Diastereo- and Enantioselective Routes to Some 2,8-Dimethyl-1,7-dioxaspiro[5.5]undecanols. Absolute Stereochemistry of (*E,E,E*)-2,8-Dimethyl-1,7-dioxaspiro[5.5]undecan-3-ol and of ((*E,E*)-8-Methyl-1,7-dioxaspiro[5.5]undecan-2-yl)methanol Present in *Bactrocera cucumis*

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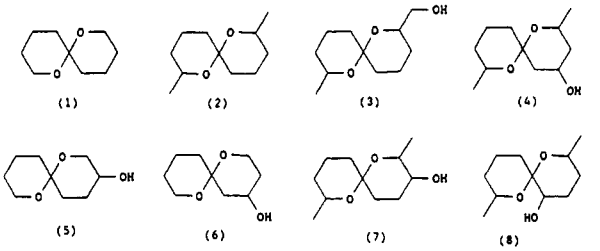
Routes to the four regioisomeric 2,8-dimethyl-1,7-dioxaspiro[5.5]undecanols have been developed, and in the racemic series, mercury(II)-mediated reactions of appropriate dienone, hydroxy enone, dienedione, and hydroxy dienone systems have been exploited. Most of the epimeric pairs of alcohols (i.e. axial or equatorial) in the *E,E*, *E,Z*, or *Z,E* spiroacetal ring systems have been characterized by detailed ^1H, ^{13}C, and correlated NMR spectroscopy and mass spectrometry. Key enantiomers of these alcohols have been obtained by elaborating chiral starting materials such as D-mannitol, L-arabinose, poly(hydroxybutyrate), and in the case of the 5-hydroxy derivative, mandelonitrile lyase mediated formation of a key chiral cyanohydrin was employed. Most of the alcohols, as their trifluoroacetates, are resolved (into enantiomers) on a Lipodex A GC column, thus facilitating their identification from natural sources. In this way, the absolute configurations of a number of 2,8-dimethyl-1,7-dioxaspiro[5.5]undecanols present in the rectal gland secretion of *Bactrocera cucumis* (cucumber fly) have been determined.

Introduction

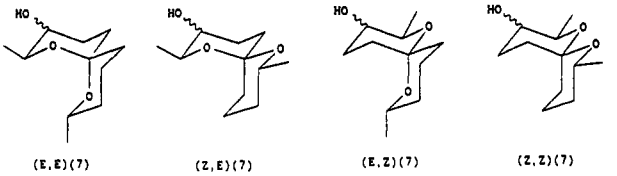
The vast majority of insect-derived spiroacetals contain nine, eleven, or thirteen carbon atoms in an unbranched arrangement[1] (e.g. **2**) and any further functionalization of these spiroacetals appears to be confined to hydroxylation,[2-4] although the purpose of this is unclear. Thus Bergstrom and Francke[5] reported that the *E,E* diastereomer of (8-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)-methanol (**3**) and 2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-4-ol (**4**), of undetermined relative stereochemistry, were significant components of the mandibular gland secretions of certain species of Andrena bees, particularly *Andrena wilkella*. With respect to Dipteran species, Baker[3] has reported the presence of both 1,7-dioxaspiro[5.5]undecan-3- and -4-ols (**5** and **6**) in the rectal gland secretion of female olive flies[6] (*Bactrocera oleae*), and examinations of (Dipteran) fruit-fly species of the Australasian region have revealed the presence of hydroxy spiroacetals in a number of cases.[2,4] This observation applies particularly to *Bactrocera cucumis* (cucumber fly)[2] and *Bactrocera cacuminatus*.[4] Until very recently, there was no information on the absolute configuration of these insect-derived hydroxy spiroacetals.

The indicated presence of hydroxy derivatives of **2** in certain insect secretions required syntheses of the possible regio- and diastereomers of the monohydroxy derivatives of **2** (i.e. **3**, **4**, **7**, **8**) for comparisons. In addition, adaptation of some diastereoselective routes has provided specific enantiomers of these systems, which have permitted the determination of the absolute configurations of two of the hydroxy derivatives present in *B. cucumis*. This work is described in the present report.



Results and Discussion

In considering the synthesis of any of the 3-, 4-, or 5-hydroxy derivatives of **2**, it must be recognized that there are two *E,E*, two *E,Z*, two *Z,E*, and two *Z,Z* isomers,[7] each as an enantiomeric pair. (For system **3**, without the possibility of axial or equatorial OH, there are four possible isomers). The situation is illustrated below for the 2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-3-ols (**7**).



The differences in energy for the *E,E*, *E,Z*, and *Z,Z* isomers (largely attributable to anomeric effects) would be expected to parallel those for the diastereomers of **2** itself,[8] with the *E,E* diastereomer most stable, and ca. 4.8

(1) Francke, W. In *Les Mediateurs Chimiques*; INRA: Versailles, 1982; p 81.
(2) Kitching, W.; Lewis, J. A.; Perkins, M. V.; Drew, R. A. I.; More, C. J.; Schurig, V.; Konig, W. A.; Francke, W. *J. Org. Chem.* **1989**, *54*, 3893.
(3) Baker, R.; Herbert, R. H. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1123.
(4) Krohn, S.; Fletcher, M. T.; Kitching, W.; Drew, R. A. I.; Moore, C. J.; Francke, W. *J. Chem. Ecol.* **1991**, *17*, 485.
(5) Bergstrom, G.; Tengö, J.; Reith, W.; Francke, W. *Z. Naturforsch.* **1982**, *37c*, 1124.
(6) In this connection see the discussion in ref 4. An examination of both wild and cultured male and female olive flies from Greece is currently being conducted.
(7) For defining relative stereochemistry in the ring systems, see: Blackwood, J. E.; Gladys, C. L.; Leonig, K. L.; Petrarcha, A. E.; Rus, J. E. *J. Am. Chem. Soc.* **1969**, *90*, 509.
(8) Delongschamps, P.; Rowan, D. D.; Pothier, N.; Sauve, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1106. For a full discussion, see: Delongschamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983.

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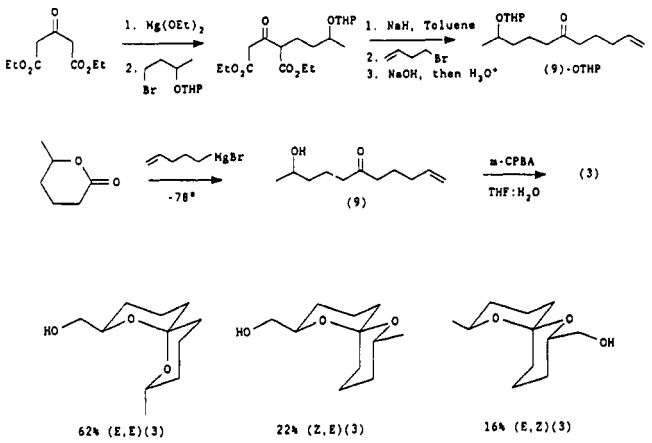
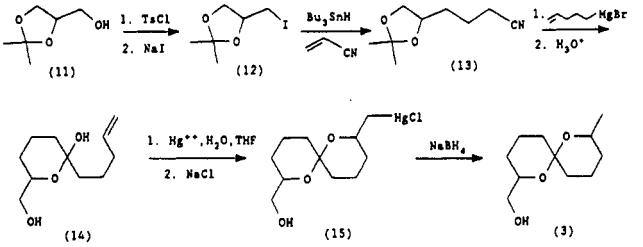
Scheme I



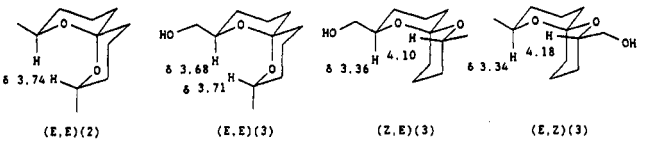
Scheme II



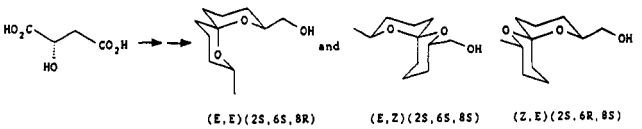
kcal/mol more stable than the *Z,Z* isomer. Just as in the case of diastereomers of **2**, diastereomeric equilibration[2] (through a notional open keto–diol form) can occur only between the *E,E* and *Z,Z* isomers and between the different *E,Z*/*Z,E* isomers because of the different relative configurations at the secondary alcohol (C2, C8) centers. Because of the substantial number of possible isomers of these alcohols, synthetic strategies were directed primarily towards the *E,E*-configured systems, but characterization of some *E,Z*/*Z,E* isomers has also been achieved.

(8-Methyl-1,7-dioxaspiro[5.5]undecan-2-yl)methanol (3). Racemic (*E,E*)-**3** has been acquired from hydroxy enone **9** by epoxidation followed by acid-catalyzed hydrolysis and cyclization[9] (Scheme I). The diethyl 3-oxoglutarate route to **9** utilizes procedures detailed[10] elsewhere for similar compounds. A more direct route to (unprotected) **9** utilized low-temperature addition of the Grignard reagent from 5-bromo-1-pentene to 5-hydroxyhexanoic acid lactone, and with short reaction times **9** was obtained free from the double addition product.[11] This hydroxy enone was quite acid sensitive (dehydration on Kieselgel) and was used without purification in the next (epoxidation) step. The anticipation was that use of *m*-CPBA in CH_2Cl_2 would result in spontaneous cyclization to the desired compound **3**; however, what appeared to be the dihydropyran derivatives predominated. Use of a 1:1 THF/H_2O medium for the epoxidation completely suppressed dihydropyran intervention, and a mixture of the desired spiroacetals (**3**) resulted in the ratio *E,E*:*Z,E*:*E,Z* = 62:22:16.

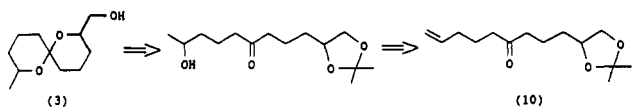
The mixture of spiroacetals was purified by open column chromatography to give (*E,E*)-**3** as a low-melting solid. This relative stereochemistry was required by the completely assigned ^{13}C and ^1H NMR spectra which are summarized in the Experimental Section. Diagnostic features appear in the ^1H NMR spectrum in that H_{2ax} and H_{8ax} at δ 3.68 and 3.71 resemble the shifts (δ 3.74) for the analogous protons in (*E,E*)-**2**,[2,12] and both H_{4ax} and H_{10ax} (each appearing as a quartet of triplets) at δ 1.96 and 1.84 must experience deshielding 1,3-diaxial interactions with oxygen,[2,13] and this is possible only in the *E,E* arrangement. Both the *E,Z* and *Z,E* isomers were isolated and characterized by ^{13}C and ^1H NMR spectroscopy and are readily differentiated by the chemical shifts and coupling constants of H_{2ax} and H_{8ax} which are influenced by 1,3-interactions with oxygen or methylene. These features are shown below.



Enantiomers of (8-Methyl-1,7-dioxaspiro[5.5]undecan-2-yl)methanol (3). The *2S,6S,8R* enantiomer (of (*E,E*)-**3**) was previously synthesized by Mori[13] from (*S*)-malic acid and was a key intermediate for (*2R,6S,8R*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane. These procedures also provided the *2S,6R,8S* and *2S,6S,8S* isomers of **3** as a mixture which could be separated as the dinitrobenzoates.



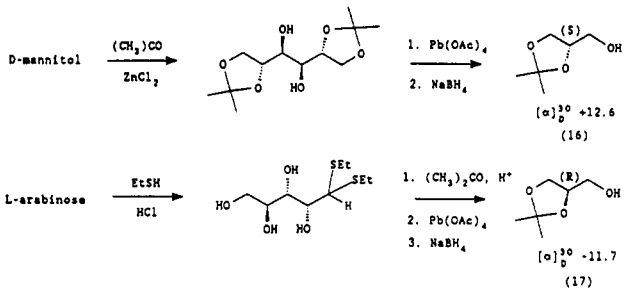
Our approach was based on the recognition of a 1,2-glycol unit in compound **3**; the other secondary alcohol center could be generated by Markovnikov oxymercuration of a terminal alkene and cyclization. Thus enone **10** became the target, with the idea that with stereocontrol at C2 (from either (*R*)- or (*S*)-glycerol acetonide)[14] and reversible oxymercuration–cyclization (*E,E*)-**3** would greatly predominate. The availability of both enantiomers of glycerol acetonide then would provide both enantiomers of (*E,E*)-**3**.



The viability of this proposal was established using racemic glycerol acetonide **11** which was converted, via the tosylate, to the iodide **12** which was engaged in a free radical addition to acrylonitrile.[15,16] The resulting 5,6-*O*-isopropylidenehexanenitrile **13** was converted to ketol **14** by treatment with pent-4-enylmagnesium bromide, followed by hydrolysis.[17] Oxymercuration of the crude ketol was conducted in a 1:1 mixture of THF–1% $HClO_4$ (H_2O) with $Hg(OAc)_2$, and the resulting mercurials could be isolated as the mercuric chlorides (**15**) after treatment with

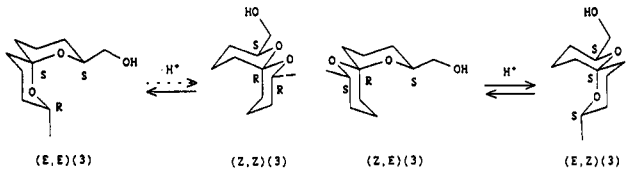
(9) Lewis, J. A., Ph.D. Dissertation, The University of Queensland, 1987.
(10) Perkins, M. V.; Fletcher, M. T.; Kitching, W.; Drew, R. A. I.; Moore, C. J. *J. Chem. Ecol.* **1990**, *16*, 2475.
(11) For a summary and the demonstration of the beneficial effects of Ce(III) mediation of organometallic addition to lactones, see: Mudryk, B.; Shook, C. A.; Cohen, T. *J. Am. Chem. Soc.* **1990**, *112*, 6389.
(12) Francke, W.; Reith, N.; Sinnwell, V. *Chem. Ber.* **1980**, *113*, 2686.
(13) Mori, K.; Watanabe, H. *Tetrahedron* **1986**, *42*, 295.
(14) For a review, see: Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447.
(15) For a full discussion, see: Giese, B. *Radicals in Organic Synthesis (Organic Chemistry Series) Vol. 5*; Pergamon Press: Oxford, 1986; especially pp 38–54.
(16) DeVoss, J. J.; Jamie, J. F.; Blanchfield, J. T.; Fletcher, M. T.; O'Shea, M. G.; Kitching, W. *Tetrahedron* **1991**, *47*, 1985.
(17) For a similar sequence, see: Perkins, M. V.; Kitching, W.; Konig, W. A.; Drew, R. A. I. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2501.

Scheme III



aqueous NaCl. ^{13}C NMR analysis established the presence of one major isomer, concluded to be the *E,E*, and two others in equal amounts. (These were considered to be the *E,Z*/*Z,E* isomers). Reductive removal of mercury with $NaBH_4$ provided isomers of the target spiroacetal **3**. This is summarized in Scheme II.

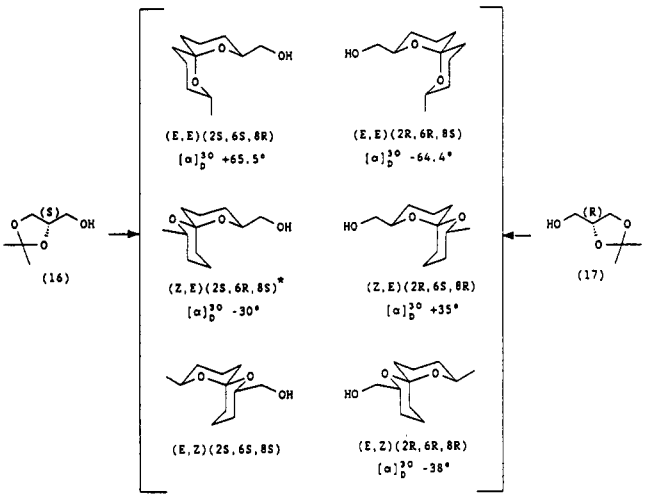
Specifically, when oxymercuration was allowed to proceed for 1 h, followed by reduction, the product distribution was 80% *E,E* and about 10% each of the *E,Z* and *Z,E* diastereomers of **3**. Note that under acidic conditions, the *E,Z*/*Z,E* interconversion can occur but neither can isomerize to the *E,E* alcohol if the configurations at C2 and C8 are unchanged (see below). However, attainment of equilibrium by allowing the reversible oxymercuration step to proceed for longer times prior to reduction did result in virtually exclusive production of (*E,E*)-**3**.[2,17]



By this procedure, the *E,E*, *E,Z*, and *Z,E* diastereomers were isolated and fully characterized as outlined previously. Thus, modification for the enantiomeric series simply required controlling the chirality at C2 by employing (*S*)-(+)- and (*R*)-(−)-glycerol acetonides (**16** and **17**, respectively), obtained by in situ reduction of the aldehydes. These were in turn obtained from D-mannitol and L-arabinose as shown in Scheme III.[18] With these approaches, both enantiomers of (*E,E*)-**3** were isolated with the 2*S*,6*S*,8*R* enantiomer originating from D-mannitol and the 2*R*,6*R*,8*S* from L-arabinose. The former exhibited $[\alpha]^{30}_D$ of +65.5° (pentane) and the latter $[\alpha]^{30}_D$ of −64.4° (pentane); such values compare favorably with $[\alpha]^{30}_D$ +68.4° (pentane) reported for the (*S*)-malic acid derived 2*S*,6*S*,8*R* isomer.[13] Examination of both enantiomers (as their trifluoroacetates) by chiral gas chromatography (Lipodex A) or by high-field (400 MHz) NMR spectra of the MTPA esters confirmed 100% ee, with no detectable level of the other antipode. Although the *E,E* diastereomers are produced in very predominating amounts, it was possible to isolate small quantities of the enantiomers of the *E,Z* and *Z,E* diastereomers. The full stereochemical profile is shown in Scheme IV.

The *E,Z* and *Z,E* diastereomers underwent surprisingly fast isomerization in chloroform solution (for example); a similar experience with such systems has been reported by Mori.[13] Nevertheless, it was possible to characterize

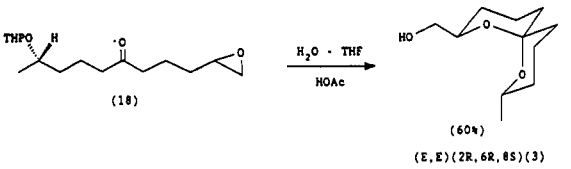
Scheme IV



*Mori[13] reports $[\alpha]^{22.5}_D$ −32.9°.

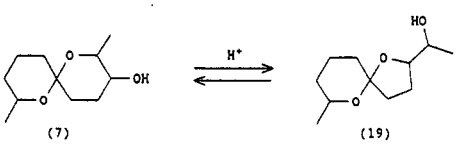
these isomers and obtain their optical rotations as shown in Scheme IV. The rotation of the 2*S*,6*R*,8*S*-*Z,E* isomer, $[\alpha]^{30}_D$ −30°, compares well with that obtained by Mori[13] (−32.9°) for the same compound by another route, and $[\alpha]^{30}_D$ +35° was measured for its 2*R*,6*S*,8*R* enantiomer. With respect to the *E,Z* diastereomers, shown in Scheme IV, $[\alpha]^{30}_D$ −38° was obtained for the 2*R*,6*R*,8*R* enantiomer, but measurement of the 2*S*,6*S*,8*S* antipode was not possible because of very small quantities and isomerization problems.

