An (*S*)-(+)-Lactic Acid Route to (2*S*,6*R*,8*S*)-2,8 Dimethyl-1,7-dioxaspiro[5,5]undecane and (2*S*,6*R*,8*S*)-2-Ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane and Demonstration of their Presence in the Rectal Glandular Secretion of *Bactrocera nigrotibialis* (Perkins)

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The chiral iodide resulting from reduction and iodination of the tetrahydropyran-2-yl ether of ethyl (*S*)-(+)-lactate has been engaged in a free-radical addition to acrylonitrile. The resulting protected hydroxy nitrile, on reaction with pent-4-enylmagnesium bromide afforded (*S*)-2-tetrahydropyran-2-yloxyundec-10-en-6-one. Oxymercuriation of this hydroxy enone, under reversible conditions, employing aqueous acid–tetrahydrofuran, effected simultaneous deprotection and cyclisation, and *in situ* biphasic demercuriation with sodium borohydride provided essentially stereochemically pure (2*S*,6*R*,8*S*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane [*i.e.* the (*E*,*E*)-diastereoisomer only]. Epoxidation of the protected hydroxy enone, followed by dimethylcuprate ring-opening and cyclisation, provided a mixture of the (*E*,*E*) and the two possible (*E*,*Z*)-diastereoisomers of 2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane with the former being the (2*S*,6*R*,8*S*) stereoisomer. Separation of the (*E*,*E*) from the two (*E*,*Z*) isomers was achieved by preparative gas chromatography. GC analysis of these samples and of the rectal glandular secretion of male *Bactrocera nigrotibialis*, using a cyclodextrin-based phase, demonstrated that the (2*S*,6*R*,8*S*)-stereoisomers of the 2,8-dimethyl-and 2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecanes were the natural products, with no detectable level of the antipodes.

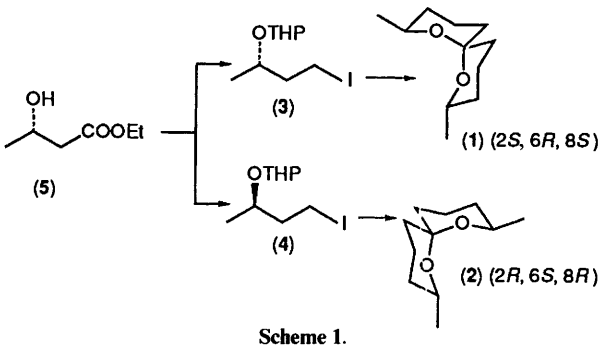
The spiroacetal unit is found in an expanding variety of naturally occurring compounds, many of which exhibit important physiological activity.[1,2] As a result, a large number of methods for generating the spiroacetal sub-structure have been developed.[3] Following Francke's demonstration[4] that 2-ethyl-1,6-dioxaspiro[4.4]nonane was the principal aggregation pheromone of the bark beetle *Pityogenes chalcographus*, relatively simple spiroacetals of various ring systems have been identified in insect species located in the orders Coleoptera, Hymenoptera, and Diptera, and these spiroacetals exhibit a wide range of behaviour as chemical messengers.[5,6] With respect to Tephritid fruit-fly species, principally derived from the genus Bactrocera,† an impressive variety of alkyl and hydroxy-substituted spiroacetals have been identified, both in extracts of the rectal gland and from aerial trapping of emitted volatiles[5,7–9] With a few exceptions, most insect-derived spiroacetals contain nine, elevent or thirteen carbon atoms in an unbranched arrangement and may have a close relation with other fatty acid derived pheromones.[10] Although these spiroacetals presumably play an important role in the life-cycle of the fruit-fly species, only in the case of the olive fly, *Dacus oleae*, has careful biological testing established this for the female-generated 1,7-dioxaspiro[5.5]-undecane, and here the enantiomers elicit sex-specific responses under the proper conditions.[11] This emphasises the necessity to establish the chirality of any spiroacetals that may be behaviour-influencing within a species and this in turn requires enantiospecific syntheses[6] and very sensitive methods for chirality determinations.[12] With respect to insect-derived spiroacetals, little is known regarding chirality, and we were particularly interested in this aspect for the unusual spiroacetals with an even number of carbon atoms, and in this category, (*E*,*E*)-2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane has been identified as a low level component in a number of species.[9,13,14] In this paper, we report efficient syntheses of both (2*S*,6*R*,8*S*)-2,8-dimethyl- and (2*S*,6*R*,8*S*)-2-ethyl-8-methyl-1,7-dioxaspiro-[5.5]undecane from ethyl (*S*)-(+)-lactate, and demonstrate their presence in the rectal gland secretion of *Bactrocera*† *nigrotibialis* (Perkins).[15]

Results and Discussion

Synthesis of the enantiomers of (*E*,*E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane, (**1**) and (**2**), was originally reported by Mori,[16] who utilised iodides (**3**) and (**4**) [derived from ethyl (*S*)-(+)-3-hydroxybutanoate (**5**)], to alkylate anions derived from methyl acetoacetate. Ethyl (*R*)-(−)-3-hydroxybutanoate was unavailable at that time (1981), and antipodal iodide (**4**) was acquired[16] by a sequence including a Walden inversion at C-3 (Mitsunobu reaction) (Scheme 1).

