 mL) were added, followed by $NaBH_4$ (1.0 g, 25 mmol) in aq 10% NaOH solution (20 mL). The mixture was stirred for 1 h, and then filtered through Celite. The filtrate was collected and the aqueous phase was extracted with Et_2O (3 × 50mL). The combined Et_2O extracts were washed with brine, and dried ($MgSO_4$). Concentration under reduced pressure provided 1.21g of crude material, to which was added concd HCl (0.5 mL) and MeOH (30 mL). The mixture was stirred for 2 h at r.t., and then quenched carefully with aq sat. $NaHCO_3$. The aqueous solution was extracted with Et_2O (3 × 30 mL), washed with brine, and dried ($MgSO_4$). After removal of the solvent, the residue was purified by flash chromatography (silica gel, hexane/Et_2O, 20:1), affording (6*S*,8*R*)-2,2,8-trimethyl-1,7-dioxaspiro[5.5]undecane (**90**) (0.24 g, 34%). Spectroscopic data were identical with those obtained for the racemate **14**-*E*, and enantioselective gas chromatography revealed that the ee was greater than 99%; $[\alpha]_D^{22}$ +46.2 (*c* = 7.09, $CHCl_3$).

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