A sequence commencing with ethyl (*S*)-lactate has also been employed for the formation of **3**. Epoxide **18**[17] on treatment with weak acid (H_2O–THF–HOAc) undergoes deprotection, epoxide hydrolysis, and cyclization to provide (*E,E*)-**3** (necessarily as the 2*R*,6*R*,8*S* enantiomer), together with the *E,Z* and *Z,E* spiroacetals (60:21:19).



The *E,E* diastereomer obtained by column chromatography exhibited $[\alpha]^{23}_D$ −56.3° (*c* 1.26, pentane), slightly lower than the value above (−64.4°) for the L-arabinose-derived material. This difference is due to slight chemical impurities, as analysis of the trifluoroacetates of this material and of the racemate (GC on Lipodex A column) provided ee = 98%.

2,8-Dimethyl-1,7-dioxaspiro[5.5]undecan-3-ols (7). A problem accompanying the synthesis of 1,7-dioxaspiro-[5.5]undecan-3-ols is their facile, mild acid-catalyzed entry into the [4.5]decane system as shown below.[3,19]

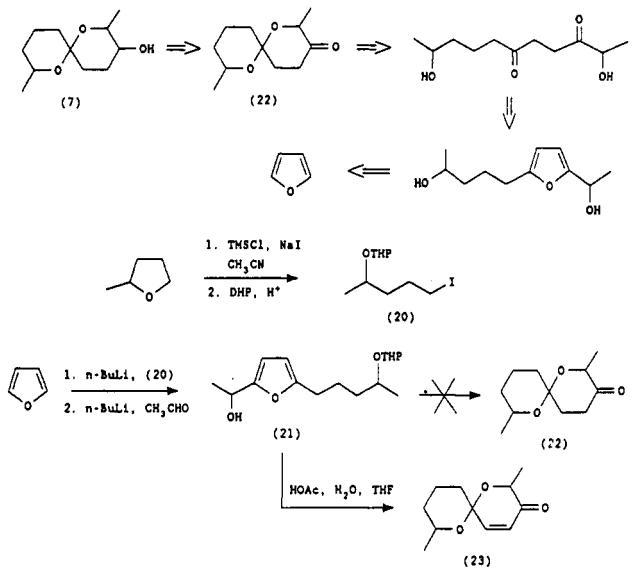


Lewis[9] has synthesized **7**, but as a mixture which also contained isomers of the 1,6-dioxaspiro[4.5]decane system (**19**). To circumvent this problem, an alternative approach

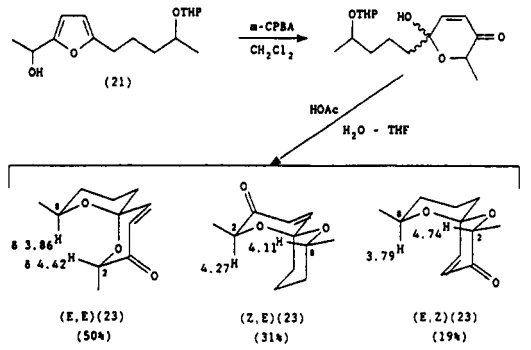
(18) For efficient procedures to obtain **16** and **17**, see: Rodriguez, E. B.; Scally, G. D.; Stick, R. V. *Aust. J. Chem.* **1990**, *43*, 1391. See also Morpain, C.; Nasser, B.; Laude, B.; Latruffe, N. *Org. Proc. Prepr.* **1990**, *22*, 540 for an improved preparation of 1,2:5,6-di-*O*-isopropylidene-D-mannitol.

(19) (a) Bestmann, H. J.; Schmidt, M. *Tetrahedron Lett.* **1986**, *27*, 1999. (b) Mori, K.; Watanabe, H.; Yanagi, K.; Minobe, M. *Tetrahedron* **1985**, *41*, 3663.

Scheme V



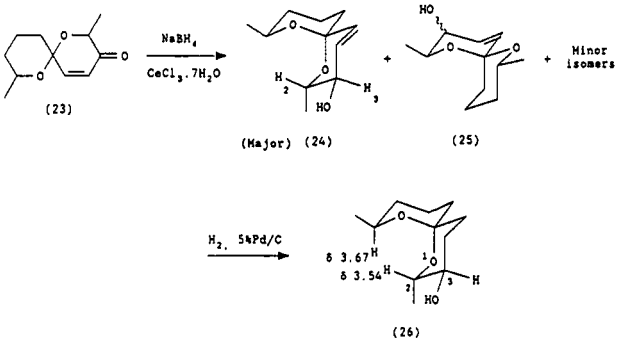
Scheme VI



was developed in that the 3-hydroxy group would result from reduction of a ketone generated in such a way that only the 1,7-dioxaspiro[5.5]undecane skeleton could form. The realization that the 3-oxo derivative represented, with the spiro carbon, a 1,4-diketone unit, suggested a furan derivative for this role (Scheme V). Thus, the 2,5-dialkylfuran **21** was synthesized as shown in Scheme V, and treatment with HOAc–H_2O–THF (4:2:1) was conducted to attempt direct conversion to the ketone **22**. The only volatile products isolated, however, were isomers of the α,β-unsaturated spiroketone **23**. Formation of this product requires oxidation of the furan ring, which is of course well-known; thus, deliberate oxidation of the furan seemed a promising and efficient route to the enone. At about this time, a report by DeShong[20] described the synthesis of α,β-unsaturated 3-oxo spiroacetals by the oxidation of α-hydroxyfurans with peracids, a procedure described earlier by Lefebvre.[21] More recently, Albizati[22] has utilized this type of chemistry to secure certain trioxa dispiroacetals. Thus in the present case, oxidation (*m*-CPBA) of **21** provided the pyranone (Scheme VI) which on treatment with THF–H_2O–HOAc provides spiroacetal **23** as a mixture of three isomers (50:31:19). These were separated by HPLC and characterized by their ^1H and ^{13}C NMR spectra, which also permitted determination of their relative stereochemistry (Scheme VI).

As expected, the *E,E* diastereomer predominated. This isomer has like chirality at the C2 and C8 centers which are formed randomly in the procedure and thus would be of the same configuration 50% of the time, whereas (*Z,E*)- and (*E,Z*)-**23** together would constitute the remainder. For the major compound, the H_{8ax} signal (at δ 3.86, caused by the deshielding effect of the 1,3-diaxial interaction with oxygen) exhibited the typical *E*-ring coupling pattern (dqd, J = 11.5, 6.2, 2.3 Hz). The H_{2ax} signal occurred at even lower field (δ 4.42). Similar analyses of the second most abundant isomer revealed H_{8ax} (δ 4.11) to possess an *E*-ring coupling pattern, whereas the minor isomer exhibited H_{8ax} at δ 3.79 with a typical *Z*-ring coupling pattern (dqd, J = 9.1, 6.3, 3.2 Hz), in line with the indicated relative stereochemistries. The ^1H NMR spectrum of the *Z,E* isomer (C_6D_6 solvent) was fully assigned by consideration of coupling patterns and 2D ^1H–^1H correlation spectra.

Reduction of Enones. A portion of the enone mixture **23** was reduced with Luche's reagent[23] ($CeCl_3 \cdot 7H_2O$ and $NaBH_4$) in methanol to afford the allylic alcohols. Purification by column chromatography provided the major product which was shown to be *E,E* ring-configured with an equatorial hydroxy group **24**. The *E,E* arrangement was confirmed by the chemical shifts of H_{2ax} (δ 3.71) and H_{8ax} (δ 3.75–3.90), both moved downfield by the 1,3-diaxial oxygen effect. H_3 was shown to be pseudoaxial on the basis of a large coupling to H_{2ax} (J = 8.9 Hz), and thus the alcohol was equatorial. The second major product was also isolated and characterized by mass spectra and ^1H and ^{13}C NMR spectra. Although direct determination of the orientation of the OH group was not possible, structure **25** follows from further work on the reduction of the individual spiroenone isomers.

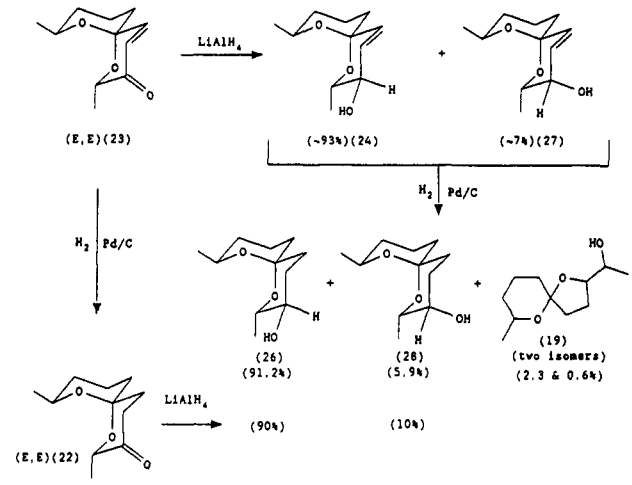


The crude mixture of allylic alcohols was hydrogenated (5% Pd/C, 1 atm, Na_2HPO_4 buffer) under conditions designed to minimize ring opening and possible isomerization to the 1,6-dioxaspiro[4.5]decane system (**19**). Separation by chromatography provided the major isomer (95%) slightly contaminated with others. The *E,E,E* relative stereochemistry (**26**) was based on complete analyses of the ^1H and ^{13}C NMR spectra, using 2D ^1H–^1H and ^{13}C–^1H correlation spectra. In particular, H_{2ax} was a doublet of quartets at δ 3.54 (J = 9.0, 6.3 Hz), and the signal at δ 3.67 for H_{8ax} exhibited an *E*-ring coupling pattern. The large coupling of 9.0 Hz between H_{2ax} and H_3 requires an equatorial hydroxyl group as in **26**.

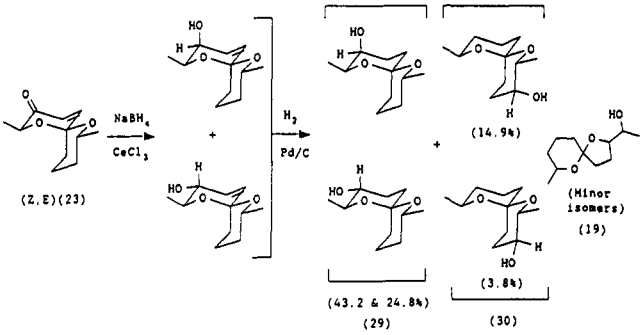
Reduction of Individual Isomers of the Spiroenones. Although available in small quantities only, the isomeric spiroenones were reduced with Luche's reagent and hydrogenated in an attempt to acquire the two *E,E* and four *E,Z* alcohols for GC/MS and NMR data. (Characterization of the reduction products is contained in the supplementary material). Thus Luche[23] reduction

(20) DeShong, P.; Waltermire, R. E.; Ammon, H. L. *J. Am. Chem. Soc.* **1988**, *110*, 1901.
(21) Lefebvre, Y. *Tetrahedron Lett.* **1972**, *2*, 133.
(22) Perron, F.; Albizati, K. F. *J. Org. Chem.*, **1989**, *54*, 2047.
(23) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

Scheme VII



Scheme VIII

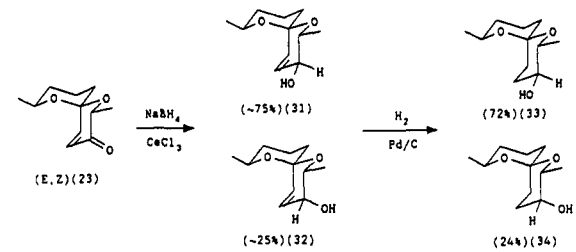


of (*E,E*)-**23** provided the allylic alcohol **24** described above and a second isomer (formulated as **27**) of the same system in 98:2 ratio, whereas $LiAlH_4$ provided a 93:7 ratio of the same allylic alcohols. The minor isomer (**27**) was characterized only by its mass spectrum, with M^+ at m/z 198 and an intense m/z 154 ion. Reduction of this 93:7 mixture (H_2/Pd/C) provided a four-component mixture of alcohols in the ratio 91.2:5.9:2.3:0.6 with the former two corresponding to the equatorial and axial alcohols (**26** and **28**) and the latter two being isomers of the [4.5]decane system (**19**). In an attempt to form a greater amount of the *E,E* axial alcohol (**28**), the *E,E* spiroenone was first hydrogenated (H_2/Pd/C) to provide the saturated spiroketone (*E,E*)-**22** which was then reduced ($LiAlH_4$). However, the mixture of epimeric alcohols was 90:10, and only GC/MS data was obtained for it. The above chemistry is summarized in Scheme VII.

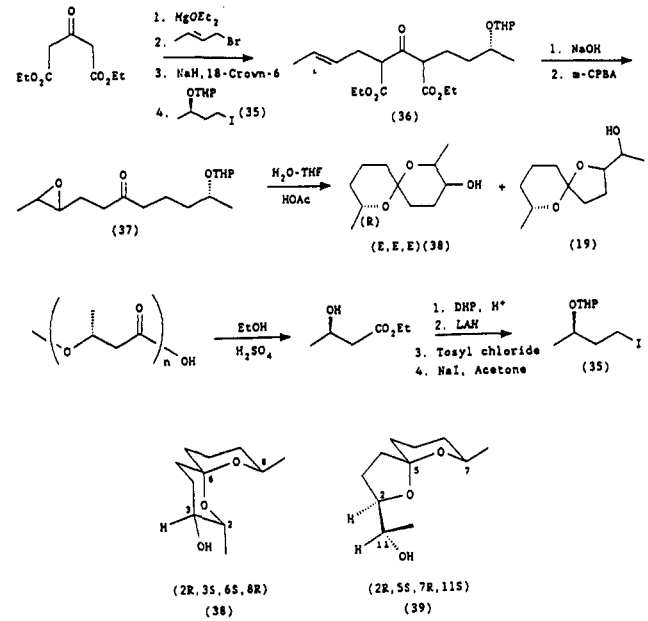
Reduction of the Spiroenone (*Z,E*)-23. Luche reduction led to two isomers in a 2:1 ratio, and if it is assumed that the ring skeletons are unchanged, both isomers incorporate the *Z,E* ring skeleton and contain a pseudoequatorial or a pseudoaxial hydroxyl group. ^1H NMR examination revealed couplings to H_3 (from H_{2ax}) of 2.7 Hz (major isomer) and 2.2 Hz (minor isomer), and it appears that distortion of the unsaturated Z ring is occurring, thus making tenuous the assignment of relative stereochemistry at C3.[24] Hydrogenation of this mixture provided saturated isomeric spiroacetals (GC/MS, polar column) as shown in Scheme VIII, with the major isomers (**29**) retaining the *Z,E* ring skeleton. Some isomerization of the ring skeleton has occurred, resulting in formation of two isomers (**30**) of the *E,Z* system, and three isomers of the [4.5]decane system (**19**).

(24) Perkins, M. V. PhD. Dissertation, The University of Queensland, 1991.

Scheme IX



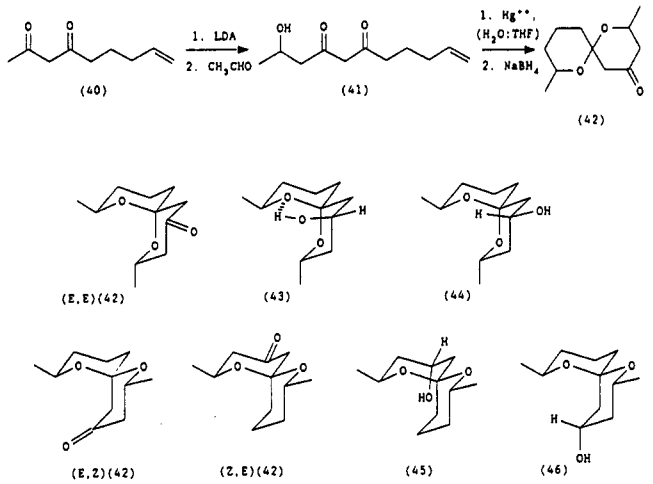
Scheme X



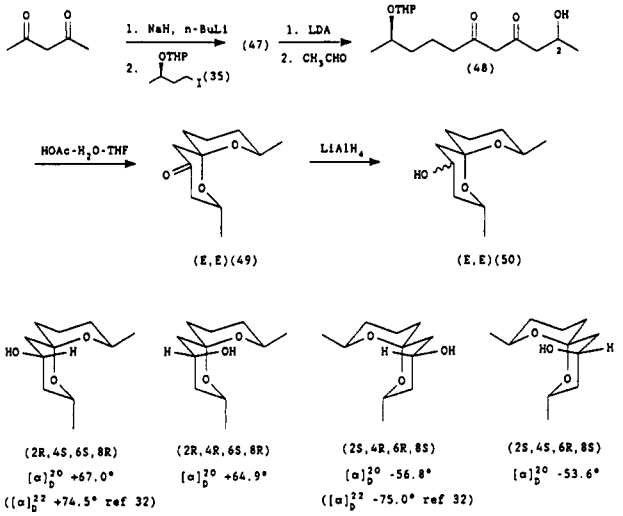
Reduction of Spiroenone (*E,Z*)-23. Luche reduction provided two isomers of the allylic alcohol in a 3:1 ratio. If the *E,Z* skeleton is maintained (and these two compounds are different from those resulting from such reduction of the *Z,E* spiroketone), the compounds are epimeric at C3 (bearing OH). H_{2ax} of the major isomer appeared as a doublet of quartets ($J_{H2ax-H3}$ = 8.9 Hz) implying an equatorial hydroxyl as in **31**. Direct confirmation that the minor compound was epimeric at C3 (i.e. **32**) was not possible as the H_{2ax} signal for this compound was obscured. Hydrogenation of this mixture again provided saturated spiroacetals (72% and 24%) shown to be epimeric 3-hydroxy compounds, which, due to their origin from the *E,Z* spiroketone, were assigned as **33** and **34**. The major isomer (**33**) was concluded to possess an equatorial hydroxyl, with $J_{H2ax-H3}$ = 9.3 Hz, a finding consistent with the conclusion that the major isomer (**31**) from Luche reduction of (*E,Z*)-**23** also possessed an equatorial hydroxyl. For the minor isomer, clear-cut ^1H signals were not discernible, but if epimeric at C3, then it represents the axial alcohol of the *E,Z* isomer (i.e. **34**). Two isomers of the [4.5]decane system (**19**) (0.06% and 0.5%) and a small amount (ca. 2%) of an isomer identical with the *major* product of hydrogenation of the *Z,E* isomer were also observed, indicating that the *E,Z* spiroketal series is less prone to rearrange than the *Z,E* series. (Scheme IX).

(2*R*,3*S*,6*S*,8*R*)-2,8-Dimethyl-1,7-dioxaspiro[5.5]undecan-3-ol (38). For the determination of the absolute configuration of the (*E,E,E*)-2,8-dimethyl-1,7-dioxaspiro-[5.5]undecan-3-ol (**26**) present in *B. cucumis*, it was necessary to acquire one enantiomer (or at least an enantiomerically-enriched sample) of this system. The approach chosen was the sequential alkylation of diethyl 3-oxoglutarate with 1-bromo-2-butene (crotyl bromide) and

Scheme XI



Scheme XII



3(*R*)-(tetrahydropyranyloxy)-1-iodobutane (**35**)[25] to yield **36**, which on hydrolysis–decarboxylation provided the protected hydroxy enone which was epoxidized forming **37**. Acid-catalyzed epoxide hydrolysis, concurrent with deprotection and cyclization, would provide the spiroacetal as shown in Scheme X.