Rotations for spiroacetals (**1**) and (**2**) were reported as $[\alpha]_D^{23}$ −51.6° and +51.7° (*c* 1.72 in pentane), respectively, and the optical purity of chemically pure isomer (**1**) could be calculated as 99.8%, if the chiral centre of (**5**) (92% optically pure) survived without any appreciable racemisation. Subsequently, Isaksson[17] described the separation of isomers (**1**) and (**2**) [and also of the enantiomers of the (*E*,*Z*)-diastereoisomer] by liquid chromatography utilising microcrystalline triacetylcellulose, and considered their isomers (**1**) and (**2**) to be >98% optically pure, with $[\alpha]_D^{24}$ −44.3° for isomer (**1**) and +44.6° for isomer

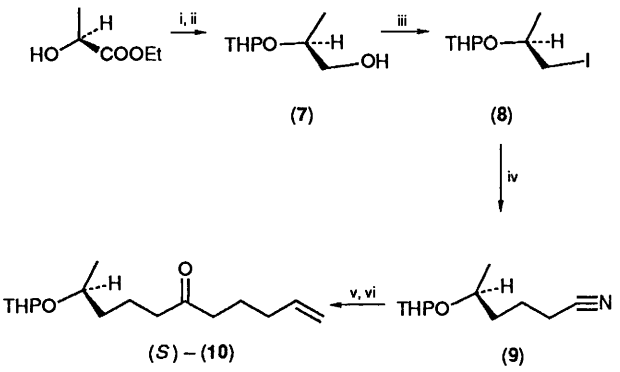
† Bactrocera is the new genus name applied in the general taxonomical revision (R. A. I. Drew, *Mem. Qld. Mus.*, 1989, 26:1-521, Brisbane, ISSN, 00A-8835) to a large number of fruit-fly species previously located in the Dacus genus.



Scheme 1.

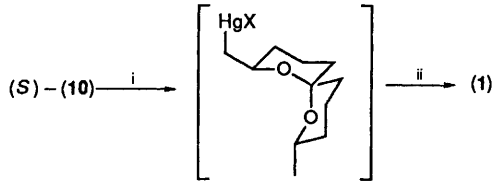
(**2**). The discrepancy in the reported optical rotations was investigated in detail by Mori[18] who utilised the now readily available ethyl (*R*)-(−)-3-hydroxybutanoate (*ca.* 100% e.e.) for direct access to key iodide (**4**) and hence isomer (**2**). In addition, a new synthesis starting with (*S*)-malic acid was reported by Mori,[18] and in this sequence the optical purity of the penultimate compound was established as 100% e.e. (from NMR spectra of derived diastereoisomeric esters). As a result, it is established that optically pure isomer (**1**) has $[\alpha]_D^{23}$ −59 to −60°. In the 'double alkylation' approach[16] to compounds (**1**) and (**2**), two units of the same chiral iodide are required to generate the protected keto diol equivalent of the spiroacetal.

Our approach to the (2*S*,6*R*,8*S*) enantiomer of the thermodynamically more stable (*E*,*E*)-diastereoisomer (**1**), utilises one unit of the chiral iodide derived from ethyl (*S*)-(+)-lactate (**6**) combined with reversible, cyclising reactions which ensure very high predominance of the (*E*,*E*) diastereoisomer through the virtue of the anomeric effect.[19] In addition, the alkene moiety present in (**10**), below in Scheme 2, permits elaboration to other systems, such as the ethyl and hydroxy methyl[18,*] derivatives. This chemistry is summarised in Scheme 2.



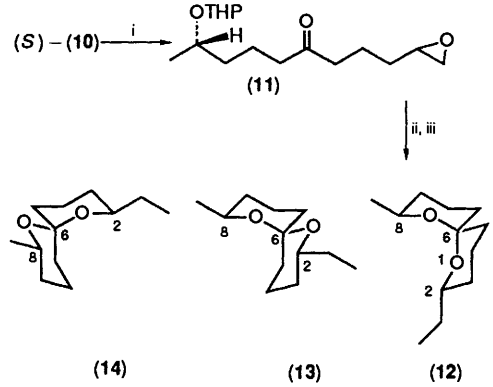
Scheme 2. *Reagents:* i, DHP, H^+; ii, $LiAlH_4$, H_2O; iii, Ph_3P, I_2, imidazole; iv, CH_2CHCN; Bu_3SnH, AIBN; v, $CH_2CH[CH_2]_3MgBr$; vi, H_2O.

Protection of ethyl (*S*)-(+)-lactate as the tetrahydropyranyl ether[20] and reduction with $LiAlH_4$ provided protected diol (**7**) which was very efficiently (*ca.* 85%) converted into iodide (**8**) using triphenylphosphine–iodide in the presence of imidazole.[21] This iodide (**8**) was then engaged in a free radical addition to acrylonitrile[22] to afford the protected hydroxy nitrile (**9**) in moderate yield (*ca.* 36% isolated after chromatography). Acquisition of key enone (*S*)-(**10**), resulted from addition of pent-4-enylmagnesium bromide to nitrile (**9**), followed by careful hydrolysis of the imino intermediate. (*S*)-(**10**) was then available for a number of transformations. Markovnikov hydration of the double bond, with concomitant deprotection of the installed hydroxy function [in (**10**)] and spiroacetalisation to provide essentially exclusively the (*E*,*E*) diastereoisomeric arrangement was envisaged to result from oxymercuration under aqueous acidic conditions, such that both oxymercuration and spiroacetalisation were reversible.[9] This proved to be the case, and subsequent demercuriation with $NaBH_4$ under biphasic conditions provided highly diasteriomerically enriched (*E*,*E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane [*E*,*E*–*E*,*Z* (98:2)], necessarily as the (2*S*,6*R*,8*S*) enantiomer (**1**) (Scheme 3). Chemically pure (**1**), acquired by preparative gas chromatography, exhibited $[\alpha]_D^{23}$ −58.7° (*c* 1.6 in pentane) and examination by chiral GC on a cyclodextrin based phase (see Figure 1) indicated an e.e. of 98%. These measurements are in agreement with the results of Mori.[18]



Scheme 3. *Reagents and conditions:* i, Hg(II), H_2O–THF, H^+, 18 h; ii, $NaBH_4$, OH^-, CH_2Cl_2, PTC.

