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A Method for the Chromatographic Resolution of Tetrahydropyran-2-ones

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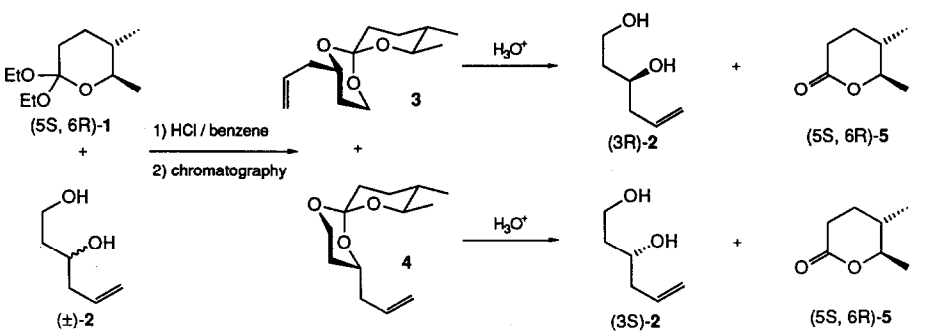
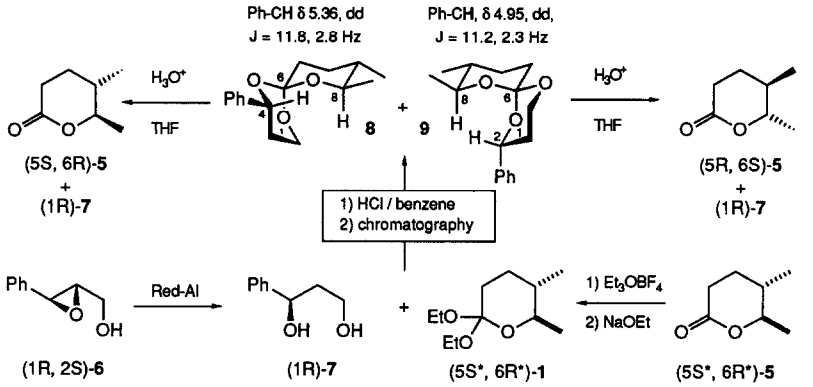
Abstract. The spirocyclic ortholactones prepared from certain tetrahydropyran-2-ones (valerolactones) and (1R)-1-phenylpropan-1,3-diol are readily separable by flash chromatography on silica gel. Hydrolysis of the resolved ortholactones then provides the pure homochiral lactones.

During work on our first synthesis of the spiroacetal fragment of Milbemycin β_3 we discovered that the diastereoisomeric spirocyclic ortholactones **3** and **4** (Scheme 1), prepared from the racemic 1,3-diol **2** and homochiral (5S, 6R)-2,2-diethoxy-5,6-dimethyl-tetrahydropyran (**1**), were easily separated by thin layer and flash chromatography[1]. Since hydrolysis of the spirocyclic ortholactones then provided lactone (5S, 6R)-**5** (from which **1** was prepared) and the homochiral diols (3R)-**2** and (3S)-**2**, a method was at hand for the chromatographic resolution of 1,3-diols[2].



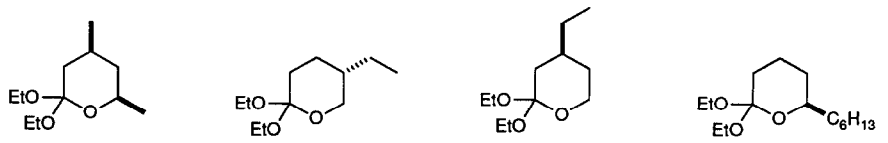
SCHEME 1. Chromatographic resolution of racemic 1,3 diols *via* spirocyclic ortholactones.

We have now adapted this chance observation to a convenient and useful method for the chromatographic resolution of certain racemic tetrahydropyran-2-ones *via* the separation and hydrolysis of their spirocyclic ortholactone derivatives prepared from (1R)-1-phenylpropan-1,3-diol (**7**)[3]. The general method is illustrated in Scheme 2 by the resolution of (5S*, 6R*)-5,6-dimethyltetrahydropyran-2-one [(5S*, 6R*)-**5**]. Racemic **5** was first converted in two steps (71% overall) to the racemic ortholactone [(5S*, 6R*)-**1**] using standard procedures[4]. Reaction of (5S*, 6R*)-**1** with (1R)-1-phenylpropan-1,3-diol (**7**) in benzene at room temperature in the presence of a trace of HCl gave a mixture of two[5] diastereoisomeric spirocyclic ortholactones **8** and **9** having the benefit of maximum anomeric stabilisation and equatorial disposition of the pendant substituents[6]. These were easily separated by column chromatography on silica gel eluting with 5% Et_2O in benzene to give pure **8** (37%) and **9** (33%) along with some mixed fractions accounting for a further 10%. Hydrolysis of the less polar isomer **8** gave a 90% yield of (+)-(5S, 6R)-5,6-dimethyltetrahydropyran-2-one [(5S, 6R)-**5**] having an optical rotation comparable to that previously reported[1,7]. Similarly, hydrolysis of diastereoisomer **9** gave (-)-(5R, 6S)-5,6-dimethyltetrahydropyran-2-one [(5R, 6S)-**5**] in 91% yield.