The advantage of this approach is its directness and that use of the (*R*)-iodide (**35**) determines the chirality of the products. The drawback is that a number of isomers of the desired [5.5]undecane system can form, as well as a greater number in the [4.5]decane system **19**. A full analysis of the stereochemical possibilities for this cyclization are given elsewhere.[24]

Two major components (36% and 30%) and a number of minor components were formed although the use of pure (*E*)-crotyl bromide would have eliminated a number of the minor isomers. The compound present at the 30% level was shown by its mass spectrum and GC characteristics to be the desired (*E,E,E*)-2,8-dimethyl-1,7-dioxaspiro-[5.5]undecan-3-ol (**38**). The other major component (36%), largely on the basis of its mass spectrum (strong *m/z* 155 corresponding to $M^{\cdot+}$ – hydroxyethyl) was concluded to be a 1′-hydroxyethyl derivative of the 1,6-dioxaspiro-[4.5]decane system (**19**) and is predicted to be **39** on the basis of stereochemical considerations and the incorporation of an *E*-ring system.

The mixture of hydroxy spiroacetals was purified by preparative GC to provide **38**, in at least 95% chemical purity contaminated with other spiroacetal isomers. The desired compound (**38**; $[\alpha]^{33}_D = +49.5°$, $c = 0.2$, pentane) was spectroscopically identical with the racemate obtained previously, and as its trifluoroacetate exhibited a single peak by chiral GC on a Lipodex A column when compared with the racemic *E,E,E* diastereomer.

2,8-Dimethyl-1,7-dioxaspiro[5.5]undecan-4-ols (4). A diastereomer of system **4** has been described[5] as a minor component of the mandibular secretion of three species of bee in the genus *Andrena*, and more recently identified[26] as a minor component in *B. tryoni*, Queensland fruit fly.

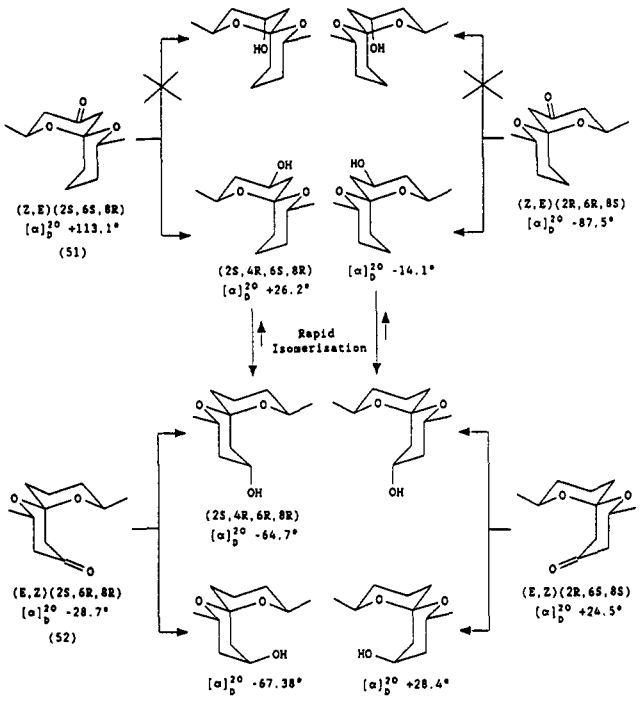
Our approach to these alcohols was based on acquisition of the corresponding ketones, followed by reduction. Thus, alkylation of the dianion from pentane-2,4-dione with 4-bromo-1-butene provided the known[27] enedione **40** from which the dianion was again generated and quenched with acetaldehyde to form the hydroxy enedione **41** in moderate yield. Attempted purification on Kieselgel led to dehydration and formation of a dihydropyran, but use of deactivated Kieselgel provided pure material. Standard oxymercuration–reduction of **41** led to ketone **42** as a mixture of three diastereomers with the *E,E* diastereomer (~85%) greatly predominating (Scheme XI). Detailed ^1H and ^{13}C NMR analyses were consistent with the major ketone being *E,E*-**42**. This was confirmed by an X-ray structure of an enantiomer of this ketone (see the supplementary material).

Reduction of the spiroketone mixture with $LiAlH_4$ led to four alcohols (36:54:8:2 in order of elution on a nonpolar column); each could be isolated by careful preparative GC. Relative configurations were established by detailed ^{13}C and ^1H NMR analyses, and for the major isomers the *E,E* ring skeleton is maintained as expected. The first eluting compound was shown to be **43**, with axial OH. An interesting feature of the ^1H NMR spectrum was the presence of HC_4OH coupling ($J = 10.2$ Hz) (correlated spectrum) consistent with the effect of D_2O addition. This J value indicates a dihedral angle of 155° according to the modified Karplus equation proposed by Fraser[28] and is a further example of hydrogen bonding to an ether type of oxygen.[29,30] The second eluting isomer was the epimeric alcohol (*E,E*). The two minor isomers were assumed to arise from the minor spiroketones (*E,Z*)-**42** and/or (*Z,E*)-**42**, and subsequently were shown to be **45** (from (*Z,E*)-**42**) and **46** (from (*E,Z*)-**42** respectively). Alcohols **45** and **46** are the major stereoisomers formed in the reduction of (*Z,E*)-**42** and (*E,Z*)-**42**, respectively.

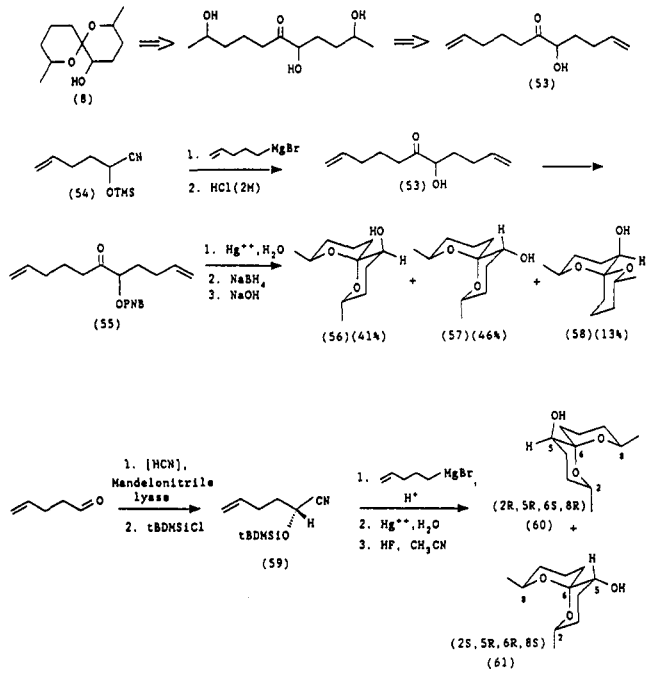
The possible presence of isomers of **4** in insect species indicated that acquisition of enantiomers of 2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-4-ols would be required. We have been able to obtain both enantiomers of each of the epimeric *E,E* ring-configured alcohols in high ee. In the first approach, chiral iodide **35**, derived from poly(β-

(25) (a) Seebach, D.; Züger, M. *Helv. Chim. Acta* **1982**, *65*, 495. (b) Mori, K.; Watanabe, H. *Tetrahedron* **1983**, *40*, 299.
(26) Krohn, S.; Kitching, W. Unpublished observations.
(27) Doherty, A. M.; Ley, S. V.; Lygo, B.; Williams, D. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1371.
(28) Fraser, R. R.; Kaufman, M.; Morand, P.; Govil, G. *Can. J. Chem.* **1969**, *47*, 404.
(29) Cocu, F. G.; Wolczunowicz, G.; Bors, L.; Posternak, Th. *Helv. Chim. Acta* **1970**, *53*, 1511.
(30) That the presence of intramolecular H bonding, as evidenced by HCOH spin coupling is a useful stereochemical tool in these systems is supported by detailed examination of the ^1H NMR spectra of certain 2-phenyl-8-methyl-1,7-dioxaspiro[5.5]undecan-4-ols, and the reported crystal structure[27] of the minor isomer resulting from $NaBH_4$ reduction of (*E,E*)-2-phenyl-8-methyl-1,7-dioxaspiro[5.5]undecan-4-one. In this case an intramolecular O···H bond exists (2.77 Å) with an –O–H···O angle of 139°. Efficient syntheses (based on Hg(II) cyclization) of these compounds[27] and full spectral details are provided elsewhere.[24]

Scheme XIII



Scheme XIV



hydroxybutyrate) was chosen as alkylating agent to install *R* chirality at C8 in the product spiroalcohol. This is shown in Scheme XII.

The presumed *E,E* ketone **49** was separated by HPLC from other isomers (C2 in **48** is a racemic center when generated by reaction of acetaldehyde) and its relative stereochemistry was confirmed by an X-ray structure which provided support for the ^{1}H NMR methods used extensively to assign relative stereochemistry in these compounds. Reduction with $LiAlH_4$[31] provided a mixture of epimeric alcohols (**50**) which were purified by preparative GC and characterized by ^{1}H and ^{13}C NMR methods as described for the racemates. The alcohols, as their trifluoroacetates, were examined by chiral GC (Lipodex A column) and shown to be enantiomerically pure, based on comparisons with the well-resolved peaks for the racemate. To obtain the antipodal alcohols, (*S*)-butane-1,3-diol (derivable via baker's yeast reduction, etc., of ethyl acetoacetate) was transformed into 3(*S*)-(tetrahydropyranyloxy)-1-iodobutane (as described above for the *R* enantiomer) and used as before in the alkylation sequence to provide the enantiomeric 4-ols shown in Scheme XIII. These are of lower ee's (ca. 80% ee by chiral GC) which is a direct reflection of the lower optical purity of the starting butane-1,3-diol. Previously, Redlich and Schneider[32] had synthesized the 2*R*,4*S*,6*S*,8*R* and 2*S*,4*R*,6*R*,8*S* isomers using the chiral iodide 1-iodo-4-(tetrahydropyranyloxy)pentane (the enantiomers of which were obtained from D-mannitol and D-glucose) as a key alkylating agent. These authors reported somewhat higher rotations (see values in parentheses in Scheme XII) but their routes did not provide the antipodes.

In addition to the enantiomeric *E,E* spiroketones (e.g. **49**), the above routes (Scheme XII) necessarily provide the (*E,Z*)-**52** and (*Z,E*)-**51** isomers, which in principle should together constitute 50% of the product. Careful HPLC separations yielded both enantiomers of each of the *E,Z* and *Z,E* ketones, with those derived from poly(β-hydroxybutyrate) possessing higher optical purity as expected. These were reduced with $LiAlH_4$ to provide epimeric alcohols which were separated by preparative gas chromatography and characterized by ^{1}H, ^{13}C, and 2D correlated NMR spectroscopy. In several cases, the amounts available were extremely small, and the measured optical rotations in these cases are approximate only. The results are summarized in Scheme XIII. It was anticipated that the enantiomeric axial alcohols would have formed in the reduction of the *Z,E* spiroketone enantiomers as shown in Scheme XIII. These alcohols were not detected however, with the reduction giving exclusively the equatorial epimers. These *Z,E* equatorial alcohols rapidly isomerized to an equilibrium mixture (1:2) with the corresponding *E,Z* equatorial alcohols (the alcohol group now located in the *E* ring). This feature, as shown in Scheme XIII, merely changes the configuration at the labile spiro center.

2,8-Dimethyl-1,7-dioxaspiro[5.5]undecan-5-ols (8). Prior to this study no isomer of **8** was known, either as a natural or synthetic sample. The presently described characterization was undertaken to facilitate comparisons with the other monohydroxy spiroacetals and to provide the basis for identification of this system from natural sources. In the racemic series it was envisaged that α-hydroxy ketone **53**, would act as the equivalent of the open-chain triol, via oxymercuration–reduction.

Hydroxy ketone **53** was acquired by utilizing the methodology of Gill,[33] whereby the Grignard reagent from 5-bromo-1-pentene was added to the *O*-trimethylsilyl ether of the cyanohydrin **54**. Use of the unprotected hydroxy dienone in an oxymercuration–cyclization–reduction sequence to obtain **8** was not promising, as only trace amounts (GC/MS) were formed with the major components appearing to be substituted methylfurans on the basis of a prominent *m/z* 85 ion in the mass spectrum. This indicated extensive (intramolecular) hydroxyl par-

(31) For a discussion of selectivity in the reduction of keto spiroacetals and the use of samarium diiodide/2-propanol, see: Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

(32) Redlich, H.; Schneider, B. *Liebigs Ann. Chem.* **1982**, 412.

(33) Gill, M.; Kietel, M. T.; Lally, D. A. *Tetrahedron Lett.* **1986**, *27*, 1933.

Table I. ^{1}H NMR Chemical Shifts for *E,E* Isomers of the Monohydroxy-Substituted 2,8-Dimethyl-1,7-dioxaspiro[5.5]undecanes with Values for the Parent Spiroacetal Included for Comparison

hydrogen	parent (2)	3eq-OH (26)	3ax-OH (28)	4eq-OH (44)	4ax-OH (43)	5eq-OH (56)	5ax-OH (57)	12-OH (3)
2ax	3.74	3.54	3.69	3.61	4.05	3.55	3.65	3.68
3ax	1.11	3.03	OH	1.06	1.19	1.14	1.37	1.14
3eq	1.39	OH	3.27	1.68	1.80	1.32	1.10	1.35
4ax	2.04	1.90		4.08	OH	1.6-8	2.15	1.96
4eq	1.40	1.53		OH	4.40	1.6-8	1.55	1.35
5ax	1.30	1.36		1.18	1.30	3.29	OH	1.23
5eq	1.63	1.66		1.97	1.80	OH	3.41	1.57
8ax	3.74	3.67	3.61	3.61	3.62	3.65	3.65	3.71
9ax	1.11	1.04		1.08	0.98	0.95	1.04	1.06
9eq	1.39	1.33		1.33	1.22	1.28	1.34	1.35
10ax	2.04	1.94		1.95	1.87	1.90	1.87	1.83
10eq	1.40	1.36		1.36	1.27	1.40	1.43	1.35
11ax	1.30	1.25		1.27	1.18	2.06	1.22	1.23
11eq	1.63	1.53		1.59	1.44	1.48	2.03	1.53
Me12	1.15	1.32	1.15	1.13	1.12	1.05	1.08	3.49
Me13	1.15	1.11	1.10	1.08	0.92	1.02	1.08	1.11

ticipation in the oxymercuration. However protection of the hydroxyl group as the *p*-nitrobenzoate (**55**) permitted the desired mode of oxymercuration–cyclization–reduction to proceed. Three compounds were formed which appear to be *p*-nitrobenzoates of **8**. Deprotection by basic hydrolysis provided the two *E,E* isomers (**56** and **57**) as major products (41% and 46% of the spiroacetals) along with a third isomer (13%), tentatively assigned structure **58**. The details are in Scheme XIV.

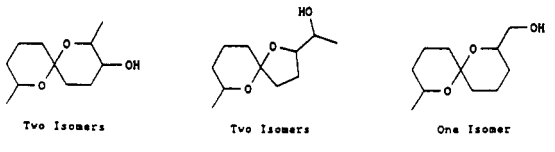
The first eluting isomer (GC on an OV101 column) was identified by analysis of the 400-MHz 2D ^{1}H–^{1}H correlated NMR spectrum as **56**, with the *E,E* ring geometry and equatorial OH. The CHO region consists of three absorptions, with those at δ 3.55 and 3.65 assigned to H_{2ax} and H_{8ax} by their distinctive coupling patterns (dqd, J = 11.2, 6.3, 2.3 Hz) and their chemical shift similarity which strongly indicates an *E,E* ring geometry. The third signal, δ 3.29 (H_5), appears as a doublet of doublets (J = 11.3 and 5.3 Hz), and the large coupling requires H_5 to be axial and hence an equatorial OH. The ^{13}C shifts were concordant; in particular C3 and C11 (in **56**) (Scheme XIV) experienced upfield shifts due to the γ-oxygen effect of OH. The second eluting compound (**57**) also possessed an *E,E* ring geometry on the basis of complete analysis of its 400-MHz ^{1}H NMR spectrum as before, with H-5 (δ 3.41) now a broad triplet ($J \sim$ 2.8 Hz) confirming an axial OH. The third and minor isomer was tentatively assigned as **58**, on the basis of its ^{1}H NMR spectrum and assumed relative stabilities of the isomers. The CHO region shows two signals at δ 3.37 and 4.12 exhibiting coupling patterns typical of H_{2ax} and H_{8ax} in *Z* and *E* rings respectively, confirming the presence of an *E,Z/Z,E* system. The signal at δ 3.43 (dd, J = 5.4, 3.3 Hz) requires an axial OH, although the ring (i.e. either *E* or *Z*) bearing the OH is unassigned. Steric interactions appear less severe in **58** than in the alternative. A full discussion is presented elsewhere.[24]

To access the enantiomeric series of alcohols chirality was introduced at the cyanohydrin stage. There is currently considerable activity in this area, and a report[34] describing cyanohydrin formation from alkanals mediated by mandelonitrile lyase (in a crude extract of almond flour) was of particular relevance. Thus 4-pentenal was treated in the manner described[34] for other alkanals (e.g. hexanal), and the resulting cyanohydrin was isolated as its *tert*-butyldimethylsilyl ether (**59**). Derivatization (as the trifluoroacetate) was also conducted to facilitate chiral GC analyses, which revealed an ee of 33% (*R* configuration by analogy), somewhat lower than reported[34] for the hexanal case (67% ee). The reasons for this lower figure are not clear, and attempts to improve this are continuing. Nevertheless, this level of induction, if transmitted to the final 5-hydroxy spiroacetal, would be adequate for establishing the elution order of the enantiomers and comparisons with natural material, should that prove necessary.

Treatment of the predominantly *R* cyanohydrin **59** in the manner described for the racemate provided a mixture of two silyl ethers which were deprotected with HF/CH_3CN. The alcohols (**60** and **61**) were separated by preparative gas chromatography and shown to be *E,E* ring configured as before, with equatorial and axial hydroxy groups, and the anticipated predominating absolute configurations shown in Scheme XIV. The racemic equatorial alcohol, as the trifluoroacetate, was separated by GC into enantiomers on a Lipodex A column, and similar examination of the optically active material ($[\alpha]^{30}_D$ +14.6°) established an ee of 33% (as originally present in the cyanohydrin) with the 2*R*,5*R*,6*S*,8*R* enantiomer (**60**) eluting first. On this basis, optically pure (2*R*,5*R*,6*S*,8*R*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-5-ol would exhibit $[\alpha]^{30}_D$ = +45°. In contrast, the axial alcohol was not enantiomerically resolved under the same conditions, although the ee would be expected to be 33% also. On this assumption, and from the measured rotation ($[\alpha]^{30}_D$ −10.2°), the 2*S*,5*R*,6*R*,8*S* isomer (axial alcohol **61**) would exhibit $[\alpha]^{30}_D \simeq -31°$.

The ^{1}H and ^{13}C NMR data for most of the synthesized alcohols are in Tables I–IV.

Absolute Stereochemistry of Some Hydroxy Derivatives Present in *B. cucumis*. The hydroxy spiroacetals present in the rectal glandular secretion of male *B. cucumis* are shown below:



The relative stereochemistries of these components were determined in the following way. As described in Scheme VII reduction of pure (*E,E*)-**23**, followed by hydrogenation, provided predominantly the epimeric alcohols possessing the *E,E* ring system (91.2% and 5.9%) (**26** and **28**, respectively), together with two isomers of the hydroxyethyl system (2.3% and 0.6%). These minor isomers have the same relative stereochemistry as the predominating equatorial and/or axial alcohols and are thus *two* of the four isomers shown below in Scheme XV. Comparison of GC retention times (on a polar column) of this alcohol mixture with those of the components in the *B. cucumis*

(34) Brussee, J.; Roos, E. C.; Van der Gen, A. *Tetrahedron Lett.* **1988**, *29*, 4485 and references therein.