Acquisition of stereoisomers (**12**), (**13**), and (**14**) of 2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane was approached by peracid epoxidation of alkene (*S*)-(**10**) followed by epoxide ring opening with dimethylcuprate[23] and cyclisation. The stereochemical deficiency in this route, *viz.* that epoxidation of (*S*)-(**10**) generates a new (racemic) chiral centre at the secondary epoxide carbon and consequently a diastereoisomeric mixture of the desired 2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane in which the (*E*,*E*) isomer cannot exceed 50%, was considered to be a minor drawback considering the route's directness and the anticipated ease of separation of the (*E*,*E*) diastereoisomer (**12**) from the two possible (*E*,*Z*) isomers (**13**) and (**14**). Thus epoxidation of (*S*)-(**10**) was conducted using *m*-CPBA in CH_2Cl_2, in the standard way and the resulting unprotected keto epoxide (**11**) was ring opened with dimethylcuprate as shown in Scheme 4.



Scheme 4. *Reagents and conditions:* i, *m*-CPBA–CH_2Cl_2; ii, Me_2CuLi, −46 °C; iii, H_2O–THF–HOAc, 2 d.

* Enantioselective synthesis of certain hydroxy substituted 2,8-dimethyl-1,7-dioxaspiro[5.5]undecanes have been achieved starting from D-mannitol, L-arabinose, and poly-(3-hydroxybutyrate). (M. F. Jacobs, M. V. Perkins, and P. J. Cassidy, unpublished results).

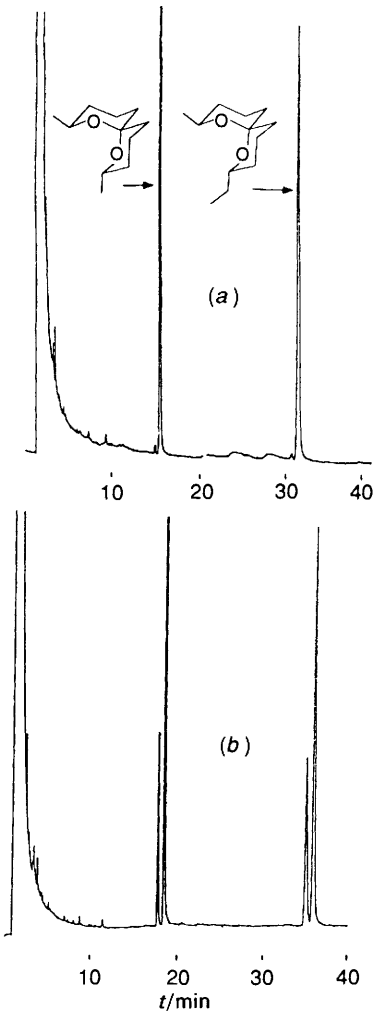


Figure 1. (*a*), Enantiomer analysis of synthesised samples of (*E,E*)-2,8-dimethyl- and 2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane showing *ca.* 98% e.e. of the (2*S*,6*R*,8*S*) configuration; (*b*), sample as in (*a*) mixed with corresponding (*E,E*)-racemates; condition: 35 m glass capillary column with perhexyl-α-cyclodextrin, column temperature 75 °C, carrier gas 0.95 bar H_2; retention times as indicated; conditions vary slightly from (*a*) to (*b*).

Preparative GC permitted acquisition of the diastereoisomerically pure (2*S*,6*R*,8*S*) isomer (**12**), with (*E,Z*)-(**13**) and (*Z,E*)-(**14**) being obtained as a pure (50:50) mixture. Isomer (**12**) $[\alpha]_D^{24}$ −72.9° (*c* 0.38 in pentane), a somewhat higher value than for the dimethyl derivative (**1**) discussed above. Examination by chiral GC using a perhexyl-α-cyclodextrin phase, provided an e.e. of 98% (Figure 1). Completely assigned ^1H and ^{13}C NMR spectra have been obtained for (±)-(**12**), and the data for the 'methyl-bearing ring' show close similarity with those for compound (**1**).[25] Isomers (**13**) and (**14**) would be expected to possess very similar chromatographic properties and are not easily separable. These have been characterised as a mixture.

Chirality of (E,E)-2,8-*Dimethyl- and* 2-*Ethyl*-8-*methyl*-1,7-*dioxaspiro*[5.5]*undecanes in* Bactrocera Nigrotibialis.—The three diastereoisomers of 2,8-dimethyl-1,7-dioxaspiro[5.5]-undecane have been demonstrated to be present in the rectal glandular secretion of certain species of fruit-flies,[9] and some aeration studies[13,15] have shown that these spiroacetals may be released into the atmosphere at mating time. Previously we reported[9] that the (*E,E*)-diastereoisomer was the major glandular component in the cucumber fly, *B. cucumis*, and that this was highly enantiomerically pure, possessing the (2*S*,6*R*,8*S*) configuration [compound (**1**)]. Although spiroacetals with odd numbers of carbon atoms greatly predominate amongst the relatively simple spiroacetals identified from insect sources,[10] some low-level *even* numbered carbon spiroacetals have been characterised. Thus, the 2-methyl,[25] 2-ethyl-8-methyl-,[8,9] and 2-butyl-8-methyl[8] derivatives of the 1,7-dioxaspiro[5.5]undecane system have been characterised, but normally at quite a low level (1–3%) and are clearly disfavoured biosynthetically. Thus it was of some interest to establish the chirality of one of these more unusual systems relative to the more abundant (*E,E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane. This comparison required a species in which an adequate level was present so that determination by chiral gas chromatography could be conducted. *B. nigrotibialis* is located throughout Malaysia, Thailand, and Laos but this species has not been cultured, and our specimens were trapped (with Cue-Lure) in the Gombok rainforest, Malaysia. The male rectal glandular secretion contains *ca.* 85% (*E,E*)-2,8-dimethyl- and *ca.* 3% of 2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane shown to be the (*E,E*) diastereoisomer by chromatographic comparisons with an authentic sample.[15]