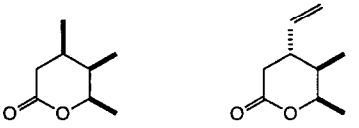
SCHEME 2. Chromatographic resolution of tetrahydropyran-2-ones *via* spirocyclic ortholactones.

To further illustrate the value of the method, the racemic ortholactones **10-13** were prepared from the corresponding lactones and converted to diastereoisomeric pairs of spirocyclic ortholactones (Table) which were resolved with similar efficiency according to the protocol outlined in Scheme 1. In each case the diastereoisomeric ortholactones were readily separated and then hydrolysed to give the homochiral lactones in *ca.* 35% yield from the diethyl ortholactone precursors. The diol **7** was recovered in 90% yield and was sufficiently pure after one recrystallisation for use in further resolutions.



The structure and stereochemistry of the spirocycles were readily assigned by NMR spectroscopy. In each case the equatorial disposition of the phenyl substituents was deduced from the coupling constants (J = 11-12, 2.3-3.0 Hz) of the doublet of doublets of the benzylic proton indicative of *trans*-diaxial and vicinal axial-equatorial H-H coupling. The diastereoisomeric pairs, which displayed consistent polarity behaviour by thin layer chromatographic analysis (see Table), were easily distinguished by differential nuclear Overhauser experiments. For example, irradiation of the C-2 axial benzylic proton in the more polar diastereoisomer **9** revealed an enhancement of the axial proton at C-8 whereas similar experiments on the less polar diastereoisomer **8** revealed no such enhancement. As can be seen from the Table, the chemical shift of the benzylic proton in the more polar diastereoisomers consistently appear at *ca.* 0.2-0.4 ppm higher field than the corresponding less polar diastereoisomers – *an observation which may be of diagnostic value in assigning the absolute configuration of unknown tetrahydropyran-2-ones.*

Our method appears to be general for comparatively simple tetrahydropyran-2-ones wherein all the substituents on the spirocyclic orthoesters occupy an equatorial position. There are a number of important limitations: for example, the tri-substituted tetrahydropyran-2-one **26**, which requires that at least one substituent occupy an axial position in the spirocyclic ortholactone, could not be resolved because the exchange reaction by which the diethyl ortholactone is converted to the spirocyclic system is messy. Similarly, resolution of the tri-substituted tetrahydropyran-2-one **27** is



26 **27**

inefficient because of the incompatibility of the terminal alkene function with the conditions used to make the diethyl ortholactone. Presumably the several unidentified by-products generated on reaction of **27** with triethyloxonium tetrafluoroborate / NaOEt are the result of elelctrophilic attack of the dioxonium ion intermediate on the alkene. Finally, attempts to extend our method to the resolution of 5-membered ring lactones failed because the exchange reaction with diol **7** leads to 4 diastereoisomeric spirocyclic ortholactones which are difficult to separate by simple column chromatography.

Although limited in scope, our method is useful for the chromatographic resolution of gram quantities of simple tetrahydropyran-2-ones; it compares favourably with other methods which have recently been devised for the chromatographic resolution of 1,2- and 1,3-diols[8, 9], ketones[10], acetals[11, 12], α-hydroxy ketones[13], and lactones[14, 15].