Table II. ^{13}C NMR Chemical Shifts for *E,E* Isomers of the Monohydroxy-Substituted 2,8-Dimethyl-1,7-dioxaspiro[5.5]undecanes with Values for the Parent Spiroacetal Included for Comparison

carbon	parent[a] (2)	3eq-OH[a] (26)	4eq-OH[a] (44)	4ax-OH[a] (43)	5eq-OH (56)	5ax-OH (57)	12-OH (3)
2	65.15	69.97	64.50/65.61	60.30	64.85/65.82	65.02/65.65	70.10
3	33.23	72.53	43.51	40.47	28.88	26.67	26.94
4	19.35	28.77	64.84	65.31	32.89/33.12	31.55/32.95	18.61/19.30
5	35.66	35.96	45.70	40.58	71.85	69.37	33.35/35.87
6	96.07	95.45	97.99	98.60	97.68	97.78	96.06
8	65.15	65.47	64.50/65.61	66.13	64.85/65.82	65.02/65.65	65.34
9	33.23	33.05	33.43	32.52	32.89/33.12	31.55/32.95	32.97
10	19.35	19.48	19.88	18.78	18.94	19.10	18.61/19.30
11	35.66	34.73	35.73	35.04	30.89	26.98	35.35/35.87
Me12	22.22	18.47	22.25 or	21.76	21.39 or	21.90	66.43
Me13	22.22	22.08	22.62	21.89	21.92	22.07	22.10

[a] Confirmed by carbon–proton correlation spectrum.

Table III. ^{1}H NMR Chemical Shifts for *Z,E* and *E,Z* Isomers of Some of the Monohydroxy-Substituted 2,8-Dimethyl-1,7-dioxaspiro[5.5]undecanes with Values for the Parent *E,Z* Spiroacetal Included for Comparison

hydrogen	(*EZ*)-2 parent	(*Z,E*)-45 4eq-OH	(*E,Z*)-4[a] 4ax-OH	(*E,Z*)-46 4eq-OH	(*Z,E*)-3 12-OH	(*E,Z*)-3 12-OH
2ax	4.26	3.15	4.47	4.16	3.35	4.18
3ax	1.13	1.13	1.22	1.09	1.13[b]	1.26
3eq	1.41	1.6–7	1.77	1.71	1.24[b]	1.26
4ax	1.74	3.55	OH	3.88	1.24	1.64
4eq	1.37	OH	4.01	OH	1.5–6	1.32
5ax	1.04	1.6–7	1.08	0.98	1.5–6	0.96
5eq	1.92	1.86	2.06	2.35	1.5–6	1.87
8ax	3.42	4.24	3.65	3.46	4.09	3.35
9ax	1.10	1.13	1.03	1.06	1.10	1.08
9eq	1.29	1.2–4	1.24	1.24	1.33	1.21
10ax	1.29	1.6–7	1.16	1.24	1.64	1.23
10eq	1.56	1.2–4	1.57	1.54	1.33	1.52
11ax	1.68[b]	1.05	1.53	1.66	0.99	1.58[b]
11eq	1.55[b]	1.6–7	1.36	1.54	1.86	1.49[b]
Me12	1.14	1.13	1.12	1.14	3.5–6	3.52
Me13	1.19	1.09	1.07	1.13	1.13	1.14

[a] See structure in Scheme XIII. [b] Assignments may be interchanged.

Table IV. ^{13}C NMR Chemical Shifts for *Z,E* and *E,Z* Isomers of Some of the Monohydroxy-Substituted 2,8-Dimethyl-1,7-dioxaspiro[5.5]undecanes with Values for the Parent *E,Z* Spiroacetal Included for Comparison

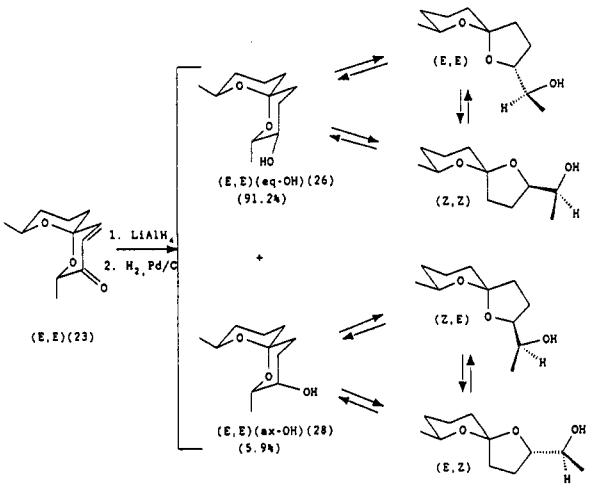
carbon	(*E,Z*)-2 parent[a]	(*Z,E*)-45 4eq-OH[a]	(*E,Z*)-4[b] 4ax-OH[a]	(*E,Z*)-46 4eq-OH[a]	(*Z,E*)-3 12-OH[a]	(*E,Z*)-3 12-OH[a]
2	65.93	66.38	60.91	64.95	73.43	70.88
3	33.53	42.70	40.53	43.54	26.56	27.18
4	19.11	65.31	65.30	64.55	18.95	18.29
5	36.61	45.50	36.68	40.04	36.65	30.08
6	97.12	98.08	99.03	98.73	97.23	97.32
8	68.54	66.28	69.54	68.77	66.35	68.69
9	32.60	33.22	31.41	32.32	33.27	32.48
10	19.23	18.84	17.41	19.02	18.81	19.33
11	30.35	30.59	36.42	36.16	30.05	36.20
Me12	22.34	22.27/22.26	21.77	21.79	66.35	66.38
Me13	22.12	22.26/22.27	21.37	21.95	22.29	22.14

[a] Confirmed by carbon–proton correlation spectrum. [b] See structure in Scheme XIII.

extract, established the *E,E* equatorial alcohol **26** as the major natural alcohol, along with minor amounts of the corresponding axial alcohol **28**. The natural hydroxyethyl isomers possess the same relative stereochemistry as these epimeric 3-hydroxy isomers. These relationships are made clear in Scheme XV. A trace of (8-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)methanol (**3**) was also present naturally, and shown to be the *E,E* diastereomer by GC comparisons.

The authentic *E,E* equatorial alcohol **26** was derivatized in the normal way with trifluoroacetic anhydride in CH_2Cl_2 but two compounds were produced, the first eluting being the unrearranged trifluoroacetate (m/z 112, characteristic of a [5.5]undecane system) followed by the rearranged [4.5]decane isomer (m/z 155 and 85). An acid induced ring opening–isomerization was thus occurring, but this was suppressed by adding triethylamine. With this derivatized sample in hand, near base-line enantiomeric resolution

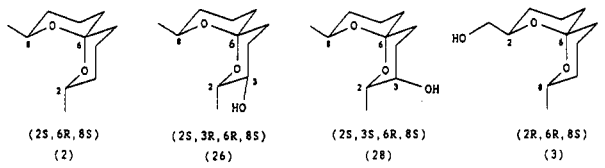
Scheme XV



(column temperature = 75 °C) was achieved by GC analysis on a Lipodex A column. With the availability of the pure 2*R*,3*S*,6*S*,8*R* enantiomer **38** as described above, the elution order was established with the 2*R*,3*S*,6*S*,8*R* isomer eluting first. This is reminiscent of the behaviour of (*E*,*E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**2**), for which the 2*R*,6*S*,8*R* enantiomer also elutes first. It was also clear that between the antipodal pair for the *E*,*E* axial alcohol **28**, the 2*R*,3*R*,6*S*,8*R* enantiomer also eluted first.

For the determination of the chirality of the spiroalcohols in *B. cucumis*, ca. 200 adult males were dissected and the glandular components extracted with CH_2Cl_2. GC analysis of the derived trifluoroacetates clearly showed that the natural *E*,*E* equatorial 3-ol possessed the 2*S*,3*R*,6*R*,8*S* configuration with none of the antipode being detectable. Determination of the ee of the minor *E*,*E* axial 3-ol was more difficult (no base-line separation at 75 °C), but it is very predominantly the 2*S*,3*S*,6*R*,8*S* enantiomer. The related hydroxyethyl substituted [4.5]decanols that are present naturally are interconvertible with the [5.5]undecan-3-ols and must therefore share their absolute configurations.

Although the hydroxymethyl derivative, (8-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)methanol (**3**), is present at a low level, its chirality was also determined. The availability of the *E*,*E* diastereomer in both racemic and optically active forms permitted chiral analysis (as the derived trifluoroacetates) with the 2*S*,6*S*,8*R* enantiomer eluting first. Analysis of the trifluoroacetylated *B. cucumis* extract showed the natural product to be predominantly the 2*S*,6*R*,8*S* isomer. The very low level present and the nearness of another peak render a precise determination impossible, but an ee of >70% is certain. The absolute configurations of several components in *B. cucumis* have now been determined and these are shown below.



Thus, the hydroxyl derivatives possess the same ring chirality as the (*E*,*E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**2**) itself and are probably directly derived from it by hydroxylation. There is some meager evidence that the level of hydroxy derivatives increases with the age of the individual, but more studies of this feature and the purpose of hydroxylation are required.

Experimental Section

General Aspects. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Preparative GC was performed with OV101 and C-20M columns. Chiral gas GC analyses were performed using either a 40-m glass capillary column with hexakis(3-*O*-acetyl-2,6-di-*O*-pentyl)-α-cyclodextrin (Lipoden A column) as the stationary phase or a 25-m bis(3-(heptafluorobutyryl)-(*R*)-camphorato)nickel(II)/OV-1 fused silica column. Optical rotations were measured using a Perkin-Elmer 141 MC or 241 MC polarimeter.

Synthesis of Compounds. Synthesis of (8-Methyl-1,7-dioxaspiro[5.5]undecan-2-yl)methanol (3). 10-Hydroxyundec-1-en-6-one (9). A solution of pentenylmagnesium bromide was prepared from 5-bromopent-1-ene (3.26 g, 21.9 mmol) and Mg (0.53 g, 21.9 mmol) in the usual manner in ether (25 mL) and added dropwise to a stirred solution of δ-caprolactone (2.5 g, 21.9 mmol) in dry THF (50 mL) under nitrogen at −78 °C over 3 h. The reaction was stirred for 1 h more, after which time saturated aqueous NH_4Cl (30 mL) was added and the mixture allowed to warm to rt. The aqueous layer extracted with ether (2 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product (3.0 g, 75%) was shown by GC and ^{13}C NMR analysis to be a mixture of enone **9** (66%) and unreacted lactone (33%). This material was found to be rather acid sensitive, decomposing during chromatography on Kieselgel. As the contaminating lactone was not expected to interfere in the subsequent reaction, further purification was not attempted in this case. On another occasion, when a higher reaction temperature was employed (−20 °C), the main product was the tertiary alcohol (double addition) and the desired hydroxy enone **9** (ca. 13%) was separated by distillation: bp 100–105 °C (0.001 mmHg); ^{13}C NMR ($CDCl_3$) δ 19.67, 22.68, 23.29, 32.95, 38.51, 44.45, 67.32, 115.06, 137.81, 211.20; ^1H NMR ($CDCl_3$) δ 1.0–2.4 (m, 16 H, including δ 1.2 (d, 3 H, CH_3)), 3.7 (m, 1 H, C*H*OH), 4.9 (m, 2 H, CH_2=), 5.7 (m, 1 H, CH=).

(8-Methyl-1,7-dioxaspiro[5.5]undecan-2-yl)methanol (3). To a stirred solution of enone **9** (1.0 g, crude from previous step, ~66%, 3.6 mmol) in THF–H_2O (1:1, 80 mL) was added *m*-CPBA (3 additions over 5 days of 1.0 g (85%), 3.8 mmol). After this time (5 days) total conversion to the spiroacetal **3** had occurred with apparently no dehydration products. The reaction was treated with saturated aqueous $NaHCO_3$, saturated $NaHSO_3$, and again with saturated $NaHCO_3$. (The contaminant in the starting material, i.e. δ-caprolactone, was presumably converted to the acid under the reaction conditions and removed by basic washing.) The resulting oily product was shown by GC analysis to be composed of three spiroacetals in the ratio 62:22:16 (0.56 g, 78%). This mixture was subjected to flash chromatography (Kieselgel 60, mesh 230–400, EtOAc–CH_2Cl_2 (20:80)) to yield three isomers. The major isomer (0.15 g, 20.9%) was shown to be spiroacetal (*E*,*E*)-**3**: mp 41.5–42.5°; HRMS (EI) found M^+ 200.1417, $C_{11}H_{20}O_3$ requires 200.1412; ^{13}C NMR (C_6D_6) δ 18.61, 19.30 (C_4, C_{10}), 22.10 (C13), 26.94 (C3), 32.97 (C9), 35.35 and 35.87 (C5 and C11), 65.34 (C8), 66.43 (C12), 70.10 (C2), 96.06 (C6); ^1H NMR (C_6D_6) (assigned with the aid of ^1H–^1H correlation spectrum) δ 1.06 (dddd, *J* = 13.0, 13.0, ~11.5, 3.8 Hz, 1 H, $H9_{ax}$), 1.11 (d, *J* = 6.3 Hz, 3 H, Me13), 1.14 (dddd, *J* = ~13, ~13, ~11, ~4 Hz, 1 H, $H3_{ax}$), 1.19–1.29 (m, 3 H, $H3_{eq}$, $H5_{ax}$, and $H11_{ax}$), 1.3–1.4 (m, 3 H, $H4_{eq}$, $H9_{eq}$, and $H10_{eq}$), 1.53 (dm, *J* = ~13.5 Hz, 1 H, $H11_{eq}$), 1.57 (dm, *J* = ~13.0 Hz, 1 H, $H5_{eq}$), 1.83 (qt, *J* = 13.4, 4.1 Hz, 1 H, $H10_{ax}$), 1.96 (qt, *J* = 13.1, 4.1 Hz, 1 H, $H4_{ax}$), 2.19 (br s, 1 H, OH), 3.49 (m (second order), 2 H, C12 CH_2), 3.68 (m, 1 H, $H2_{ax}$ (overlaps with $H8_{ax}$)), 3.71 (m, 1 H, $H8_{ax}$ (overlaps with $H2_{ax}$)).

(±)-5,6-*O*-Isopropylidenehexanenitrile (13). To a refluxing solution of the known iodide[14] **12** (7.03 g, 29 mmol) in benzene (20 mL) containing acrylonitrile (15.4 g, 290 mmol) and AIBN (20 mg) (N_2 atmosphere) was added tributyltin hydride (9.60 g, 33 mmol) in benzene (50 mL) over 1 h. The cloudy white solution was refluxed for a further hour. After removal of benzene (under reduced pressure) CH_2Cl_2 (150 mL) was added and the solution filtered (Celite), with the filtrate being added to 3% aqueous NH_3 (100 mL) and vigorously shaken. Saturated NaCl solution (100 mL) was added, and the organic layer was separated. This procedure was repeated on the organic layer, and the combined aqueous layers were further extracted with CH_2Cl_2 (2 × 100 mL). The organic layer was dried ($MgSO_4$) and filtered with the CH_2Cl_2 being removed to yield the crude oil. Flash chromatography (silica; 10% ethyl acetate–hexane) provided the nitrile **13** (1.96 g, 40%) which was used without further purification: HRMS (CI, NH_3) found $(M + 1)^+$ 170.1168, $C_9H_{16}O_2N$ requires 170.1181; HRMS (EI) found $(M - CH_3)^+$, 154.0874, $C_8H_{12}NO_2$ requires 154.0868; ^{13}C NMR ($CDCl_3$) δ 17.03, 21.95, 25.49, 26.78, 32.28, 69.03, 74.93, 109.00, 119.35; ^1H NMR ($CDCl_3$) δ 1.32 (s 3 H, CH_3), 1.38 (s, 3 H, CH_3), 1.64–1.84 (m, 4 H, CH_2), 2.42–2.38 (t, *J* = 7.08 Hz, 2 H, CH_2CN), 3.51 (dd, *J* = 6.67, 6.71 Hz, 1 H, CHO), 4.01–4.12 (m, 2 H, CH_2O).

Tetrahydropyran 14. The above nitrile **13** (1.9 g, 11.2 mmol) in dry ether (20 mL) was added dropwise to a solution of the Grignard reagent prepared in the normal way from 4-pentenyl bromide (2.07 g, 13.9 mmol) and Mg (0.33 g, 12.7 mmol) in ether (25 mL). After addition was complete, the solution was refluxed for 3 h, cooled, and diluted with ether (50 mL). The reaction was quenched with 5% aqueous HCl (50 mL) and stirred overnight. The ether layer was separated and the aqueous layer extracted with ether (4 × 50 mL). The combined ether layers were then washed with saturated $NaHCO_3$ (3 × 50 mL) and saturated NaCl

solution (3 × 50 mL). The ether layer was dried ($MgSO_4$) and evaporated to yield a yellowish oil (2.0 g, 85%), which was purified by distillation (Kugelrohr, 100 °C, 5 mm): HRMS (CI) found (M + 1)$^+$, 201.1487, $C_{11}H_{21}O_3$ requires 201.1490; HRMS (EI) found (M − OH)$^+$, 183.1386, $C_{11}H_{19}O_2$ requires 183.1385; ^{13}C NMR ($CDCl_3$) δ 16.85, 22.39, 28.44, 33.83, 33.91, 37.04, 69.87, 74.88, 108.78, 114.50, 138.66; ^1H NMR ($CDCl_3$) δ 1.40–1.90 (m, 12 H, CH_2), 3.75–4.90 (m, 3 H, CHO), 4.94 (m, 2 H, $=CH_2$), 5.77 (m, 1 H, m, CH=).

[(8-(Hydroxymethyl)-1,7-dioxaspiro[5.5]undecan-2-yl)-methyl]mercuric Chloride (15). The above tetrahydropyran (14) (0.50 g, 1.15 mmol) was stirred in THF–H_2O (1% $HClO_4$) (1:1, 40 mL). $Hg(OAc)_2$ (0.85 g, 2.5 mmol) was added in one portion, and stirring was continued for 1 h. Excess saturated NaCl solution was added, and the THF was removed under reduced pressure. CH_2Cl_2 (30 mL) was added, and the organic layer was separated and washed with aqueous $NaHCO_3$ (2 × 30 mL) and cold water (2 × 30 mL) and then dried ($MgSO_4$). The filtered solution was evaporated to yield the crude mercurial **15** (0.45 g, 42%): ^{13}C NMR ($CDCl_3$) δ 18.14, 18.86, 26.53, 34.55, 34.58, 35.18, 39.48, 66.13, 68.27, 70.31, 96.71; ^1H NMR ($CDCl_3$) δ 1.07–2.93 (m, 12 H, CH_2), 2.03–2.25 (AB part of ABX pattern, J_{AB} = 10.7, J_{BX} = 8.6, J_{AX} = 5.0 Hz, 2 H, CH_2HgCl), 3.48 (dd, J = 11.4, 7.1 Hz, 1 H, CH_2OH), 3.61 (m, 2 H, one of CH_2OH, and CHO), 3.90 (m, 1 H, other CHO).

(8-Methyl-1,7-dioxaspiro[5.5]undecan-2-yl)methanol (3). The above mercurial **15** (0.6 g, 1.28 mmol) was dissolved in CH_2Cl_2 (10 mL) and water (5 mL). This system was cooled in ice, and 10% aqueous NaOH (10 mL) was added, followed by benzyltriethylammonium chloride (1.25 g, 5.52 mmol) and $NaBH_4$ (0.68 g, 17.94 mmol). After being for 0.5 h, the solution was filtered (Celite), and the filtrate was extracted with ether (3 × 50 mL). The organic layer was washed with aqueous NaCl (2 × 50 mL), separated, and dried ($MgSO_4$). Solvent removal left an oil (0.22 g, 80%), GC/MS analysis of which indicated three isomers of the title spiroacetal **3**, (80%, 10%, 10%) corresponding to the *E,E*, *Z,E*, and *E,Z* diastereomers. Purification and separation of these isomers was effected by chromatography (silica, Kieselgel 230–400 mesh, CH_2Cl_2/ethyl acetate, 8:2). (These isomers provided ^1H and ^{13}C NMR spectra identical with those described above for samples acquired by a different route. The spectral data for the *Z,E* and *E,Z* isomers are provided in the supplementary material).