Examination of a mixture of racemic (*E,E*)-2,8-dimethyl- and racemic (*E,E*)-2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecanes on a perhexyl-α-cyclodextrin phase demonstrated that the enantiomeric pairs were nicely resolved (Figure 1). Similar examination of our synthesised (2*S*,6*R*,8*S*) enantiomers of each of the above (*E,E*) diastereoisomers confirmed their high optical purity, with e.e. of 98% in each case (Figure 1). Under the same conditions, the extra of *B. nigrotibialis* showed only the (2*S*,6*R*,8*S*) enantiomers of each of the (*E,E*) diastereoisomers, and if the (2*R*,6*S*,8*R*) enantiomer of 2,8-dimethyl-1,7-dioxaspiro-[5.5]undecane was present at all, the level was certainly less than 1%. However for the less abundant 2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane the accuracy of the result is necessarily lower, although no peak corresponding to the (2*R*,6*S*,8*R*) enantiomer could be seen. These results are shown in Figure 2.

The chirality of (*E,E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]-undecane from three insect sources has now been determined to be (2*S*,6*R*,8*S*) in each case.[9,*] Although generalisation may be difficult, it is likely that the (2*S*,6*R*,8*S*) configuration with also characterise the 2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane from insect sources, as found for *B. nigrotibialis*. It would be of some interest to establish the situation for 2-butyl-8-methyl-1,7-dioxaspiro[5.5]undecane, but the level of this *even* numbered carbon spiroacetal in *B. latifrons*[8] is very low. Efforts in these areas are continuing.

Experimental

^1H NMR spectra were recorded at 400 MHz (FT mode) using a JEOL JNM-GX400 spectrometer. Deuteriochloroform was employed as solvent and chemical shifts are relative to internal tetramethylsilane (δ 0.0) of residual chloroform (δ 7.24). ^{13}C NMR spectra were recorded at 100 MHz, utilising $CDCl_3$ as solvent and chemical shifts are relative to the central component of the $CDCl_3$ triplet at δ 77.00. High resolution mass spectra were recorded on a Kratos MS-25RFA spectrometer and chemical ionisation spectra refer to ammonia as ionising gas. Gas chromatographic analyses were performed using a Hewlett-Packard 5710A gas chromatograph using OV1 or BP5 capillary columns, or a Varian Model 3700 gas chromatograph using an OV101 capillary column. Combined gas chromatography mass

* Present as a glandular component in male *Andrena wilkella*, Prof. W. Francke, personal communication, June, 1988.

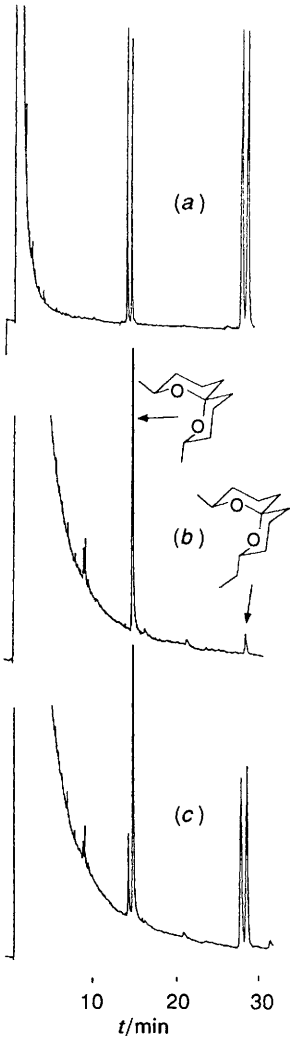


Figure 2. (*a*), Enantiomer resolution of racemic (*E,E*)-2,8-dimethyl- and (*E,E*)-2-ethyl-8-methyl-1,7-dioxaspiro[5.5]undecane; (*b*), corresponding analysis for the rectal glandular extract (male) of *B. nigrotibialis*, showing one enantiomer only of each of the above (*E,E*) spiroacetals (**1**) and (**12**); (*c*), sample as in (*b*) admixed with the corresponding (*E,E*) racemates; conditions: as outlined for Figure 1.

spectrometry was performed on a Hewlett-Packard 5970B mass selective detector. Preparative gas chromatography was performed using a Shimadzu gas chromatograph Model GC-9A equipped with OV101 and C-20M columns. IR spectra were recorded on a Perkin-Elmer Model 397 spectrometer. Optical rotations were measured using a Perkin-Elmer 141 MC or 241 MC polarimeter.

Ethyl (S)-(−)-2-*Tetrahydropyran-2-yloxypropionate* (**6**).—Pyridinium toluene-*p*-sulphonate (*ca.* 100 mg) was added to a stirred solution of ethyl (*S*)-lactate (15.0 g, 0.127 mol) and 3,4-dihydro-2*H*-pyran (15.0 g, 0.178 mol) in dry dichloromethane (200 ml) contained in a flask fitted with a reflux condenser and drying tube. After 3 h at room temperature, the mixture was washed with saturated aq. $NaHCO_3$, dried ($MgSO_4$), and the solvent removed under reduced pressure. The resulting oil was distilled (76–78 °C at 0.25 mmHg) to yield ethyl 2-tetrahydropyran-2-yloxypropionate (23.9 g, 93%) as a mixture of two diastereoisomers; *m/z* (CI) 203 ($M^+ + 1$, 29.1%), 103 (12.0), 102 (100), 101 (47.6), 86 (52.0), and 84 (30.3) (Found: $M^+ + 1$, 203.1272. Calc. for $C_{10}H_{19}O_4$: 203.1283).