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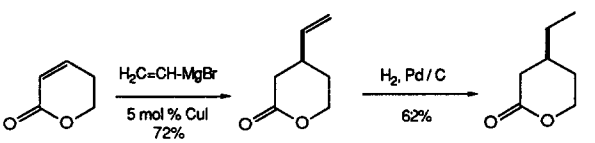
EXPERIMENTAL

General. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 270 MHz and 90 MHz respectively and chemicals shifts are reported relative to tetramethylsilane at δ 0.00. All coupling constants (J) are recorded in Hertz. Signals are assigned as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), or broad (br). ^{13}C NMR spectra were recorded using the central peak of the $CDCl_3$ signal as an internal standard (δ 77.2). Carbon-proton couplings were determined by DEPT and INEPT techniques and are recorded by citing the number of protons attached to carbon in parenthesis. All infrared (IR) spectra were recorded as thin films in the Fourier transform mode. All mass spectra were recorded in the EI mode (unless otherwise stated) on samples judged to be ≥90% pure by ^{1}H and/or ^{13}C NMR spectroscopy and TLC analysis. Optical rotations were measured on an Optical Activity AA-100 polarimeter using 5 or 50 mm cells.

PREPARATION OF RACEMIC TETRAHYDROPYRAN-2-ONES 5, 14, 17 AND 20

(5S*, 6R*)-5,6-Dimethyltetrahydropyran-2-one [(5S*, 6R*)-**5**] was prepared from racemic *trans*-2,3-epoxybutane as previously described[1]. (4R*, 6R*)-4,6-Dimethyltetrahydropyran-2-one [(4R*, 6R*)-**14**] was prepared by the method of McKelvey and coworkers[16]. (5S*)-5-Ethyltetrahydropyran-2-one [(5S*)-**17**] was prepared by the method of Yeates[17]. (6R*)-6-*n*-Hexyl-tetrahydropyran-2-one [(6R*)-**23**] was obtained from Aldrich Chemical Co. (4S*)-4-Ethyltetrahydropyran-2-one [(4S*)-**20**] was prepared as shown in Scheme 3:



SCHEME 3

(4S*)-4-Ethenyl-tetrahydropyran-2-one (29) – Vinylmagnesium bromide (0.9 M in THF, 33 ml, 30 mmol) was added to a rapidly stirred suspension of CuI (0.192 g, 1 mmol) in THF (22 ml) at -78°C. After 15 min, the 5,6-dihydro-2H-pyran-2-one (**28**) (1.96 g, 20 mmol) in THF (22 ml) was added dropwise over 60 min whilst maintaining the temperature at -78°C. After addition was complete, the mixture was stirred for a further 30 min and then poured into saturated ammonium chloride solution. The organic layer was separated and the aqueous layer extracted with ether (2 x 50 ml). The combined organic layers were washed with water and brine, dried over magnesium sulphate, and concentrated *in vacuo* to give a pale yellow oil which was distilled *via* kugelrohr to give the title compound **29** (1.84 g, 14.5 mmol, 72%) as a colourless oil: b. p. (bath) 150°C / 0.3 mm Hg; **IR** 3081, 2978, 2911, 1732,

1642, 1478, 1403, 1254, 1223, 1174, 1079, 997, 965, 921, 791 cm^{-1}; **^{1}H NMR** 5.7 (1H, ddd, J = 6, 10.2, 16.2), 5.02 (1H, m), 4.96 (1H, dm, J = 16.2), 4.34 (1H, ddd, J = 4.6, 4.6, 11.4); 4.22 (1H, ddd, J = 3.9, 9.8, 11.4), 2.58 (2H total, 1H dd superimposed on a 1H multiplet, J = 1.6, 18.7), 2.24 (1H, dd, J = 11.2, 18.7), 1.92 (1H, ddq, J = 14.6, 4.3, 1.6), 1.63 (1H, ddt, J = 14.6, 9.2, 4.9).

(4S*)-4-Ethyl-tetrahydropyran-2-one (20) – The alkene **29** (2.00 g, 15.86 mmol) in *t*-BuOH (30 ml) was hydrogenated at atmospheric pressure over 5% Pd/C in the usual way. When hydrogen absorbtion ceased, the mixture was filtered through Celite, concentrated *in vacuo*, and distilled *via* kugelrohr to give the title compound (4S*)-**20** (1.255 g, 62%) as a colourless oil: b. p. 140°C (bath) / 0.7 mm Hg; **IR** 2984, 2878, 1736, 1462, 1402, 1256, 1223, 1176, 1089, 1071, 954, 798 cm^{-1}; **^{1}H NMR** 4.34 (1H, ddd, J = 10.8, 4.8, 4.0), 4.19 (1H, ddd, J = 11.3, 10.3, 3.5), 2.62 (1H, ddd, J = 17.4, 6.0, 1.5), 2.07 (1H, dd, J = 17.2, 10.0), 1.74-1.95 (2H, m), 1.46 (1H, ddt, J = 9.5, 7.4, 5.1), 1.33 (2H, dq, J = 7.0, 7.0), 0.87 (3H, t, J = 7.0).