(*S*)-2,3-*O*-Isopropylideneglycerol (16). 1,2:5,6-Di-*O*-isopropylidene-D-mannitol was prepared according to the procedure of Stick and co-workers[18] and had mp 119–121 °C after two recrystallizations from CH_2Cl_2/hexane (lit. mp 121–122 °C). (*S*)-2,3-*O*-Isopropylideneglycerol (**16**) was obtained from this mannitol derivative by cleavage with $Pb(OAc)_4$ followed by in situ reduction with $NaBH_4$, as described fully by Stick.[18] Purification was effected by distillation (Kugelrohr, 80 °C, 11 mm, 72%): $[\alpha]_D$ +12.6° (*c* 7.22 in MeOH) [lit.[18] $[\alpha]_D$ +11.5° (*c* 7.25 in MeOH)]. Treatment with tosyl chloride in $CHCl_3$–Et_3N provided the tosylate (90%) as a slightly orange oil, which was characterized by its ^1H and ^{13}C NMR spectra: ^{13}C NMR ($CDCl_3$) δ 21.39, 24.93, 26.41, 65.86, 69.40, 72.71, 109.78, 127.73, 129.73, 132.41, 144.91; ^1H NMR ($CDCl_3$) δ 1.30 (s, 6 H, CH_3), 2.43 (s, 3 H, Ar-CH_3), 3.60–4.40 (m, 5 H, CHO), 7.37 and 7.83 (d, J = 8 Hz, 4 H, Ar-H). The crude tosylate was dissolved in dry acetone containing an excess of NaI (20 molar excess) and refluxed for ca. 22 h to provide the optically active iodide[14] (84%) obtained as a clear oil by distillation (Kugelrohr, 75–80 °C, 1 mm): ^{13}C NMR ($CDCl_3$) δ 6.62, 25.53, 27.07, 69.53, 75.58, 110.33; ^1H NMR ($CDCl_3$) δ 1.23 and 1.33 (s, each 3 H, CH_3), 3.10–3.33 (m, 2 H, CH_2I), 3.63–4.33 (m, 3 H, CHO). The 2,2-dimethyl-4-(iodomethyl)-1,3-dioxolane thus obtained was used directly in the free radical addition to acrylonitrile as described above for the racemic series.

(*R*)-2,3-*O*-Isopropylideneglycerol (17) was obtained via a sequence commencing with L-arabinose and which has been fully described by Stick.[18] The crude material was purified by distillation (Kugelrohr, 80 °C, 11 mm, 44% from L-(+)-arabinose diethyl dithioacetal), $[\alpha]_D$ −11.7° (*c* 6.45 in CH_3OH) [lit.[18] $[\alpha]_D$ −11.5° (*c* 6.20 in CH_3OH)]. The ^1H and ^{13}C NMR spectra were identical with those of the racemate and the (*S*)-(+)-isomer. This material was again converted to the antipodal tosylate and iodide as outlined above and used in the sequence commencing with addition to acrylonitrile.

These sequences then provided the enantiomers of (8-methyl-1,7-dioxaspiro[5.5]undecan-2-yl)methanol (**3**) listed below with their rotations. Their relationships are made clear in Scheme IV.

(*E,E*)-(2*S*,6*S*,8*R*)-3: $[\alpha]_D$ +65.5° (*c* 8.01, *n*-pentane) [lit.[13] $[\alpha]_D$ +68.6° (*c* 1.26 in pentane)]. **(*E,E*)-(2*R*,6*R*,8*S*)-3**: $[\alpha]_D$ −64.4° (*c* 1.27, pentane). **(*E,Z*)-(2*R*,6*R*,8*R*)-3**: $[\alpha]_D$ −38° (*c* 1.88, pentane). **(*Z,E*)-(2*S*,6*R*,8*S*)-3**: $[\alpha]_D$ −30° (*c* 0.25, pentane) (lit.[13] $[\alpha]_D$ −32.9°). **(*Z,E*)-(2*R*,6*S*,8*R*)-3**: $[\alpha]_D$ **35°** (*c*, pentane).

The (*E,E*)-(2*R*,6*R*,8*S*)-**3** isomer was also obtained by treatment of 1,2-epoxy-6-oxo-10-(tetrahydropyranyloxy)undecane (*S* configuration at C10) (**18**) being derived from (*S*)-(+)-lactic acid, which has been fully described elsewhere,[17] with aqueous HOAc–THF, $[\alpha]^{23}_D$ −56.3° (*c* 1.26, pentane).

Synthesis of 2,8-Dimethyl-1,7-dioxaspiro[5.5]undecan-3-ol (7). 1-Iodo-4-(tetrahydropyranyloxy)pentane (20) was acquired by treatment of 1-iodo-4-hydroxypentane (from 2-methyltetrahydrofuran/chlorotrimethylsilane and NaI in acetonitrile, followed by hydrolytic workup on basic alumina) with dihydropyran in CH_2Cl_2 in the normal way. Chromatography on Kieselgel (mesh 70–230) eluting with $CHCl_3$–EtOAc (85:15) provided the iodide **20** (80%) as a mixture of two diastereomers: ^{13}C NMR ($CDCl_3$) δ 6.81, 7.12, 19.11, 19.73, 19.83, 21.42, 25.35, 25.38, 29.37, 29.69, 31.03, 31.07, 37.12, 38.01, 62.55, 62.60, 69.83, 72.86, 95.68, 98.58; ^1H NMR ($CDCl_3$) δ 1.04 (d, J = 6.1 Hz, 3 H, CH_3) (major isomer), 1.15 (d, J = 6.3 Hz, 3 H, CH_3) (minor isomer), 1.4–1.55 (m, 10 H), 1.55–1.7 (m, 2 H), 1.7–2.1 (m, 8 H), 3.08–3.20 (m, 4 H, CH_2I), 3.38–3.44 (m, 2 H), 3.63–3.89 (m, 4 H), 4.55 (dd, $J \sim 4$, 3 Hz, 1 H, one OCHO), 4.59 (dd, $J \sim 4$, 3 Hz, 1 H, other OCHO).

Furan 21. Furan (1.36 g, 0.02 mol) in anhydrous THF (10 mL) was added dropwise to a stirred solution of *n*-BuLi (10 mL, 1.6 M, 0.016 mol) in THF (100 mL) (nitrogen atmosphere) at rt. The resulting mixture was stirred for 1 h, after which the iodide **20** (4.0 g, 0.0134 mol) in THF (15 mL) was added dropwise and the stirring was continued for 2.5 h. Treatment with saturated aqueous NH_4Cl (50 mL) was followed by separation of the organic layers and extraction of the aqueous layer with ether (2 × 100 mL). The combined organic layers were washed with saturated aqueous NaCl (2 × 50 mL), dried ($MgSO_4$), and evaporated to give an oil. This oil was subjected to chromatography on Kieselgel 60 (mesh 70–230), eluting with $CHCl_3$ giving 2-(4′-(tetrahydropyranyloxy)pentyl)furan (2.5 g, 78%) as a mixture of diastereomers: ^{13}C NMR ($CDCl_3$) δ 19.06, 19.70, 20.00, 21.52, 23.92, 24.30, 25.48, 25.53, 27.92, 27.97, 31.16, 31.18, 35.91, 38.69, 62.40, 62.74, 70.72, 73.64, 95.59, 98.68, 104.65, 104.69, 109.95, 109.97, 140.62, 140.68, 156.12, 156.29. To a stirred solution of the above monoalkylated furan (2.0 g, 8.4 mmol) in dry THF (80 mL) under a nitrogen atmosphere was added *n*-BuLi (8.5 mL, 1.6 M, 13.6 mmol) in THF (20 mL) dropwise, and the resulting solution was stirred for 1.5 h. The mixture was then cooled in an ice bath, and acetaldehyde (freshly distilled, 1.2 g, 27.3 mmol) in dry THF (10 mL) was added dropwise. After the addition was complete, the mixture was allowed to warm slowly to rt and stirred overnight. The product was isolated by quenching with saturated aqueous NH_4Cl, extraction of the aqueous layer with ether (2 × 100 mL), washing the combined organic layers with saturated NaCl (2 × 50 mL), drying ($MgSO_4$), and evaporation to give an oil. Chromatography on Kieselgel 60 (mesh 70–230) eluting with $CHCl_3$–EtOAc (70:30) gave the furan **21** (0.7 g, 29.5%) as a mixture of four diastereomers, but exhibiting only two GC peaks. (The furan **21** was also prepared by the double alkylation of furan, firstly with the iodide **20** followed by acetaldehyde without the isolation of the intermediate monoalkylated furan.) In terms of stoichiometry total conversion in the first alkylation was assumed, leading to an (isolated) yield of furan **21** of ca. 20%. ^{13}C NMR: The spectrum is of a mixture of diastereomers, but unless otherwise noted each signal represents one carbon from a pair of diastereomers produced by the chiral C2′ center.) ($CDCl_3$) δ 19.08, 19.68, 19.88, 21.14 (broad, two carbons), 21.46, 23.84, 24.19, 25.46, 25.50, 27.95, 27.99, 31.11, 31.11, 35.80, 36.84, 62.43, 62.64, 63.53 (two carbons), 70.83, 73.46, 95.69 and 95.71 (one carbon split by interaction of C_2 with other two remote chiral centers), 98.45, 105.24, 105.27, 105.55, 105.58, 155.59, 155.75, 155.79, 155.86.

2,8-Dimethyl-1,7-dioxaspiro[5.5]undec-4-en-3-one (23). *m*-CPBA (80%, 0.65 g, 3.0 mmol) was added to a stirred cold (0.0

°C) solution of furan **21** (0.6 g, 2.1 mmol) in CH_2Cl_2 (50 mL), and the reaction mixture was allowed to warm slowly to rt. After 2 h, the reaction mixture was washed with saturated aqueous $NaHSO_3$ (25 mL) and finally saturated $NaHCO_3$ (25 mL). The organic layer was then dried ($MgSO_4$) and the solvent removed by evaporation. Chromatography on Kieselgel 60 (mesh 70–230, $CHCl_3$) gave a dihydropyranone (0.5 g, 79%) as a mixture of diastereomers. ^{13}C NMR: (This compound contains four chiral centers with the possibility of eight diastereomers. The diastereomeric composition was not obvious from the ^{13}C NMR. The signals observed are reported without indication of the number of carbons they represent.) ($CDCl_3$) δ 19.00, 19.30, 19.41, 19.55, 19.89, 20.16, 20.55, 21.51, 25.38, 31.11, 31.35, 31.45, 36.25, 36.33, 36.74, 40.19, 40.93, 41.39, 41.49, 62.73, 63.19, 63.80, 70.57, 70.81, 71.34, 73.75, 94.19, 94.26, 96.68, 97.32, 98.70, 126.38, 126.40, 126.77, 147.59, 147.67, 147.94, 197.28, 197.54, 197.64. The dihydropyranone was nonvolatile (decomposing on injection into a GC) and unstable (decomposing on storage at −10 °C in freezer) and was thus not characterized further but simply hydrolyzed to the spirocyclic α,β-unsaturated ketones. Thus the dihydropyranone mixture (0.5 g, 1.68 mmol) was stirred in a mixture of THF–HOAc–H_2O (4:2:1,7 mL) at rt for 3 days and then treated with saturated aqueous $NaHCO_3$ (15 mL) followed by solid $NaHCO_3$ (~6 g) to neutralize the acetic acid. Extraction with ether (3 × 50 mL), drying ($MgSO_4$), and evaporation gave the spiroacetal **23** (0.25 g, 76%) as a mixture of three diastereomers in the ratio 50:31:19 (*E,E*:*Z,E*:*E,Z*). A sample of the mixture obtained using the above procedure was subjected to preparative HPLC (column dimensions 21.4-mm i.d. × 25-cm length; silica, 0.25% isopropyl alcohol in hexane) to give each of the isomers pure. **Isomer 1 [(2*SR*,6*RS*,8*SR*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undec-4-en-3-one (23)** (*E,E* ring skeleton)]: HRMS (CI) found $(M + 1)^+$ 197.1185, $C_{11}H_{17}O_3$ requires 197.1177; ^{13}C NMR ($CDCl_3$) δ 15.26 (C12), 18.19 (C10), 21.76 (C13), 32.05 and 33.69 (C11 and C9), 68.04 and 69.85 (C2 and C8), 93.77 (C6), 126.73 (C4), 148.67 (C5), 197.79 (C3); ^1H NMR ($CDCl_3$) δ 1.16 (d, *J* = 6.2 Hz, 3 H, Me13), 1.26 (tdd, *J* = 13.4, 11.5, 4.0 Hz, 1 H, $H9_{ax}$), 1.36 (d, *J* = 6.8 Hz, 3 H, Me12), 1.49–1.69 (2nd order m, 3 H, $H9_{eq}$ and $H10_{eq}$ and $H11_{ax}$), 1.81 (dddd, *J* = 13.0, 4.1, 2.4, 1.5 Hz, 1 H, $H11_{eq}$), 1.92 (qt, *J* = 13.3, 4.1 Hz, 1 H, $H10_{ax}$), 3.86 (dqd, *J* = 11.5, 6.2, 2.3 Hz, 1 H, $H8_{ax}$), 4.42 (q, *J* = 6.8 Hz, 1 H, $H2_{ax}$), 5.98 (d, *J* = 10.1 Hz, 1 H, H4/H5), 6.6 (d, *J* = 10.1 Hz, 1 H, H5/H4). **Isomer 2 [(2*SR*,6*SR*,8*RS*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undec-4-en-3-one (23)** (*Z,E* ring skeleton)]: HRMS (CI) found $(M + 1)^+$ 197.1189, $C_{11}H_{17}O_3$ requires 197.1177; ^{13}C NMR ($CDCl_3$) δ 18.42 and 18.64 (C10 and C12), 21.73 (C13), 32.10 and 32.14 (C9 and C11), 67.04 and 74.47 (C2 and C8), 94.52 (C6), 125.79 (C4), 149.81 (C5), 197.95 (C3); ^1H NMR ($CDCl_3$) δ 1.13 (d, *J* = 6.4 Hz, 3 H, Me13), 1.25 (tdd, *J* = ~13, ~11, ~4 Hz, 1 H, $H9_{ax}$), 1.50 (d, *J* = 7.2 Hz, 3 H, Me12), 1.6–1.7 (m, 3 H), 1.79–1.92 (m, 2 H), 4.11 (dqd, *J* = 11.6, 6.2, 2.3 Hz, 1 H, $H8_{ax}$), 4.27 (q, *J* = 7.2 Hz, 1 H, $H2_{ax}$), 6.00 (d, *J* = 10.2 Hz, 1 H, H4/H5), 6.72 (d, *J* = 10.2 Hz, 1 H, H5/H4). **Isomer 3 [(2*SR*,6*RS*,8*RS*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undec-4-en-3-one (23)** (*E,Z* ring skeleton)]: ^{13}C NMR ($CDCl_3$) δ 15.43 (C12), 18.00 (C10), 21.49 (C13), 31.17 and 33.86 (C9 and C11), 70.07 and 70.95 (C2 and C8), 93.77 (C6), 126.32 (C4), 146.88 (C5), 196.67 (C3); ^1H NMR ($CDCl_3$) δ 1.23 (d, *J* = 6.2 Hz, 3 H, Me13), 1.36 (d, *J* = 6.9 Hz, 3 H, Me12), 1.35–1.44 (m, 1 H), 1.61–1.80 (m, 4 H), 1.91–1.99 (m, 1 H), 3.79 (dqd, *J* = 9.1, 6.2, 3.2 Hz, 1 H, $H8_{ax}$), 4.74 (q, *J* = 6.9 Hz, 1 H, $H2_{ax}$), 6.02 (d, *J* = 10.3 Hz, 1 H, H4/H5), 7.11 (d, *J* = 10.4 Hz, 1 H, H5/H4); (C_6D_6) δ 0.98–1.25 (m, 6 H (including 1.04 (d, *J* = 6.3 Hz, 3 H, Me13)), 1.39–1.66 (m, 6 H (including 1.41 (d, *J* =6.8 Hz, 3 H, Me12), 3.37 (dqd, *J* = 9.1, 6.3, 3.2 Hz, 1 H, $H8_{ax}$), 4.82 (q, *J* = 6.8 Hz, 1 H, $H2_{ax}$), 5.85 (d, *J* = 10.3 Hz, 1 H, H4/H5), 6.43 (d, *J* = 10.3 Hz, 1 H, H5/H4).

2,8-Dimethyl-1,7-dioxaspiro[5.5]undec-4-en-3-ol (24 and 25). $NaBH_4$ (42 mg, 1.1 mmol) was added to a solution of the above mixture of ketones **23** (0.18 g, 0.92 mmol) and $CeCl_3 \cdot 7H_2O$ (0.4 g, 1.1 mmol) in methanol (5 mL) at rt. After the mixture was stirred for 40 min, NaOH (2%, 15 mL) and EtOAc (15 mL) were added and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried ($MgSO_4$) and evaporated to give an oil (0.15 g, 82.5%) which appeared by GC/MS to be a mixture of allylic alcohols. A sample of the mixture was subjected to chromatography on Kieselgel 60 (mesh 70–230, EtOAc–CH_2Cl_2, 20:80) to yield the two major reduction products whose identities were confirmed by comparison with the products of reduction of individual isomers of ketone **23**. **Isomer 1 [(2*SR*,3*RS*,6*RS*,8*SR*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undec-4-en-3-ol (24)** (*E,E* ring skeleton, equatorial alcohol)]: ^{13}C NMR ($CDCl_3$) δ 18.10, 18.34, 22.10, 32.42, 34.04, 66.56, 68.67, 70.19, 94.43, 131.92, 132.09; (C_6D_6) 18.34, 18.76, 22.32, 32.84, 34.56, 66.43, 68.94, 70.15, 94.63, 132.05, 132.19; ^1H NMR ($CDCl_3$) δ 1.1–1.9 (m, 13 H, including 1.13 (d, *J* = 6.3 Hz, 3 H, Me13) and 1.31 (d, *J* = 6.1 Hz, 3 H, Me12)), 3.71 (dq, *J* = 8.9, 6.1 Hz, 1 H, $H2_{ax}$), 3.75–3.90 (m, 2 H, $H8_{ax}$ and $H3_{ax}$), 5.63 (dd, *J* = 10.0, 2.0 Hz, 1 H, H4/H5), 5.80 (dd, *J* = 10.0, 1.7 Hz, 1 H, H5/H4); (C_6D_6) 1.0–1.4 (m, 11 H, including 1.14 (d, *J* = 6.1 Hz, 3 H, Me13), and 1.30 (d, *J* = 6.1 Hz, 3 H, Me12)), 1.60–1.70 (m, 1 H), 1.90–2.05 (m, 1 H), 3.65 (br d, *J* = ~9 Hz, 1 H, $H3_{eq}$), 3.82 (dq, *J* = 8.8 Hz, 6.1 Hz, 1 H, $H2_{ax}$), 3.90 (dqd, *J* = 11.5, 6.1, 2.2 Hz, 1 H, $H8_{ax}$), 5.55 and 5.60 (ABX system, J_{AB} = 10.0, J_{AX} = 2.0, J_{BX} = 1.7 Hz, 2 H, H4 and H5 ($H3_{eq}$ is X)).