$\delta_C(CDCl_3)$ 13.87, 13.94, 17.75, 18.46, 18.86, 18.90, 25.07, 25.15, 30.12, 30.22, 60.38, 60.46, 61.96, 62.09, 69.72, 72.27, 97.27, 98.00, 172.94, and 173.02; $\delta_H(CDCl_3)$ 1.145 (t, *J* 7.1 Hz, 3 H, CH_2CH_3), 1.15 [t, *J* 7.1 Hz, 3 H, CH_2CH_3 (overlaps with other methyl)], 1.25 (d, *J* 6.8 Hz, 3 H, $OCCH_3$), 1.31 (d, *J* 6.8 Hz, 3 H, $OCCH_3$), 1.35–1.8 (m, 12 H), 3.29–3.40 (m, 2 H), 3.67–3.83 (2 H), 4.0–4.1 (m, 5 H), 4.27 (q, *J* 7.1 Hz, 2 H, OCH_2–CH_3), and 4.55–4.60 (m, 2 H); $[\alpha]_D^{23}$ −45.5° (*c* 2.5 in $CHCl_3$) (lit.,[21] $[\alpha]_D^{23}$ −41.1°, *c* 2.1 in $CHCl_3$).

(S)-(+)-2-*Tetrahydropyran-2-yloxypropan-1-ol* (**7**).—To an ice cooled solution of $LiAlH_4$ (8.25 g, 0.218 mol) in dry ether (200 ml) under a nitrogen atmosphere, the ester (**6**) (20.0 g, 0.99 mol) in ether (100 ml), was added dropwise during 1.5 h. The reaction was stirred for a further 1 h and then saturated aqueous NH_4Cl (50 ml) was added. Precipitated salts were filtered off and washed well with ether and the combined organic phases were separated, dried ($MgSO_4$), and the solvent was removed under reduced pressure to yield an oil. Distillation (74 °C at 0.25 mmHg) provided the alcohol (**7**) (14.0 g, 88.5%) as a mixture of two diastereoisomers; *m/z* (EI) 160 (M^+, 0%), 129 (24), 101 (20), 87 (20), 86 (33), 85 (67), 84 (32), 83 (20), 74 (13), 67 (48), 59 (58), 58 (39), 57 (100), 56 (73), and 55 (97) (Found: M^+, 161.1172. Calc. for $C_8H_{17}O_3$: 161.1178); $\delta_C(CDCl_3)$ 16.85, 17.57, 19.76, 20.55, 24.91, 25.16, 30.82, 31.30, 62.76, 64.09, 65.87, 66.86, 74.50, 76.96, 98.78, and 99.34; $\delta_H(CDCl_3)$ 1.01 (d, *J* 6.3 Hz, 3 H, CH_3), 1.09 (d, *J* 6.3 Hz, 3 H, CH_3), 1.37–1.50 (m, 8 H), 1.58–1.75 (m, 5 H), 2.73 (br s, 1 H, OH?), 3.33–3.45 (m, 6 H), 3.65–3.90 (m, 4 H), 4.44 (dd, *J* 5.6 and 1.9 Hz, 1 H, OCHO), and 4.62 (dd, *J* 5.1 and 2.8 Hz, 1 H, OCHO); $[\alpha]_D^{23}$ +3.66 (*c* 3.9 in $CHCl_3$) (lit.,[21] $[\alpha]_D^{23}$ +17.0 *c* 2.3 in $CHCl_3$).

(S)-(+)-1-*Iodo-2-tetrahydropyran-2-yloxypropane* (**8**).—A mixture of alcohol (**2**) (11.0 g, 0.069 mol), triphenylphosphine (54.17 g, 0.206 mol), imidazole (14.0 g, 0.206 mol) and iodine (34.9 g, 0.137 mol) in toluene (500 ml) were stirred at reflux with a bath temperature of 120 °C for 1.5 h. To the cooled, stirred mixture, saturated aqueous $NaHCO_3$ (500 ml) was added, followed by iodine (I_2) (in portions) until the iodine colour persisted in the toluene phase. The solution was stirred for a further 10 min, after which time, aqueous sodium thiosulphate was added to discharge the iodine colour. The toluene layer was separated, washed with water (150 ml), dried ($MgSO_4$), and the toluene removed under reduced pressure. The residue (consisting of triphenylphosphine oxide and the product) was triturated with hexane (200 ml) and the insoluble triphenylphosphine oxide removed by filtration. Evaporation of the hexane yielded the iodide (**8**) (15.8 g, 85%); *m/z* (EI) 270 (M^+, 0%), 269 (27.3), 228 (33.1), 170 (12.3), 169 (87.3), 168 (14.4), 143 (11.8), 142 (10.2), 141 (13.6), 129 (28.7), 128 (11.3), 127 (24.6), 103 (41.3), 102 (13.2), 101 (87.8), 87 (54.0), 86 (24.2), 85 (100), 84 (23.8), 83 (15.2), 73 (12.5), 71(16.8), and 67 (44.2) (Found: $M^+ - 1$, 269.0039. Calc. for $C_8H_{14}O_2I$: 269.0038); $\delta_C(CDCl_3)$ 11.43, 12.36, 19.27, 19.49, 19.75, 21.63, 25.30, 25.34, 30.61, 30.84, 62.46, 62.52, 71.60, 71.80, 96.93, and 97.88; $\delta_H(CDCl_3)$ 1.21 (d, *J* 6.2 Hz, 3 H, CH_3), 1.27 (d, *J* 6.3 Hz, 3 H, CH_3), 1.43–1.85 (m, 12 H), 3.15–3.21 (m, 3 H), 3.28–3.32 (m, 1 H), 3.41–3.47 (m, 2 H), 3.68–3.74 (m, 2 H), 3.79–3.85 (m, 1 H), 3.90–3.96 (m, 1 H), 4.65–4.68 (m, 2 H, OCHO); $[\alpha]_D^{22}$ +2.7° (*c* 2.5 in $CHCl_3$).