PREPARATION OF RACEMIC 2,2-DIETHOXY-TETRAHYDROPYRANS 1, 10, 11, 12, AND 13

The ortholactones **1**, **10**, **11**, **12**, and **13** were prepared by the following general procedure. The products were easily hydrolysed and suffered minor deterioration on kugelrohr distillation but this could be minimised by using glassware which was pre-treated with methanolic KOH. In general the diethoxy ortholactones were contaminated with up to 10% of products derived from loss of ethanol during distillation as judged by high field ^{1}H NMR spectroscopy.

(5S*, 6R*)-2,2-Diethoxy-5,6-dimethyl-tetrahydropyran (1) – To *freshly prepared*[18] triethyloxonium tetrafluoroborate (3.45 g, 18. 1 mmol) was added a solution of racemic lactone **5** (2.09 g, 15.7 mmol) in *dry* dichloromethane (30 ml) under argon and the mixture stirred at room temperature for 24 h. The solution was cooled to -78°C and with rapid magnetic stirring, a solution of NaOEt in *anhydrous* ethanol (40 ml, 1.18 M, 47.1 mmol NaOEt) was added dropwise. After 45 min at -78°C the mixture was allowed to warm to room temperature whereupon the bulk of the solvent was removed *in vacuo* and the residue quenched with aqueous $NaHCO_3$. The organic product was extracted into ether, washed with water, and dried over K_2CO_3. Concentration *in vacuo* followed by kugelrohr distillation from a base-washed flask gave the racemic ortholactone **1** (2.24 g, 11.1 mmol, 71%) as a colourless oil. **IR** 2974, 2932, 2881, 1452, 1379, 1222, 1167, 1075, 1009 cm^{-1}; **^{1}H NMR** (90 MHz) 3.8-3.3 (5H total consisting of a 1H m and 2 overlapping q, J = 7), 2.2-1.1 (14H, m), 0.85 (3H, d, J = 7).

(4R*, 6R*)-2,2-Diethoxy-4,6-dimethyl-tetrahydropyran (10) - Prepared in 70% yield as described above: **IR** 2974, 2929, 1457, 1374, 1303, 1229, 1174, 1075, 1012 cm^{-1}; **^{1}H NMR** 3.73 (1H, ddq, J = 10.9, 6.5, 2.3), 3.63-3.45 (4H, m consisting of 4 overlapping dq), 1.96 (1H, ddd, J = 12, 4, 1.25), 1.74-1.94 (1H, m), 1.54 (1H, dm, J = 12), 1.21 (3H, t, J = 7), 1.19 (3H, d, J = 6.5), 1.18 (3H, t, J = 7), 0.91 (3H, d, J = 6.5), 1-1.25 (2H, m); **^{13}C NMR** 112.6 (0), 69.2 (1), 57.3 (2), 55.1 (2), 41.1 (2), 39.4 (2), 27.3 (1), 21.8 (3), 21.5 (3), 15.5 (3), 15.1 (3).

(5S*)-2,2-Diethoxy-5-ethyl-tetrahydropyran (11) - Prepared in 75% yield as described above: **IR** 2969, 2934, 2878, 1465, 1450, 1367, 1213, 1166, 1082, 993, 947 cm^{-1}; **^{1}H NMR** 3.76 (1H, ddd, J = 10.8, 4.3, 1.9), 3.57 (2H, q, J = 7.0), 3.51 (2H, dq, 7.0, 1.1), 3.36 (1H, dd, J = 10.8. 10.3), 1.97 (1H, ddd, J = 13, 4, 4), 1.77 (1H, dddd, J = 12.5, 8, 4, 1.8), 1.59 (1H, ddd, J = 11.2, 11, 4.5), 1.49 (1H, ddd, J = 14, 7, 3), 1.41-1.14 (3H, m), 1.2 (6H, t, J = 7.2), 0.89 (3H, t, J = 7.5).

(4S*)-2,2-Diethoxy-4-ethyl-tetrahydropyran (12) – Prepared in 54% yield as described above: **IR** 2972, 2933, 2878, 1461, 1444, 1382, 1318, 1281, 1216, 1194, 1153, 1082, 1054, 1018, 992, 963, 889, 815 cm^{-1}; **^{1}H NMR** 3.82 (1H, ddd, J = 6.6, 5.2, 1.5), 3.74-3.46 (5H, m), 2.03 (1H, ddd, J = 5.4, 3.7, 1.9), 1.75-1.50 (2H, m), 1.30-1.12 (10H, m), 0.9 (3H, t, J = 7.3).