(2*SR*,3*RS*,6*RS*,8*SR*)-2,8-Dimethyl-1,7-dioxaspiro[5.5]undecan-3-ol (26). The remainder of the alcohol mixture (**24** and **25**) (0.1 g, 0.5 mmol) was added to a prereduced solution of 5% Pd/C (40 mg) and Na_2HPO_4 (100 mg) in methanol (5 mL) under H_2. The mixture was shaken for 2 h, after which the catalyst was removed by filtration through Celite. The solvent was removed under reduced pressure and the crude product (95 mg, 94%) was subjected to chromatography on Kieselgel 60 (mesh 70–230) eluting with CH_2Cl_2–EtOAc (90:10 increasing to 80:20) to give the major isomer **26** (*E,E* ring skeleton, equatorial alcohol) (15 mg, 14.8%): HRMS (CI) found $(M + 1)^+$ 201.1496, $C_{11}H_{21}O_3$ requires 201.1491; ^{13}C NMR (C_6D_6) (assignments confirmed by carbon proton correlation spectrum) δ 18.47 (C12), 19.48 (C10), 22.08 (C13), 28.77 (C4), 33.05 (C9), 34.73 (C11), 35.96 (C5), 65.47 (C8), 69.97 (C2), 72.53 (C3), 95.45 (C6); ^1H NMR (C_6D_6) (assignments confirmed by proton proton correlation spectrum) δ 1.04 (dddd, *J* = 13.0, 13.0, 11.5, 4.0 Hz, 1 H, $H9_{ax}$), 1.11 (d, *J* = 6.1 Hz, 3 H, Me13), 1.25 (td, *J* = 13.0, 4.2 Hz, 1 H, $H11_{ax}$), 1.32 (d, *J* = 6.3 Hz, 3 H, Me12), 1.33 (m, 1 H, $H9_{eq}$ (overlaps with $H5_{ax}$ and $H10_{eq}$)), 1.36 (m, 1 H, $H10_{eq}$ (overlaps with $H5_{ax}$ and $H9_{eq}$)), 1.36 (td, *J* = 13.0, 13.0, 4.5 Hz, 1 H, $H5_{ax}$ (overlaps with Me12, $H9_{eq}$ and $H10_{eq}$)), 1.53 (dm, *J* = ~13 Hz, 2 H, $H4_{eq}$ and $H11_{eq}$), 1.66 (ddd, *J* = 13.2, 4.2, 2.2 Hz, 1 H, $H5_{eq}$), 1.90 (dddd, *J* = ~13, ~13, ~13, 4.2 Hz, 1 H, $H4_{ax}$), 1.94 (qt, *J* = 13.0, 4.2 Hz, 1 H, $H10_{ax}$), 3.03 (br ddd, *J* = ~13, ~9, ~2 Hz, 1 H, $H3_{ax}$), 3.54 (dq, *J* = 9.0, 6.3 Hz, 1 H, $H2_{ax}$), 3.67 (dqd, *J* = 11.5, 6.1, 2.2 Hz, 1 H, $H8_{ax}$). The alcohol just described was, in some chromatographic fractions, slightly contaminated with its *E,Z* (equatorial OH) isomer.

(2*R*,3*S*,6*S*,8*R*)-2,8-Dimethyl-1,7-dioxaspiro[5.5]undecan-3-ol (38). (*R*)-3-(Tetrahydropyranyloxy)butyl iodide (**35**) was obtained from commercially available poly(β-hydroxybutyrate) in the manner described by Mori.[25] Alkylation of diethyl 3-oxoglutarate with crotyl bromide (mixture of trans and cis isomers) was conducted in the reported manner,[35] and the crude product was purified by flash chromatography on Merck Kieselgel 60 (mesh 230–400) eluting with hexane–ether (6:1) to provide a clear oil (76%), corresponding to the monoalkylated product: ^{13}C NMR ($CDCl_3$) δ 13.96 (2 C), 17.77, 30.99, 48.33, 58.86, 61.38, 61.47, 126.17, 128.48, 166.48, 168.64, 197.22; ^1H NMR (in part) δ 1.22 (6 H, t, *J* = 7.1 Hz, CH_2CH_3), 1.57 (3 H, d, *J* = 5 Hz, CH_3CH=), 2.49 (2 H, m), 3.51 (2 H, br s), 4.14 (4 H, q, *J* = 7.1 Hz, OCH_2), 5.40 (2 H, m). This material (3.6 g, 14 mmol) in dry toluene (13 mL) was added dropwise to a suspension of NaH (0.67 g, 14 mmol, 50% dispersion in oil) and 18-crown-6-ether (0.35 g) in dry toluene (26 mL) (N_2 atmosphere). After 1 h, (*R*)-3-(tetrahydropyranyloxy)butyl iodide (**35**) (4.0 g, 14 mmol) was added, and the mixture was refluxed for 48 h, after which time the yellow solution (and precipitate) was concentrated in vacuo. The residue (presumably mainly **36**, see Scheme X) was mixed with 15% aqueous NaOH solution and refluxed for 20 h. The cooled mixture was extracted with ether (3 × 75 mL), and the combined extracts were dried ($MgSO_4$) and then concentrated in vacuo to provide 3.15 g (84%) of a yellow oil, considered to be the tetrahydropyranyl ether of (*R*)-10-hydroxy-2-undecen-6-one. A portion of this oil was chromatographed on silica, eluting with hexane–ether (10–20%

(35) Naoshima, Y.; Ike, H.; Ogawa, T.; Nakayama, T.; Kondo, H. *Agric. Biol. Chem.* **1984**, *49*, 2151.

ether). Although considerable deprotection occurred under these conditions, a sample (~100% by GC) was obtained for spectral characterization: HRMS found $(M + NH_4)^+$ 286.2367, $C_{16}H_{28}O_3 + NH_4$ requires 286.2382; found $(M + 1)^+$ 269.2148, $C_{16}H_{29}O_3$ requires 269.2116; ^{13}C NMR ($CDCl_3$) δ 17.85, 19.73, 20.08, 21.57, 25.49, 26.80, 31.22, 36.05, 42.57, 43.81, 62.87, 73.84, 98.85, 125.85, 129.56, 210.53. (One diastereomer). $[\alpha]^{23}_D$ +35.8° (*c* 0.497 in CH_3OH). This enone (0.5 g, 1.8 mmol) was dissolved in CH_2Cl_2 (40 mL) and treated with *m*-CPBA (0.4 g (85%), 2 mmol) After ca. 36 h, the reaction mixture was washed with 10% Na_2CO_3, $NaHSO_3$ solution, separated, and concentrated to provide an oil, presumed to be epoxide **37**. This was used directly in the next step without characterization. Epoxide **37** was dissolved in a solution of glacial acetic acid–THF–H_2O (4:2:1) (10 mL), and the mixture was stirred at rt for 3 days. Neutralization with 10% Na_2CO_3 was followed by extraction with EtOAc. The combined organic fractions were washed again with Na_2CO_3 and saturated NaCl, dried ($MgSO_4$), and concentrated in vacuo. The crude oil (0.35 g, 97%) was analyzed by GC/MS, and a number of components incorporating the [5.5]- and [4.5]spiro systems were present. However ca. 30% was the desired hydroxy spiroacetal **38**. Substantial purification of the desired spiroacetal **38** was achieved by chromatography on Kieselgel, but further purification resulted from preparative GC, and in this way the title compound **38** was obtained and exhibited ^1H and ^{13}C NMR spectra and mass spectral behavior identical with those of the racemic compound, $[\alpha]^{33}_D$ +49.5° (c, 0.2 pentane). None of the antipode was detectable by chiral GC of the sample, as the trifluoroacetate.

Synthesis of 2,8-Dimethyl-1,7-dioxaspiro[5.5]undecan-4-ols (4). 2-Hydroxyundec-10-ene-4,6-dione (41). Non-8-ene-2,4-dione (**40**)[27] (4.0 g, 26.0 mmol) in THF (15 mL) was added dropwise to a stirred solution of lithium diisopropylamide [from diisopropylamine (7.6 mL, 54.2 mmol) and *n*-BuLi (35 mL of 1.6 M in hexane, 56 mmol)] in dry THF (100 mL) at −78 °C under N_2. The resulting solution was stirred at −78 °C for 3 h, acetaldehyde (1.25 g, 28.5 mmol) in THF (10 mL) was added, and the mixture was allowed to warm to rt over 3 h. The mixture was poured into a saturated NH_4Cl solution (30 mL), extracted with ether (2 × 100 mL), dried ($MgSO_4$), and evaporated to give an oil (4.8 g, ~95%). This oil was identified by GC/MS as a mixture of the dione **41** (~50%) and unreacted starting material (~50%). The mixture proved difficult to purify, but the desired dione was obtained reasonably pure (~90%) by flash chromatography (silica gel deactivated with 10% water, ether:hexane 50:50): ^{13}C NMR ($CDCl_3$) (enol form) δ 22.87, 24.84, 33.08, 36.93, 47.32, 65.02, 100.26, 115.44, 137.69, 192.28, and 194.92 (C4 and C6); ^1H NMR ($CDCl_3$) δ 1.24 (d, *J* =6.2 Hz, 3 H, CH_3), 1.7 (p, *J* = 7.5 Hz, 2 H, $CH_2CH_2CH_2$), 2.09 (q, *J* = 7.0 Hz, 2 H, =$CHCH_2$), 2.29 (t, *J* = 7.5 Hz, 2 H, $COCH_2CH_2$), 2.45 (m (2nd order), 2 H, $CHOHCH_2CO$), 3.6 (s, 0.3 H, $COCH_2CO$) (keto form)), 4.23 (qddd, *J* = 6.0, 6.0, 1.8, 1.4 Hz, 1 H, CHOH), 4.95–5.08 (m, 2 H, CH_2=CH), 5.51 (s, 0.85 H, COCH=CO (enol form)), 5.78 (dddd, *J* = 16.8, 9.9, 6.7 Hz, 1 H, CH_2CH=CH_2).

This dione however was quite unstable, and harsh chromatography, heating, attempted preparative GC purification, and even standing at room temperature caused decomposition. The major decomposition product was isolated by column chromatography and identified as 6-methyl-4-oxo-2-(pent-4′-enyl)-5,6-dihydropyran.[24]

2,8-Dimethyl-1,7-dioxaspiro[5.5]undecan-4-one (42). Mercuric acetate (0.58 g, 1.8 mmol) was added in one portion to a stirred solution of dione **41** (0.3 g 1.5 mmol) in 20 mL of THF–1% $HClO_4$ (1:1), and stirring was continued for 0.5 h. The reaction mixture was treated sequentially with NaOH (10%, 10 mL) (yellow precipitate forms), CH_2Cl_2 (10 mL), benzyltriethylammonium chloride (1.0 g), and finally $NaBH_4$ (0.07 g, 1.8 mmol). The mixture was allowed to stir for 1 h and then diluted with ether (150 mL). The metallic mercury was removed by filtration through Celite, which was rinsed with ether. The combined organic layers were washed with saturated NaCl solution, dried ($MgSO_4$), and evaporated to yield an oil (0.23 g, 77%). GC/MS analysis of this product indicated the presence of three isomers of the spiroacetal **42** in the ratio 74:17:9. Minor peaks due to reduction of the 4-keto group were also identified. The minor spiroketones were identified by their mass spectra, which were similar. A sample of the mixture was purified by preparative GC to give pure (2*SR*,6*RS*,8*SR*)-2,8-dimethyl-1,7-dioxaspiro-[5.5]undecan-4-one (**42**) (*E*,*E* ring skeleton): HRMS found M^+ 198.1248, $C_{11}H_{18}O_3$ requires 198.1255; ^{13}C NMR (C_6D_6) δ 19.28 (C10), 21.68 (C12), 21.78 (C13), 32.18 (C9), 34.50 (C11), 48.38 (C3), 51.69 (C5), 64.88 (C2), 66.21 (C8), 99.26 (C6), 203.60 (C4); ^1H NMR (C_6D_6) δ 0.97 (tdd, *J* = 13.4, 11.5, ~4 Hz, 1 H, $H9_{ax}$), 0.98 (d, *J* = 6.1 Hz, 3 H, Me12), 0.99 (d, *J* = 6.1 Hz, 3 H, Me13), 1.07 (td, *J* = 13.3, 4.6 Hz, 1 H, $H11_{ax}$), 1.23 (ddddd, *J* = 13.4, 3.9, ~3.5, 2.2, 1.5# Hz, 1 H, $H9_{eq}$), 1.30 (ddddd, *J* = 13.4, 4.6, ~4, ~3.5, 2.7 Hz, 1 H, $H10_{eq}$), 1.52 (dddd, *J* = 13.4, 3.9, 2.7, 1.5# Hz, 1 H, $H11_{eq}$), 1.76 (br dd, *J* = 14.4, 11.5, 0.7* Hz, 1 H, $H3_{ax}$), 1.84 (qt, *J* = 13.4, 3.9 Hz, 1 H, $H10_{ax}$), 1.95 (br d, *J* = 14.4, 0.7* Hz, 1 H, $H5_{ax}$), 2.16 (ddd, *J* = 14.4, 2.7, 1.9# Hz, 1 H, $H3_{eq}$), 2.41 (dd, *J* = 14.4, 1.9# Hz, 1 H, $H5_{eq}$), 3.47 (dqd, *J* = 11.5, 6.3, 2.2 Hz, 1 H, $H8_{ax}$), 3.81 (dqd, *J* = 11.5, 6.1, 2.7 Hz, 1 H, $H2_{ax}$) (*1,3-diaxial coupling; #*W* coupling).

(Subjecting the dihydropyran to the above mercuration conditions with extended initial reaction time (12 h) also leads to the formation of the spiroketone. Apparently under these aqueous acid conditions the enol ether is hydrated allowing formation of the spiroketone.)

2,8-Dimethyl-1,7-dioxaspiro[5.5]undecan-4-ol (4). The crude product from the previous step (0.2 g, ~1.0 mmol) in dry ether (10 mL) was added dropwise to a stirred solution of $LiAlH_4$ (0.045 g, 1.2 mmol) in dry ether (30 mL) at rt. After 0.5 h the reaction mixture was carefully poured into water (50 mL). The precipitate was removed by filtration, and the aqueous solution was extracted with ether (2 × 50 mL). The organic layer was dried ($MgSO_4$) and evaporated to give a mixture (0.16 g, 80%) of four isomeric alcohols (**4**) in the ratio 36:54:8:2 (GC/MS; in order of elution on nonpolar GC column). Use of $NaBH_4$ reduction produced slightly less of the *E*,*E* axial alcohol **43**. Each of these alcohols was isolated by preparative GC. **Isomer 1 (36%) (2*SR*,4*SR*,6*RS*,8*SR*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-4-ol (43)** (*E*,*E* ring skeleton, axial alcohol): HRMS found M^+ 200.1416, $C_{11}H_{20}O_3$ requires 200.1412; ^{13}C NMR (C_6D_6) (assignments confirmed by proton carbon correlation spectrum) δ 18.78 (C10), 21.76 (C12), 21.89 (C13), 32.52 (C9), 35.04 (C11), 40.47 and 40.58 (C3 and C5), 60.30 (C2), 65.31 (C4), 66.13 (C8), 98.6 (C10); ^1H NMR (C_6D_6) (assignments confirmed by proton proton correlation spectrum) δ 0.92 (d, *J* = 6.1 Hz, 3 H, Me13), 0.98 (dddd, *J* = 13.0, 13.0, 11.2, 4.0 Hz, 1 H, $H9_{ax}$ (partly overlaps with Me13)), 1.13 (d, *J* = 6.3 Hz, 3 H, Me12), 1.18 (m, 1 H, $H11_{ax}$), 1.19 (m, 1 H, $H3_{ax}$), 1.22 (m, 1 H, $H9_{eq}$), ~1.27 (m, 1 H, $H10_{eq}$), 1.30 (m, 1 H, $H5_{ax}$), 1.44 (dddd, *J* = 13.0, 4.0, 2.2, 1.2# Hz, 1 H, $H11_{eq}$), 1.8 (m, 2 H, $H3_{eq}$ and $H5_{eq}$), 1.87 (tq, *J* = 13.0, 3.8 Hz, 1 H, $H10_{ax}$), 3.62 (dqd, *J* = 11.5, 6.1, 2.2 Hz, 1 H, $H8_{ax}$), 4.05 (m, 2 H, $H2_{ax}$ and $H4_{ax}$) superimposed), 4.28 (br d, *J* = 10.2 Hz, 1 H, OH). (This signal collapses to a singlet on irradiation of 4.05 ppm. Addition of D_2O causes this signal to disappear and sharpens the signal at 4.05 ppm.) **Isomer 2 (54%) (2*SR*,4*RS*,6*RS*,8*SR*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-4-ol (44)** (*E*,*E* ring skeleton, equatorial alcohol): HRMS found M^+ 200.1412, $C_{11}H_{20}O_3$ requires 200.1412; ^{13}C NMR (C_6D_6) (assignments confirmed by proton carbon correlation spectrum) δ 19.88 (C10), 22.25 and 22.62 (C12 and C13), 33.43 (C9), 35.73 (C11), 43.51 (C3), 45.70 (C5), 64.50 (C2 or C8), 64.84 (C4), 65.61 (C2 or C8), 97.99 (C6); ^1H NMR (C_6D_6) (assignments confirmed by proton proton correlation spectrum) δ 1.06 (dt, *J* = 12.0, 11.5 Hz, 1 H, $H3_{ax}$), 1.08 (d, *J* = 6.1 Hz, 3 H, Me12 or Me13), 1.08 (m, 1 H, $H9_{ax}$), 1.13 (d, *J* = 6.3 Hz, 3 H, Me12 or Me13), 1.18 (dd, *J* = 12.0, 11.0 Hz, 1 H, $H5_{ax}$), 1.27 (td, *J* = 13.0, 4.5 Hz, 1 H, $H11_{ax}$), 1.33 (dm, *J* = 13.5 Hz, 1 H, $H9_{eq}$), 1.36 (dm, *J* = 13.0 Hz, 1 H, $H10_{eq}$), 1.59 (dddd, *J* = 13.0, 4.0, 2.2, 1.2# Hz, 1 H, $H11_{eq}$), 1.68 (dddd, *J* = 12.0, 5.0, 2.2, 1.8# Hz, 1 H, $H3_{eq}$), 1.95 (qt, *J* = 13.0, 4.0 Hz, 1 H, $H10_{ax}$), 1.97 (dddd, *J* = 12.0, 5.0, 1.8#, 1 H, $H5_{eq}$), 3.61 (dqd, *J* = 11.5, 6.3, 2.2 Hz, 2 H, $H2_{ax}$ and $H8_{ax}$), 4.08 (dddd, *J* = 11.5, 11.0, 5.0, 5.0 Hz, 1 H, $H4_{ax}$) (#*W* coupling). **Isomer 3 (8%) (2*SR*,4*RS*,6*SR*,8*RS*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-4-ol (45)** (*Z*,*E* ring skeleton, equatorial alcohol). **Isomer 4 (2%) (2*SR*,4*RS*,6*RS*,8*RS*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-4-ol (46)** (*E*,*Z* ring skeleton, equatorial alcohol). These later two isomers provided ^1H and ^{13}C NMR spectra identical with those described later for samples acquired by a different route.