(S)-+)-5-*Tetrahydropyran-2-yloxyhexanenitrile* (**9**).—Tributyltin hydride (9.5 g, 32.6 mmol) and azoisobutyronitrile, AIBN (*ca.* 50 mg) in dry benzene (100 ml) was added dropwise during 1 h to a stirred solution of the iodide (**8**) (8.0 g, 29.6 mmol), acrylonitrile (15.7 g, 296 mmol), and AIBN (*ca.* 20 mg) in benzene (100 ml) at reflux under a nitrogen atmosphere. The reaction was heated for a further 10 min and then cooled, and the benzene was removed under reduced pressure. An aqueous

solution of NaF (10 g in 50 ml) was added to the residue and the mixture stirred for 30 min after which dichloromethane (200 ml) was added, and the mixture filtered. The organic layer was separated, washed with dilute ammonia (50 ml), dried ($MgSO_4$), and evaporated to give an oil. The crude product was subjected to flash chromatography [Kieselgel 60, 230–400, ethyl acetate–hexane (20:80)] to give the nitrile (**9**) (two isomers in the ratio 59:41) (2.1 g, 36%); *m/z* (CI) 198 ($M^+ + 1$, 13.8), 114. (12.9), 102 (24.0), 101 (11.8), 85 (100), and 66 (16.7) (Found: $M^+ + 1$, 198.1489. Calc. for $C_{11}H_{20}O_2$: 198.1494); $\delta_C(CDCl_3)$ 16.78, 17.07, 19.08, 19.78, 19.93, 21.28, 21.30, 21.60, 25.25 (2 peaks superimposed), 30.98, 31.07, 35.18, 35.80, 62.66, 62.92, 69.86, 73.15, 96.01, 98.83, 119.48, and 119.69; $\delta_H(CDCl_3)$ 1.05 [d, *J* 6.3 Hz, 3 H, CH_3 (major isomer)], 1.17 [d, *J* 6.3 Hz, 3 H, CH_3 (minor isomer)], 1.40–1.83 (m, 20 H), 2.27–2.38 (m, 4 H), 3.37–3.44 (m, 2 H), 3.64–3.86 (m, 4 H), and 4.52–4.57 (m, 2 H, 2 × OCHO); ν_{max} 2 245.0w cm^{-1} (C≡N); $[\alpha]_D^{22}$ +27.3° [*c* 3.3 in $CHCl_3$, two isomers (59:41)].

(S)-2-*Tetrahydropyran*-2-*yloxyundec*-10-*en*-6-*one* (**10**).—Pent-4-enylmagnesium bromide, prepared from pent-4-enyl bromide (2.04 g, 13.7 mmol) and magnesium (0.34 g, 14.0 mmol) in ether in the usual way, was heated under reflux and the nitrile (**9**) (1.8 g, 9.13 mmol) in ether (10 ml) was added dropwise. After addition was complete, the reaction was heated under reflux for a further 5 h and then water (50 ml) was carefully added. The reaction mixture was stirred for a few minutes until the white solid dissolved. The layers were separated and the aqueous layer extracted with diethyl ether (2 × 50 ml) and the combined ether extracts were dried ($MgSO_4$) and evaporated to give an oil which was subjected to chromatography (Kieselgel 60, mesh 70–230) using CH_2Cl_2–EtOAc (80:20) as eluant to give the enone (**10**) as an oil (1.8 g, 73.5%) (as a mixture of two isomers in the ratio 53:47); *m/z* (EI) 268 (M^+, 0%), 184 (4.8), 183 (3.6), 167 (41.3), 112 (11.5), 97 (20.7), and 85 (100); *m/z* (CI) 269 ($M^+ + 1$, 17.2), 185 (49.4), 168 (14.4), and 167 (100); $\delta_C(CDCl_3)$ 18.95, 19.62, 19.69, 19.92, 20.01, 21.41, 22.66 (2 superimposed peaks), 25.36, 25.39, 31.05, 31.09, 35.97 (2 superimposed peaks), 35.88, 36.72, 41.69, 41.72, 42.62, 42.66, 62.45, 62.68, 70.58, 73.68, 95.61, 98.70, 115.00, 115.03, 137.83, 137.87, 210.66, and 210.87; $\delta_H(CDCl_3)$ 1.025 [*d*, *J* 6.1 Hz, 3 H, CH_3 (major isomer)], 1.14 [d, *J* 6.1 Hz, 3 H, CH_3 (minor isomer)], 1.30–1.80 (m, 24 H), 1.97 (br q, *J* 6.8 Hz, 4 H, 2 × $CH_2CH{=}CH_2$), 2.30–2.37 (m, 8 H, 2 × $CH_2C{=}OCH_2$), 3.36–3.43 (m, 2 H), 3.59–3.87 (m, 4 H), 4.54 (dd, *J ca.* 4 and *ca.* 3 Hz, 1 H, –CH–O), 4.60 br t, *J ca.* 3.5 Hz, 1 H, CH–O), 4.85–4.96 (m, 4 H, $CH_2{=}C$), and 5.68 (dddd, *J* 17.1, 10.2, 6.8, and 6.8 Hz, 2 H, 2 × $-CH{=}CH_2$).