(*R*)-8-(Tetrahydropyranyloxy)nonane-2,4-dione (47). The dianion from pentane-2,4-dione (1.92 g, 19 mmol) was generated

in THF (20 mL) by treatment with NaH and *n*-BuLi in the reported way.[27] To this dianion solution, maintained at −15 °C, was added (*R*)-3-(tetrahydropyranyloxy)butyl iodide (**35**) (3.30 g, 12 mmol) in dry THF (10 mL). The solution was allowed to warm to 0 °C over 1 h and then stirred at this temperature for a further 3 h. The reaction mixture was poured into a stirred mixture of ether (40 mL) and saturated NH_4Cl solution (40 mL). The organic layer was separated and combined with the further ether extractions (2 × 20 mL) of the aqueous layer. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure to yield the dione **47** which was purified by flash chromatography (silica, 230–400 mesh; hexane–CH_2Cl_2), 1.33 g (44%); $[\alpha]^{25}_D$ −6.5° (*c* 2.95, pentane); HRMS (CI) found $(M + 1)^+$ 257.1737, $C_{14}H_{25}O_4$ requires 257.1753; ^{13}C NMR (mixture of two diastereomers) ($CDCl_3$) δ 193.84, 193.81, 191.51, 191.40, 99.77, 99.74, 98.81, 95.77, 73.66, 70.62, 62.80, 62.63, 38.16, 38.06, 36.82, 35.95, 31.19, 31.15, 25.49, 25.44, 24.97, 24.91, 21.92, 21.54, 21.51, 20.01, 19.82, 19.05; ^1H NMR ($CDCl_3$) 1.07 (d, *J* = 6.18 Hz, 3 H, CH_3), 1.19 (d, *J* = 6.18 Hz, 3 H, CH_3), 1.35–1.90 (m, 20 H, CH_2), 2.011 (s, 3 H, $COCH_3$), 2.013 (s, 3 H, $COCH_3$), 2.24 (t, *J* = 7.53 Hz, 2 H, $COCH_2$), 2.26 (t, *J* = 7.25 Hz, 2 H, $COCH_2$), 3.43–3.46 (m, 2 H), 3.53 (s, 0.5 H, $COCH_2CO$, keto form), 3.54 (s, 0.5 H, $COCH_2CO$, keto form), 3.69 (sextet, *J* ~ 5.9 Hz, 1 H), 3.76 (sextet, *J* = 5.9 Hz, 1 H), 3.81–3.90 (m, 2 H), 4.58 (t, *J* = 2.95 Hz, 1 H), 4.65 (t, *J* = 3.49 Hz, 1 H), 5.45 (s) and 5.46 (s), for enol forms.

(10*R*)-2-Hydroxy-10-(tetrahydropyranyloxy)undecane-4,6-dione (48). Dione **47** (1.33 g, 5.2 mmol) in dry THF (8 mL) was added dropwise to a stirred solution of LDA (11.4 mmol) in THF (20 mL) maintained at −78 °C under nitrogen. The resulting dark red solution was stirred at −78 °C for 2 h and then quenched with acetaldehyde (0.227 g, 5.2 mmol). The solution was allowed to warm to 0 °C over 3 h and then poured into saturated NH_4Cl solution (40 mL). The organic phase was separated and combined with the ether extracts (3 × 20 mL) of the aqueous phase, dried ($MgSO_4$), and concentrated under reduced pressure. The crude dione **48** (76% by GC) was used without further purification: HRMS (CI) found $(M + 1 - H_2O)^+$ 283.1941, $C_{16}H_{28}O_5 + H - H_2O$ requires 283.1909; ^{13}C NMR ($CDCl_3$) δ 193.00, 192.96, 177.64, 177.39, 103.87, 98.71, 98.70, 95.76, 75.54, 75.49, 70.52, 70.49, 62.71, 62.59, 42.54 (2 C), 36.63, 35.73, 34.73, 34.65, 31.14, 31.09, 25.43, 25.38, 22.52, 22.20, 21.45, 20.27 (2 C), 19.91, 19.76, 19.07; ^1H NMR ($CDCl_3$) δ 1.05 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.17 (d, *J* = 6.35 Hz, 3 H, CH_3), 1.25–1.76 (m, 20 H, CH_2), 1.381 (d, *J* = 6.34 Hz, 3 H, $CH(OH)CH_3$), 1.384 (d, *J* = 6.34 Hz, 3 H, $CH(OH)CH_3$), 2.16–2.34 (m, 8 H, CH_2CO), 3.41–3.44 (m, 2 H, CHO), 3.67 (sextet, *J* = 6.10 Hz, 1 H), 3.74 (sextet, *J* = 6.10 Hz, 1 H), 3.76–3.85 (m, 2 H, CHO), 4.43 (m, 2 H), 4.57 (t, *J* = 3.91 Hz, 1 H), 4.62 (t, *J* = 3.91 Hz, 1 H), 5.25 (s) and 5.27 (s) for enol forms.

4-Oxo-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (49). The above crude dione **48** (3.05 g) was stirred for 40 h in a mixture of glacial acetic acid (100 mL), THF (50 mL), and water (25 mL). Ether (100 mL) was added, and the vigorously stirred mixture was carefully neutralized with saturated aqueous $NaHCO_3$ (30 mL) and then with solid Na_2CO_3. The ether layer was separated and after addition to further ether extracts (3 × 100 mL) of the aqueous phase, washed with saturated NaCl solution (2 × 50 mL), separated, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was initially purified by flash chromatography (silica, 230–400 mesh Kieselgel; hexane–CH_2Cl_2), and the three diastereomers of the ketone were separated by preparative HPLC to yield the *E,E* isomer **49** (1.037 g), (*Z,E*)-**51** (0.094 g), and (*E,Z*)-**52** (0.155 g): HRMS (EI) found M^+ 198.1255, $C_{11}H_{18}O_3$ requires 198.1254. **Isomer 1**: The ^1H and ^{13}C NMR spectra for the *E,E* racemate **42** were listed earlier. **Isomer 2 (2*S*,6*S*,8*R*)-4-oxo-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (51)** (*Z,E* ring skeleton): ^{13}C NMR (C_6D_6) δ 18.86, 21.97, 22.28, 32.56, 33.42, 46.81, 51.20, 66.53, 67.62, 98.80, 204.37; ^1H NMR (C_6D_6) δ 0.94 (m, 1 H, $H9_{ax}$), 0.99 (d, *J* = 6.10 Hz, 3 H, CH_3), 1.01 (d, *J* = 6.34 Hz, 3 H, CH_3), 1.26 (m, 2 H, $H9_{eq}$ and $H10_{eq}$), 1.48 (m, 1 H, $H11_{eq}$), 1.71 (qt, *J* = 13.67, 3.91 Hz, 1 H, $H10_{ax}$), 2.01 (ddd, *J* = 15.87, 3.42, 0.74 Hz, 1 H, $H3_{eq}$), 2.20 (ddd, *J* = 15.87, 10.98, 0.73 Hz, 1 H, $H3_{ax}$), 2.26 (dd, *J* = 15.38, 0.74 Hz, 1 H, $H5_{eq}$), 2.46 (dd, *J* = 15.38, 0.73 Hz, 1 H, $H5_{ax}$), 3.57 (dqd, *J* = 10.99, 6.10, 3.82 Hz, 1 H, $H2_{ax}$), 4.02 (dqd, *J* = 11.23, 6.34, 4.15 Hz, 1 H, $H8_{ax}$). **Isomer 3 (2*S*,6*R*,8*R*)-4-oxo-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (52)** (*E,Z* ring skeleton): ^{13}C NMR ($CDCl_3$) δ 18.78, 21.46, 21.82, 31.66, 35.39, 46.93, 48.74, 66.21, 69.68, 100.45, 206.0; ^1H NMR ($CDCl_3$) δ 1.15 (d, *J* = 6.35 Hz, 3 H, CH_3), 1.25 (m, 1 H, $H9_{ax}$ or $H9_{eq}$), 1.30 (d, *J* = 6.11 Hz, 3 H, CH_3), 1.52 (m, 1 H, $H10_{eq}$ or $H10_{ax}$), 1.59 (m, 1 H, $H9_{eq}$ or $H9_{ax}$), 1.64 (m, 1 H, $H11_{ax}$ or $H11_{eq}$), 1.72 (m, 1 H, $H11_{eq}$ or $H11_{ax}$), 1.80 (m, 1 H, $H10_{ax}$ or $H10_{eq}$), 2.20 (ddd, *J* = 14.16, 10.99, 0.73 Hz, 1 H, $H3_{ax}$), 2.27 (dd, *J* = 14.16, 0.73 Hz, 1 H, $H5_{ax}$), 2.35 (ddd, *J* = 14.16, 2.93, 1.95 Hz, 1 H, $H3_{eq}$), 2.91 (dd, *J* = 14.16, 1.95 Hz, 1 H, $H5_{eq}$), 3.71 (dqd, *J* = 9.28, 6.35, 3.18 Hz, 1 H, $H8_{ax}$), 4.46 (dqd, *J* = 10.99, 6.11, 2.93 Hz, 1 H, $H2_{ax}$).

Reduction of (*E,E*)-(2*R*,6*S*,8*R*)-4-Oxo-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (49). Reduction with $LiAlH_4$ was conducted as described for the racemate. The epimeric 4-ols (86%) were separated by preparative GC and exhibited mass and ^1H and ^{13}C NMR spectra in agreement with those described for the racemate. The optical rotations are shown within Scheme XII.

Reduction of (*Z,E*)-(2*S*,6*S*,8*R*)-4-Oxo-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (51) (Scheme XIII). Reduction with $LiAlH_4$ in ether was anticipated to provide the epimeric alcohols (81%) (as shown in Scheme XIII) but the axial epimer was not detected. The equatorial alcohol so obtained rapidly isomerized, by configurational change at the spirocenter to the *E,Z* system, to give a mixture of the *Z,E* and *E,Z* equatorial alcohol. Preparative GC separation of these isomers enabled characterization. **(2*S*,4*R*,6*S*,8*R*)-2,8-Dimethyl-1,7-dioxaspiro[5.5]undecan-4-ol** (*Z,E* ring skeleton, equatorial alcohol): ^{13}C NMR (C_6D_6) δ 18.84 (C10), 22.26 and 22.27 (C12 and C13), 30.59 (C11), 33.22 (C9), 42.70 (C3), 45.50 (C5), 65.31 (C4), 66.28 (C8), 66.38 (C2), 98.08 (C6); ^1H NMR (C_6D_6) δ 1.04–1.14 (m, 3 H, $H3_{ax}$, $H11_{ax}$, and $H9_{ax}$), 1.09 (d, *J* = 6.35 Hz, 3 H, CH_3), 1.13 (d, *J* = 6.35 Hz, 3 H, CH_3), 1.18–1.39 (m, 2 H, $H10_{eq}$, $H9_{eq}$), 1.56–1.67 (m, 3 H, $H3_{eq}$, $H5_{ax}$, $H10_{ax}$, $H11_{eq}$), 1.86 (ddd, *J* = 12.70, 4.89, 1.71 Hz, 1 H, $H5_{eq}$), 3.15 (dqd, *J* = 10.74, 6.35, 2.69 Hz, 1 H, $H2_{ax}$), 3.55 (br m, 1 H, $H4_{eq}$), 4.24 (dqd, *J* = 11.72, 6.35, 2.2 Hz, 1 H, $H8_{ax}$).

Reduction of (*E,Z*)-(2*S*,6*R*,8*R*)-4-Oxo-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (52) (Scheme XIII). Reduction as before provided the epimeric alcohols (89%) which were separated by preparative GC. **Isomer 1 (2*S*,4*S*,6*R*,8*R*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-4-ol** (*E,Z* ring skeleton, axial alcohol): ^{13}C NMR (C_6D_6) δ 17.41 (C10), 21.37 (C13), 21.77 (C12), 31.41 (C9), 36.42 (C11), 36.68 (C5), 40.53 (C3), 60.91 (C2), 65.30 (C4), 69.54 (C8), 99.03 (C6); ^1H NMR (C_6D_6) δ 1.03 (m, 1 H, $H9_{ax}$), 1.07 (d, *J* = 6.35 Hz, 3 H, CH_3), 1.08 (dd, *J* = 14.16, 2.44 Hz, 1 H, $H5_{ax}$), 1.12 (d, *J* = 6.35 Hz, 3 H, CH_3), 1.16 (m, 1 H, $H10_{eq}$ or $H10_{ax}$), 1.22 (td, *J* = 12.60, 2.19 Hz, 1 H, $H3_{ax}$), 1.24 (m, 1 H, $H9_{eq}$), 1.36 (m, 1 H, $H11_{eq}$ or $H11_{ax}$), 1.53 (m, 1 H, $H11_{ax}$ or $H11_{eq}$), 1.57 (m, 1 H, $H10_{ax}$ or $H10_{eq}$), 1.77 (dq, *J* = 13.20, 2.45 Hz, 1 H, $H3_{eq}$), 2.06 (dt, *J* = 14.16, 2.45 Hz, 1 H, $H5_{eq}$), 3.65 (dqd, *J* = 7.08, 6.35, 3.91 Hz, 1 H, $H8_{ax}$), 4.01 (br m, 2 H, $H4_{eq}$ and OH), 4.47 (dqd, *J* = 12.0, 6.35, 2.44 Hz, 1 H, $H2_{ax}$). **Isomer 2 (2*S*,4*R*,6*R*,8*R*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-4-ol** (*E,Z* ring skeleton, equatorial alcohol): ^{13}C NMR (C_6D_6) δ 19.02 (C10), 21.79 (C12), 21.95 (C13), 32.32 (C9), 36.16 (C11), 40.04 (C5), 43.54 (C3), 64.55 (C4), 64.95 (C2), 68.77 (C8), 98.73 (C6); ^1H NMR (C_6D_6) δ 0.98 (dd, *J* = 12.67, 11.23 Hz, 1 H, $H5_{ax}$), 1.06 (m, 1 H, $H9_{ax}$), 1.09 (q, *J* = 11.72 Hz, 1 H, $H3_{ax}$), 1.13 (d, *J* = 6.35 Hz, 3 H, CH_3), 1.14 (d, *J* = 6.35 Hz, 3 H, CH_3), 1.24 (m, 2 H, $H9_{eq}$ and $H10_{eq}$ or $H10_{ax}$), 1.54 (m, 2 H, $H11_{eq}$ or $H11_{ax}$ and $H10_{ax}$ or $H10_{eq}$), 1.66 (m, 1 H, $H11_{ax}$ or $H11_{eq}$), 1.71 (dddd, *J* = 11.96, 4.64, 2.19, 1.95 Hz, 1 H, $H3_{eq}$), 2.35 (ddd, *J* = 12.69, 4.64, 1.95 Hz, 1 H, $H5_{eq}$), 3.46 (dqd, *J* = 9.28, 6.35, 2.93 Hz, 1 H, $H8_{ax}$), 3.88 (tt, *J* = 11.23, 4.64 Hz, 1 H, $H4_{ax}$), 4.16 (dqd, *J* = 12.69, 6.35, 2.19 Hz, 1 H, $H2_{ax}$).

The optical rotations for the alcohols described above are shown in Scheme XIII.

Synthesis of 2,8-Dimethyl-1,7-dioxaspiro[5.5]undecan-5-ols (8). 2-(Trimethylsiloxy)hex-5-enenitrile (54). Trimethylsilyl cyanide (3.0 g, 30 mmol) mixed with ZnI_2 (~2 mg) was added dropwise, from a pressure equalizing dropping funnel, to neat pent-4-en-1-ol (2.5 g, 30 mmol) in a carefully dried 15-mL distillation flask containing N_2. Heat was evolved during the addition, and after 0.5 h, the mixture was distilled to give the cyanohydrin (3.0 g, 55%): bp 90 °C (10 mm); ^{13}C NMR ($CDCl_3$) δ −0.45, 28.52, 35.21, 60.62, 116.14, 119.84, 136.15; ^1H NMR ($CDCl_3$) δ 0.18 (s, 9 H, $SiCH_3$), 1.86 (q, *J* = 7 Hz, 2 H, CH_2), 2.20 (q, *J* = 7 Hz, 2 H, CH_2), 4.38 (t, *J* = 6.6 Hz, 1 H, CHO), 5.05 (m, 2 H,

CH_2=), 5.75 (m, 1 H, CH=).

5-Hydroxy-6-oxoundeca-1,10-diene (53). The above protected cyanohydrin **54** (1.0 g, 5.5 mmol) in ether (5 mL) was added dropwise to a refluxing solution of the Grignard reagent prepared from 5-bromopent-1-ene (1.23 g; 8.25 mmol) and magnesium (0.2 g, 8.25 mmol) in ether (20 mL). The reaction was monitored by GC, and after 1 h the reaction mixture was cooled to 20 °C, quenched with 2 M HCl (20 mL), and stirred for 16 h. The ether layer was separated and combined with the ether extracts (3 × 50 mL) of the aqueous phase. The combined organic layers were dried ($MgSO_4$) and concentrated to yield the hydroxy dienone **53** (0.81 g, 81%): ^{13}C NMR ($CDCl_3$) δ 22.47, 29.00, 32.91, 36.89, 76.69, 115.50, 115.55, 137.28, 137.47, 212.07; ^1H NMR ($CDCl_3$) δ 1.56 (m, 1 H, CHCO), 1.72 (m, 2 H, CH_2), 1.88 (m, 1 H, CHCO), 2.05 (q, J = 7.5 Hz, 2 H), 2.1–2.25 (m, 2 H), 2.36–2.52 (m, 2 H, CH_2), 3.5 (br s, 1 H, OH), 4.15 (dd, J = 8.5, 3.4 Hz, 1 H, CHO), 4.95–5.05 (m, 4 H, 2 CH_2=), 5.71–5.82 (m, 2 H, 2 CH=).

5-((*p*-Nitrobenzoyl)oxy)-6-oxo-1,10-undecadiene (55). Hydroxy ketone **53** (0.65 g, 3.6 mmol) and *p*-nitrobenzoyl chloride (1.2 g, 6.5 mmol) were stirred at rt in dry pyridine (50 mL) for 2 h. The reaction mixture was the poured into water which was extracted with ether (2 × 200 mL). The ether layer was washed with HCl (5%, 2 × 200 mL), saturated $NaHCO_3$ (2 × 200 mL), and water (2 × 100 mL) and then dried ($MgSO_4$). Solvent removal (reduced pressure) provided the *p*-nitrobenzoate **55** (1.0 g, 85%): ^{13}C NMR ($CDCl_3$) δ 20.07, 29.32, 29.52, 32.76, 37.68, 78.88, 115.36, 116.14, 123.51, 130.80, 134.75, 136.31, 137.56, 150.67, 164.04, 205.87; ^1H NMR ($CDCl_3$) δ 1.69 (m, 2 H), 1.9–2.08 (m, 4 H), 2.23 (br q, J = 7.5 Hz, 2 H), 2.4–2.6 (m, 2 H, CH_2C=O), 4.9–5.05 (m, 4 H, 2 =CH_2), 5.25 (dd, J = 8.0, 4.7 Hz, 1 H, CHO), 5.65–5.84 (m, 2 H, 2 CH=), 8.20 and 8.26 (AB pattern, J_{AB} = 9 Hz, 4 H, ArH).

2,8-Dimethyl-1,7-dioxaspiro[5.5]undeca-5-ols (56 and 57). The *p*-nitrobenzoate **55** (0.8 g, 2.4 mmol) and $Hg(OAc)_2$ (1.6 g, 5.0 mmol) were stirred together for 2 h in THF–1% $HClO_4$ (1:1, 20 mL). The solution was then treated with NaOH solution (10%, 15 mL) and finally $NaBH_4$ (0.2 g, 5.2 mmol). Removal of the mercury in the usual way and product isolation provided a mixture of the *p*-nitrobenzoates of the title hydroxy spiroacetal in the ratio 36:39:25. Each showed a molecular ion (m/z 349, 1%) in the low resolution GC/MS examination. These isomers were not purified but hydrolyzed overnight with a mixture of NaOH (10%, 100 mL) and THF (100 mL). The reaction mixture was diluted with ether (200 mL), and the ether layer was separated and combined with the ether extracts (2 × 100 mL) of the aqueous layer. The combined ether fractions were washed with saturated $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), and concentrated to provide a mixture of three spiroacetals (0.36 g, 75%) in the ratio 41:46:13. The mixture was purified by preparative GC to provide the following diastereomers. **Isomer 1 (2*SR*,5*SR*,6*RS*,8*SR*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-5-ol (41%)** (*E,E* ring skeleton, equatorial alcohol): HRMS (EI) found M^+ 200.1407, $C_{11}H_{20}O_3$ requires 200.1412; ^{13}C NMR (C_6D_6) δ 18.94 (C10), 21.39 and 21.92 (C12 and C13), 28.88, 30.89, 32.89, 33.12 (C3, C4, C9 and C11), 64.85, 65.82, 71.85 (C2, C5 and C8), 97.68 (C6); ^1H NMR (C_6D_6) (assigned with the aid of a ^1H–^1H correlation spectrum) δ 0.95 (dddd, J = 12.8, 12.8, 11.2, 4.0 Hz, 1 H, $H9_{ax}$ (partly overlaps with Me13)), 1.02 (d, J = 6.3 Hz, 3 H, Me13), 1.05 (d, J = 6.3 Hz, 3 H, Me12), 1.14 (dddd, J = 13.0, 13.0, 11.2, 4.5 Hz, 1 H, $H3_{ax}$), 1.28 (dm, J = 12.8 Hz, 1 H, $H9_{eq}$), 1.32 (dm, J = 13.0 Hz, 1 H, $H3_{eq}$), 1.40 (dm, J = 13.0 Hz, 1 H, $H10_{eq}$), 1.48 (dm, J = 13.8 Hz, 1 H, $H11_{eq}$), 1.64–1.79 (m, 2 H, $H4_{ax}$ and $H4_{eq}$), 1.90 (qt, J = 13.0, 3.8 Hz, 1 H, $H10_{ax}$), 2.06 (td, J = 13.0, 4.5 Hz, 1 H, $H11_{ax}$), 3.29 (dd, J = 11.3, 5.3 Hz, 1 H, $H5_{ax}$), 3.55 (dqd, J = 11.2, 6.3, 2.3 Hz, 1 H, $H2_{ax}$), 3.65 (dqd, J = 11.2, 6.3, 2.3 Hz, 1 H, $H8_{ax}$). **Isomer 2 (2*SR*,5*RS*,6*RS*,8*SR*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-5-ol (57) (46%)** (*E,E* ring skeleton, axial alcohol): HRMS (EI) found M^+ 200.1415, $C_{11}H_{20}O_3$ requires 200.1412; ^{13}C NMR (C_6D_6) δ 19.10 (C10), 21.90, 22.07 (C12, C13), 26.67, 26.98, 31.55, 32.95 (C3, C4, C9 and C11), 65.02, 65.65, 69.37 (C2, C5, C8), 97.78 (C6); ^1H NMR (C_6D_6) (assigned with the aid of ^1H–^1H correlation spectrum) δ 1.04 (m, 1 H, $H9_{ax}$ (overlaps with methyls)), 1.08 (d, J = 6.1 Hz, 6 H, Me12 and Me13), 1.10 (m, 1 H, $H3_{eq}$ (overlaps with methyl)), 1.22 (td, J = 13.0, 4.5 Hz, 1 H, $H11_{ax}$), 1.30–1.45 (m, 3 H, $H3_{ax}$ (δ = 1.34–1.42), $H9_{eq}$ (δ = 1.30–1.37) and $H10_{eq}$ (δ = 1.39–1.45)), 1.55 (dddd, J = 13.5, 3.8, 2.75, 2.75 Hz, 1 H, $H4_{eq}$), 1.87 (qt, J = 13.0, 4.0 Hz, 1 H, $H10_{ax}$), 2.03 (dddd, J = 13.0, 4.5, 2.5, 1.2 Hz, 1 H, $H11_{eq}$), 2.15 (dddd, J = 13.5, 13.5, 4.75, 2.75 Hz, 1 H, $H4_{ax}$), 3.41 (br t, J = 2.75 Hz, 1 H, $H5_{ax}$), 3.65 (dqd, J = 11.2, 6.1, 2.3 Hz, 2 H, $H2_{ax}$ and $H8_{ax}$).

2-(*tert*-Butyldimethylsiloxy)hex-5-enenitrile (59). To a solution of 4-pentenal (1.00 g, 12 mmol) in ethanol (6 mL) under argon was added the mandelonitrile lyase extract (18 mL) prepared as described by Brussee.[34] A 1 M KCN–HOAc buffer (pH 5.4, 15 mL) was mixed with ethanol (6.3 mL), cooled to 0 °C, and added dropwise over 1 h to a stirred, chilled (0 °C) enzyme/aldehyde mixture. After a further 3 h, the reaction mixture was extracted with ether (3 × 30 mL), and these combined layers were washed with a 10% aqueous NaCl solution (3 × 10 mL). The ether solution was dried ($MgSO_4$) and concentrated (reduced pressure) to yield the cyanohydrin (0.95 g, 72%): HRMS found M^+ 111.0686, C_6H_9NO requires 111.0684: HRMS (for trifluoroacetate) found M^+ 207.0495, $C_8H_8NO_2F_3$ requires 207.0507; ^{13}C NMR ($CDCl_3$) δ 28.67, 34.18, 60.63, 116.68, 139.78, 136.03; ^1H NMR ($CDCl_3$) δ 1.93 (m, 2 H), 2.26 (m, 2 H), 4.47 (t, 1 H), 5.05–5.10 (m, 2 H), 5.78 (m, 1 H). A solution of imidazole (0.83 g, 12.2 mmol) in anhydrous DMF (15 mL) was cooled to 0 °C, and *tert*-butyldimethylsilyl chloride (1.47 g, 9.7 mmol) was added. This solution was stirred for 0.25 h, the above cyanohydrin (0.90 g, 8.1 mmol) was added, and the mixture was stirred for a further hour. The solution was poured into water (25 mL) and extracted with ether (3 × 50 mL). These ether extracts were combined, dried ($MgSO_4$), and concentrated to yield an oil, which was distilled (78 °C, 2 mm) to provide the silyl ether **59**: 0.61 g (33%); HRMS (CI) found $(M + NH_4)^+$ 243.1924, $C_{12}H_{27}N_2OSi$ requires 243.1892; found $(M - (CH_3)_3C)^+$ 168.0848, $C_8H_{14}NOSi$ requires 168.0844; ^{13}C NMR ($CDCl_3$) δ −5.38, −5.17, 18.00, 25.48, 28.54, 36.40, 61.16, 116.16, 119.93, 136.26; ^1H NMR ($CDCl_3$) δ 0.11 (s, 3 H), 0.17 (s, 3 H), 0.89 (s, 9 H), 1.87 (m, 2 H, CH_2), 2.22 (q, J = 7.3 Hz, 2 H, CH_2), 4.41 (t, J = 6.47 Hz, 1 H, C*H*OH), 5.04 (m, 2 H, CH_2=), 5.76 (m, 1 H, =CH).

(2*R*,5*R*,6*S*,8*R*)- and (2*S*,5*R*,6*R*,8*S*)-2,8-Dimethyl-1,7-dioxaspiro[5.5]undecan-5-ols (60 and 61). The nitrile **59** (0.50 g, 2.22 mmol) in dry ether (5 mL) was added dropwise to a stirred solution of the Grignard reagent prepared from 4-pentenyl bromide (0.5 g, 3.33 mmol) and magnesium (0.081 g, 3.33 mmol) in dry ether (5 mL). This reaction mixture was stirred and refluxed for 4 h, cooled to 0 °C, and hydrolyzed with 5% HCl solution. The aqueous layer was saturated with salt and extracted with ether (3 × 30 mL) with the combined ether layers being washed with saturated aqueous $NaHCO_3$ (2 × 30 mL) and saturated aqueous NaCl (30 mL). The ether solution was dried ($MgSO_4$) and concentrated to provide the ***tert*-butyldimethylsilyl ether of 5-hydroxy-1,10-undecadien-6-one** (ca. 250 mg): HRMS found $(M + 1)^+$ 297.2274, $C_{17}H_{32}O_2Si$ + H requires 297.2250; ^{13}C NMR ($CDCl_3$) δ −4.92, 18.08, 22.12, 25.73, 28.96, 33.15, 34.11, 36.66, 78.20, 115.10, 115.14, 137.74, 138.05, 213.79; ^1H NMR ($CDCl_3$) δ 0.02 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$), 0.90 (s, 9 H, $C(CH_3)_3$), 1.65 (m, 4 H, CH_2), 2.04 (m, 4 H, CH_2), 2.52 (t, 1 H, $COCH_2$), 4.00 (dd, J = 7.08, 5.13 Hz, 1 H, CHO), 4.93–5.04 (m, 4 H, CH_2=), 5.75 (m, 2 H, =CH). This dienone (250 mg, 0.84 mmol) was dissolved in a 1:1 mixture of THF–0.1% $HClO_4$ (20 mL) and stirred at rt. Mercuric acetate (0.59 g, 1.85 mmol) was added in one portion, and stirring was continued for 4 h. CH_2Cl_2 (5 mL), 10% aqueous NaOH (5 mL), and benzyltriethylammonium chloride (1.0 g) were added. $NaBH_4$ (0.02 g, 0.63 mmol) was then added carefully. After stirring for 0.5 h, the solution was filtered through Celite as described previously. Standard workup then provided two isomers of the silyl-protected spiroalcohols on the basis of GC/MS examination, with both exhibiting strong peaks at m/z 257 ($M^+ - C(CH_3)_3$). Deprotection in the normal way with HF in CH_3CN provided two isomers of 2,8-dimethyl-1,7-dioxaspiro[5.5]undecan-5-ol (65%), both possessing the *E,E* ring skeleton. Alcohol **60** was predominantly the 2*R*,5*R*,6*S*,8*R* enantiomer whereas alcohol **61** was predominantly the 2*S*,5*R*,6*R*,8*S* enantiomer, and their optical characteristics are outlined in the text. These isomers exhibited mass and ^1H and ^{13}C NMR spectra in agreement with those for the racemates.

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Supplementary Material Available: Spectroscopic characterization of the reduction products of individual isomers of 2,8-dimethyl-1,7-dioxaspiro[5.5]undec-4-en-3-one (**23**) and of the *Z,E* and *E,Z* isomers of **3**, low-resolution mass spectral data of compounds **3**, **9**, **13**, **14**, **20**, **21**, **23–26**, **41–48**, **51–57**, and **59**, ^1H and/or ^{13}C NMR spectra for compounds **3**, **13–15**, **21–26**, **41–48**, **51**, **52**, **55–57**, and **59** and reduction product of **52** isomer **1**, and crystallography for (*E,E*)-(2*R*,6*S*,8*R*)-4-oxo-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane (**49**) (59 pages). Ordering information is given on any current masthead page.

Enantioselective Synthesis of 2-Alkyl-5-methylene-1,3-dioxolan-4-ones and Exo-Selective Diels–Alder Reactions with Cyclopentadiene

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Highly stereoselective syntheses of chiral dienophiles (*R*)-**1** and (*R*)-**2** are described. Diazotization of L-serine in the presence of HCl and then treatment of the resulting β-hydroxy-α-chloropropionic acid (*S*)-**7** with KOH provides potassium glycidate ((*R*)-**8**) in good yield and high enantiomeric purity. Treatment of (*R*)-**8** with PhSH in MeOH then provides α-hydroxy acid (*S*)-**10** that can be purified by recrystallization. Condensation of (*S*)-**10** with either pivalaldehyde or cyclohexanecarboxaldehyde followed by oxidation to the sulfone and DBU-promoted elimination of benzenesulfinic acid then provides dienophiles (*R*)-**1** and (*R*)-**2**, respectively. Highly exo-selective Diels–Alder reactions of (*R*)-**1** and (*R*)-**2** with cyclopentadiene are also described. The major cycloadduct (−)-**15** (94% of total) from the Diels–Alder reaction of **1** was shown to have an enantiomeric purity of ≥99% ee. This figure defines the lower limit of enantiomeric purity of (*R*)-**1**. The diastereofacial selectivity of the Diels–Alder reactions of **1** in the exo manifold (50:1) is greater than that of **2** (20:1), as would be expected on the basis of the different steric requirements of the *tert*-butyl and cyclohexyl substituents of the two reagents. Consequently, dienophile **1** is the preferred reagent for complex synthetic applications, either as a chiral ketene equivalent or in contexts in which the α-hydroxy acid functionality will be preserved in the ultimate synthetic target. Finally, the possible role of dipole effects on the exo selectivity of the Diels–Alder reactions of these and related dienophiles are briefly discussed.

In connection with work on the synthesis of kijanolide, tetronolide, and chlorothricolide, we developed the chiral 5-methylene-1,3-dioxolan-4-ones **1** and **2** for use in asymmetric Diels–Alder constructions of the spiro tetronate top-half fragments.[1,2] We have previously reported syntheses of racemic **1** and **2** and the application of racemic **2** in a highly stereoselective synthesis of kijanolide intermediate **5** by way of the remarkable exo-selective Diels–Alder reaction with triene **3** (Scheme I).[1i,3] We report herein enantioselective syntheses of (*R*)-**1** and (*R*)-**2** and the Diels–Alder reactions with cyclopentadiene that serve to define the enantiomeric purity, the diastereofacial selectivity, and the absolute configuration of these novel, chiral dienophiles.[4]

Racemic **1** was first prepared in our laboratory in 1985 from methyl glycidate by using the sequence reported in our preliminary communication.[3,5] The exo-selective Diels–Alder reaction with cyclopentadiene was also fully characterized at that time. While further developments and synthetic applications of this Diels–Alder methodology were still in progress, Seebach described the enantioselective syntheses of (*S*)-**1** from (*S*)-lactic acid by the sequence shown below.[6] Mattay and co-workers subsequently described the Diels–Alder reactions of (*S*)-**1** with cyclopentadiene and several hetero dienes.[7] While Seebach's synthesis of **1** is very direct, it suffers in that the condensation of (*S*)-lactic acid and pivalaldehyde generates a 4:1 mixture of diastereomeric acetals from which the

(1) Studies on the synthesis of kijanolide and tetronolide: (a) Takeda, K.; Kato, H.; Sasahara, H.; Yoshii, E. *J. Chem. Soc., Chem. Commun.* **1986**, 1197. (b) Marshall, J. A.; Grote, J.; Shearer, B. *J. Org. Chem.* **1986**, *51*, 1633. (c) Takeda, K.; Urahata, M.; Yoshii, E.; Takayanagi, H.; Ogura, H. *Ibid.* **1986**, *51*, 4735. (d) Takeda, K.; Yano, S.; Sato, M.; Yoshii, E. *Ibid.* **1987**, *52*, 4135. (e) Marshall, J. A.; Grote, J.; Audia, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 1186. (f) Takeda, K.; Kobayashi, T.; Saito, K.; Yoshii, E. *J. Org. Chem.* **1988**, *53*, 1092. (g) Takeda, K.; Yano, S.; Yoshii, E. *Tetrahedron Lett.* **1988**, *29*, 6951. (h) Roush, W. R.; Brown, B. B.; Drozda, S. E. *Ibid.* **1988**, *29*, 3541. (i) Roush, W. R.; Brown, B. B. *Ibid.* **1989**, *30*, 7309. (j) Marshall, J. A.; Salovich, J. M.; Shearer, B. G. *J. Org. Chem.* **1990**, *55*, 2398. (k) Boeckman, R. K., Jr.; Barta, T. F.; Nelson, S. G. *Tetrahedron Lett.* **1991**, *32*, 4091. (l) Boeckman, R. K., Jr.; Estep, K. G.; Nelson, S. G.; Walters, M. S. *Ibid.* **1991**, *32*, 4095. (j) For the first total synthesis of tetronolide: Takeda, K.; Kawanishi, E.; Nakamura, H.; Yoshii, E. *Ibid.* **1991**, *32*, 4925.

(2) Studies on the synthesis of chlorothricolide: (a) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041. (b) Ireland, R. E.; Thompson, W. J.; Srouji, G. H.; Etter, R. *Ibid.* **1981**, *46*, 4863. (c) Hall, S. E.; Roush, W. R. *J. Org. Chem.* **1982**, *47*, 4611. (d) Snider, B. B.; Burbaum, B. W. *Ibid.* **1983**, *48*, 4370. (e) Schmidt, R. R.; Hirsenkorn, R. *Tetrahedron Lett.* **1984**, *25*, 4357. (f) Marshall, J. A.; Audia, J. E.; Grote, J. *J. Org. Chem.* **1984**, *49*, 5277. (g) Boeckman, R. K., Jr.; Barta, T. E. *Ibid.* **1985**, *50*, 3421. (h) Roush, W. R.; Kageyama, M. *Tetrahedron Lett.* **1985**, *26*, 4327. (i) Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1986**, *51*, 635. (j) Marshall, J. A.; Audia, J. E.; Shearer, B. G. *Ibid.* **1986**, *51*, 1730. (k) Marshall, J. A.; Audia, J. E.; Grote, J.; Shearer, B. G. *Tetrahedron*, **1986**, *42*, 2893. (l) Marshall, J. A.; Shearer, B. G.; Crooks, S. L. *J. Org. Chem.* **1987**, *52*, 1236. (m) Roush, W. R.; Riva, R. *Ibid.* **1988**, *53*, 710. (n) Danishefsky, S. J.; Audia, J. E. *Tetrahedron Lett.* **1988**, *29*, 1371. (o) Okumura, K.; Okazaki, K.; Takeda, K.; Yoshii, E. *Ibid.* **1989**, *30*, 2233. (p) Poss, A. J.; Brodowski, M. H. *Ibid.* **1989**, *30*, 2505. (q) Roth, G. P.; Rithner, C. D.; Meyers, A. I. *Tetrahedron* **1989**, *45*, 6949. (r) Total synthesis of (±)-24-*O*-methylchlorothricolide: Takeda, K.; Igarashi, Y.; Okazaki, K.; Yoshii, E.; Yamaguchi, K. *J. Org. Chem.* **1990**, *55*, 3431. (s) Schmidt, R. R.; Hirsenkorn, R. *Liebigs Ann. Chem.* **1990**, 883. (t) Hirsenkorn, R.; Haag-Zeino, B.; Schmidt, R. R. *Tetrahedron Lett.* **1990**, *31*, 4433. (u) Roush, W. R.; Kageyama, M.; Riva, R.; Brown, B. B.; Warmus, J. S.; Moriarty, K. J. *J. Org. Chem.* **1991**, *56*, 1192.

(3) Roush, W. R.; Essenfeld, A. P.; Warmus, J. S.; Brown, B. B. *Tetrahedron Lett.* **1989**, *30*, 7305.

(4) For a review of asymmetric Diels–Alder reactions: Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876.

(5) The synthesis of racemic **1** and the Diels–Alder reaction with cyclopentadiene are described in the 1985 Ph.D. Thesis of A. P. Essenfeld, M.I.T., Cambridge, MA (text pages 108–119; experimental section pages 161–175).

(6) (a) Zimmermann, J.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1104. (b) Details of the preparation of **6**: Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313. (c) For an improved method of synthesis of **6** with 97:3 diastereoselectivity: Chapel, N.; Greiner, A.; Ortholand, J.-Y. *Tetrahedron Lett.* **1991**, *32*, 1441.

(7) (a) Mattay, J.; Mertes, J.; Maas, G. *Chem. Ber.* **1989**, *122*, 327. (b) Mattay, J.; Kneer, G.; Mertes, J. *SynLett* **1990**, 145.

0022-3263/92/1957-3380$03.00/0