(2S,6R,8S)-2,8-*Dimethyl*-1,7-*dioxaspiro*[5.5]*undecane* (**1**).—The enone (**10**) (0.3 g, 1.12 mmol) and $Hg(OAc)_2$ (0.43 g, 1.34 mmol) were stirred in a mixture of THF and aqueous 1% $HClO_4$ (1:1; 30 ml) for 18 h. The reaction was then treated sequentially with aq. NaOH (30 ml; 10%), dichloromethane (30 ml), benzyltriethylammonium chloride (*ca.* 1.0 g), and finally $NaBH_4$ (0.06 g, 1.6 mmol), after which it was stirred for 40 min. The metallic mercury was removed by filtration through Supercell and the organic layer extracted with ether (3 × 50 ml). The combined ethereal phase was dried ($MgSO_4$) and evaporated to yield (predominantly by GC analysis) the spiroacetal (**1**) (0.20 g, 90%) with a small amount of the *E,Z* isomer [*E,E*–E,Z (98:2)]. Pure (**1**) was obtained by preparative gas chromatography (Found: C, 71.3; H, 11.25. $C_{11}H_{20}O_2$ requires C, 71.69; H, 10.93%); *m/z* (GC–MS) 184 (M^+, 8.8%), 169 (2.2), 140 (14.0), 115 (97.3), 114 (44.0), 112 (100), 97 (60.9), 84 (12.6), 83 (23.7), 73 (18.0), 71. (15.3), 70 (16.2), 69 (48.3), 58 (19.7), 55 (58.5), 43. (74.8), 42 (36.2), and 41 (53.0); $\delta_H(C_6D_6)$ 19.35 (C4 and C10), 22.22 (C12 and C13), 33.23 (C3 and C9), 35.66 (C5 and C11), 65.15 (C2 and C8), and 96.07 (C6); $\delta_H(C_6D_6)$ 1.11 (tdd, *J* 13.1, 11.23, and 3.9 Hz, 2 H, 3-H_{ax} and 9-H_{ax}), 1.15 (d, *J* 6.35 Hz, 6 H, 12-Me and 13-Me), 1.30 (td, *J* 13.1 and 4.5 Hz, 2 H, 5-H_{ax} and 11-H_{ax}), 1.39 (ddddd, *J* 13.1, 4.3, 2.2 and 1.5[#],? ($J_{3eq,9eq;4eq,10eq}$ cannot be measured as signals 3-H_{eq}, 9-H_{eq}, and 4-H_{eq},10-H_{eq} are almost coincident) Hz, 2 H, 3-H_{eq}:9-H_{eq}), 1.40 [ddddd, *J* 13.1, 4.5, 3.9, 2.4, ? (see above comment) Hz, 2 H, 4-H_{eq} and 10-H_{eq}], 1.63 (dddd, *J* 13.1, 4.3, 2.5, 1.5[#] Hz, 2 H, 5-H_{eq} and 11-H_{eq}), 2.04 (qt, *J* 13.1 and 4.3 Hz, 2 H, 4-H_{ax} and 10-H_{ax}), and 3.74 (dqd, *J* 11.23, 6.35, and 2.2 Hz, 2 H, 2-H_{ax}:8-H_{ax}) ([#] Signifies a W coupling); $[\alpha]_D^{23}$ −58.7° (*c* 1.6 in pentane) (lit., $[\alpha]_D^{23}$ −58.8°, *c* 1.27)[18] (*NB* Chiral GC analysis using a perhexyl-α-cyclodextrin stationary phase gave an e.e. 98%).

1,2-*Epoxy*-10-(*tetrahydropyran*-2-*yloxy*)*undecan*-6-*one* (**11**).—The enone (**10**) (1.0 g, 3.73 mmol) and *m*-chloroperbenzoic acid (85%; 1.14 g, 5.6 mmol) were stirred in dichloromethane (50 ml) for 5 h. The reaction was then treated sequentially with saturated aqueous $NaHCO_3$ (20 ml), saturated aqueous $NaHSO_3$ (from sodium metabisulphite in water) (20 ml), and finally saturated aqueous $NaHCO_3$ (20 ml). The organic layer was dried ($MgSO_4$) and evaporated to give the epoxide (**11**) (0.9 g, 85%) as a mixture of two isomers: *m/z* 284 (M^+, 0.6%), 183 (28.8), 115 (23.1), 85 (100), 67 (13.9), 43 (19.3), and 42 (19.3) (Found: M^+, 284.1983. Calc. for $C_{16}H_{28}O_4$: 284.1988); $\delta_C(CDCl_3)$ 18.91, 19.54, 19.68, 19.87, 19.94, 20.03 (two superimposed peaks), 21.37, 25.32, 25.35, 31.02, 31.06, 31.62, 31.64, 35.83, 36.66, 41.87, 41.89, 42.55, 42.60, 46.57, 46.59, 51.82 (two superimposed peaks), 62.47, 62.66, 70.57, 73.63, 95.62, 98.65, 210.26, and 210.46; $\delta_H(CDCl_3)$ 1.01 (d, *J* 6.1 Hz, 3 H, CH_3), 1.13 (d, *J* 6.1 Hz, 3 H, one CH_3), 1.25–1.80 (m, 28 H), 2.25–2.42 (m, 10 H), 2.65 (br t, *J* 4.5 Hz, 2 H), 2.78–2.83 (m, 2 H), 3.35–3.43 (m, 2 H), 3.60–3.86 (m, 4 H), and 4.51–4.63 (m, 2 H).

2-*Ethyl*-8-*methyl*-1,7-*dioxaspiro*[5.5]*undecane* (**12**), (**13**), *and* (**14**).—Dimethyl cuprate (2.3 mmol) was prepared[24] by the dropwise addition of methyl-lithium (1.4M; 3.3 ml, 4.6 mmol) to a slurry of CuI (0.44 g, 2.3 mmol) in dry ether (20 ml) at 0 °C. On addition of 1 equiv. of MeLi a bright yellow suspension was observed, but by completion of the addition the solution was clear. The mixture was stirred for 15 min and then cooled to −46 °C (solid CO_2–cyclohexanone). The epoxide (**11**) (0.2 g, 0.70 mmol) in ether (5 ml) was added dropwise over 10 min and the reaction stirred for a further 45 min after which saturated aqueous NH_4Cl (10 ml) was added at −46 °C and the solution warmed to room temperature. The reaction mixture was diluted with ether and the aqueous layer extracted with ether (2 × 30 ml). The combined organic layers were dried ($MgSO_4$) and evaporated to give an oil (0.3 g), which was dissolved in a mixture of HOAc–THF–H_2O (4:2:1; 3 ml) and stirred at room temperature for 2 d. The mixture was then treated with saturated aqueous $NaHCO_3$, followed by solid Na_2CO_3 until it was basic. The solution was extracted with ether (3 × 50 ml) and the combined extracts were dried ($MgSO_4$) and evaporated to give an oil (crude 0.21 g). This oil was purified by preparative gas chromatography to give pure (2S,6R,8S)-2-*ethyl*-8-*methyl*-1,7-*dioxaspiro*[5.5]*undecane* (**12**) (0.02 g, 14.3%); *m/z* 198 (M^+, 31.9%), 140 (23.0), 129 (55.4), 128 (18.4), 126 (39.7), 115 (100), 114 (21.0), 112 (71.6), 111 (25.3), 99 (14.0), 97 (34.3), 84 (13.2), 71 (17.2), 68 (28.5), 44 (20.7), and 42 (28.5) (Found: M^+, 198.1621. Calc. for $C_{12}H_{22}O_2$: 198.1621); $\delta_C(C_6D_6)$ 10.51 (C13), 19.30 and 19.43 (C4 and C10), 22.20 (C14), 29.76 (C12), 31.32 (C3), 33.28 (C9), 35.75 and 35.98 (C5 and C11), 65.17 (C8), 70.30 (C2), and 95.87 (C6); $\delta_H(C_6D_6)$ 1.0 (t, *J* 7.4 Hz, 3 H, 13-Me), 1.11 (dtd, *J* 13.1, 11.2, and 3.9 Hz, 2 H, 3-H_{ax} superimposed), 1.17 (d, *J* 6.1 Hz, 3 H, 14-Me), 1.31 (td, *J* 13.1 and 4.4 Hz, 1 H, 5-H_{ax} or 11-H_{ax}), 1.32 (td, *J* 13.1 and 4.4 Hz, 1 H, 5-H_{ax} or 11-H_{ax}), 1.36–1.46 (m, 4 H, overlapping 3-H_{eq}, 4-H_{eq}, 9-H_{eq}, and 10-H_{eq}; each d of m), 1.5–1.59 [m, 2 H, 2 H on C-12 (2nd order)], 1.61–1.68 (m, 2 H, 5-H_{eq} and 11-H_{eq},

overlapping), 2.03 (qt, *J* 13.4 and 4.2 Hz, 1 H, 4-H_{ax} or 10-H_{ax}), 2.05 (qt, *J* 13.4 and 4.2, 1 H, 4-H_{ax} or 10-H_{ax}), 3.51 (dddd, *J* 11.2, 8.3, 4.6, and 2.2 Hz, 1 H, 2-H_{ax}), and 3.78 (dqd, *J* 11.2, 6.1, and 2.2 Hz, 1 H, 8-H_{ax}); $[\alpha]_D^{24}$ −72.9° (*c* 0.38 in pentane). The sample was analysed by chiral gas chromatography using a perhexyl-α-cyclodextrin stationary phase and an e.e. of 98% was found.

Also obtained was (2R,6S,8S)- *and* (2R,6R,8S)-2-*ethyl*-8-*methyl*-1,7- *dioxaspiro*[5.5]*undecane* (**13**) and (**14**) as a pure mixture (0.013 g, 9.5%); *m*/*z* 198 (M^+, 22.6%), 169 (18.9), 129 (72.3), 128 (19.7), 126 (16.2), 115 (100), 114 (18.6), 112 (28.6), 111 (38.5), 99 (12.9), 97 (37.0), 73 (12.6), 71 (14.9), and 68 (17.5) (Found: M^+, 198.1616. Calc. for $C_{12}H_{22}O_2$: 198.1620); $\delta_C(C_6D_6)$ 10.09, 10.68, 18.93, 18.97, 19.23, 20.13, 22.24, 22.42, 28.93, 29.81 (2 superimposed peaks), 30.71, 31.06, 31.19, 32.52, 33.58, 36.50, 36.78, 65.98, 68.51, 70.90, 73.84, 97.01, and 97.25; $\delta_H(C_6D_6)$ 0.94 (t, *J* 7.4 Hz, 3 H, *E*,*Z* or *Z*,*E* CH_2CH_3), 0.97 (t, *J* 7.4 Hz, 3 H, *E*,*Z* or *Z*,*E* CH_2CH_2), 1.0–1.8 [m, 32 H, including 1.16 (d, *J* 6.35 Hz, 3 H, *Z*,*E* Me14, collapses to singlet on irradiation of 4.34), 1.18 (d, *J* 6.1 Hz, 3 H, *E*,*Z* Me14, collapses to singlet on irradiation of 3.44)], 1.95 (dm, *J ca.* 13 Hz, 1 H, *E*,*Z* 5-H_{eq} or *Z*,*E* 11-H_{eq}), 1.97 (dm, *J ca.* 13 Hz, *E*,*Z* 5-H_{eq} or *Z*,*E* 11-H_{eq}), 3.07 (dddd, *J* 9.8, 7.3, 4.7, and 2.9 Hz, 1 H, *Z*,*E* 2-H_{ax}), 3.44 (dqd, *J* 9.3, 6.1, and 3.0 Hz, 1 H, *E*,*Z* 8-H_{ax}), 4.07 (dddd, *J* 12.0, 6.5, 6.4, and 2.2 Hz, *E*,*Z* 2-H_{ax}), and 4.34 (dqd, *J* 11.2, 6.3, 2.3 Hz, 1 H, *Z*.*E* 8-H_{ax}); $[\alpha]_D^{23}$ +15.8° [*c* 0.31 in pentane, *E*,*Z* and *Z*,*E* (50:50)].

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