(6R*)-2,2-Diethoxy-6-*n*-hexyl-tetrahydropyran (13) - Prepared in 73% yield as described above: **IR** 2931, 2860, 1458, 1443, 1227, 1202, 1180, 1070, 1000, 981 cm^{-1}; **^{1}H NMR** 3.60-3.38 (5H, m), 2.00-1.86 (1H, m), 1.70-1.55 (1H, m), 1.55-1.00 (14H, m), 1.14 (3H, t, J = 7.3), 1.12 (3H, t, J = 7.3), 0.81 (3H, distorted t, J = 6.9).

PREPARATION AND CHROMATOGRAPHIC RESOLUTION OF SPIROCYCLIC ORTHOLACTONES

(4R, 6R, 8S, 9R)-4-Phenyl-8,9-dimethyl-1,5,7-trioxaspiro[5.5]undecane (8) - To a solution of racemic ortholactone (5S*, 6R*)-**1** (0.82 g, 4.06 mmol) and (1R)-diol (7) (0.80 g, 4.81 mmol) in benzene (10 ml) was injected a pipette-full of HCl vapour. After stirring for 15 min at room temperature, TLC analysis [silica gel eluting with 5% ether in benzene] revealed two components in equal proportion. An excess of finely powdered anhydrous potassium carbonate was added and the mixture stirred for a further 30 min. After filtration and concentration, the residue was chromatographed on silica gel eluting with 5% ether in petroleum ether. The less polar component (0.400 g, 1.52 mmol, 37%) was obtained as a colourless oil after kugelrohr distillation [b. p. 180°C (bath) / 0.2 mm Hg] and identified as the title compound **8**: **IR**: 2967, 2930, 2878, 1454, 1381, 1261, 1233, 1220, 1164, 1125, 1061, 1000, 965, 897, 753, 700 cm^{-1} ; **^{1}H NMR** 7.40-7.21 (5H, m), 5.36 (1H, dd, J = 11.8, 2.8), 4.12 (1H, ddd, J = 11.8, 11.0, 2.5), 3.78 (1H, ddd, J = 11, 5.2, 1.4), 3.41 (1H, dq, J = 9.2, 6.1), 2.08-1.90 (2H, m), 1.78-1.28 (5H, m), 1.26 (3H, d, J = 6.1), 0.86 (3H, d, J = 6.3); **^{13}C NMR** 142.1 (0), 128.4 (1), 127.7 (1), 126.2 (1), 110.3 (0), 74.6 (1), 70.8 (1), 58.7 (2), 36.5 (1), 34.8 (2), 33.0 (2), 29.3 (2), 19.4 (3), 17.5 (q); **LRMS** (EI mode) m/z 262 (M^+, 2%), 218 (6), 176 (31), 156 (21), 117 (100), 118 (41), 104 (49), 91 (9), 84 (11), 77 (10), 56 (13), 49 (15), 41 (10).

(2R, 6R, 8R, 9S)-4-Phenyl-8,9-dimethyl-1,5,7-trioxaspiro[5.5]undecane (9) - The more polar component (0.350 g, 1.33 mmol, 33%), isolated from the experiment described above, was obtained as a colourless oil after kugelrohr distillation [b. p. 180°C (bath) / 0.2 mm Hg] and identified as the title compound **9**: **IR** 2966, 2930, 2881, 1453, 1381, 1261, 1237, 1164, 1128, 1062, 997, 970, 916, 752, 699 cm^{-1}; **^{1}H NMR** 7.4-7.2 (5H, m), 4.95 (1H, dd, J = 11.2, 2.3), 4.52 (1H, ddd, J = 12.5, 10, 2.5), 3.86 (1H, ddd, J = 11.2, 4.8, 1.1), 3.38 (1H, dq, J = 9.7, 6.2), 2.1-1.9 (2H, m), 1.8-1.2 (5H, m), 1.25 (3H, d, J = 6.2), 0.82 (3H, d, J = 6.6); **^{13}C NMR** 142.1 (0), 128.5 (1), 127.7 (1), 125.8 (1), 110.2 (0), 74.6 (1), 69.3 (1), 59.9 (2), 36.6 (1), 34.7 (2), 32.5 (2), 29.2 (2), 19.4 (3), 17.4 (3); **LRMS** (EI mode) m/z 262 (M^+, 1%), 176 (32), 156 (40), 129 (11), 117 (100), 104 (28), 91 (12), 84 (14), 77 (10), 69 (11), 56 (18), 41 (13).

(4R, 6R, 8S, 10R)-4-Phenyl-8,10-dimethyl-1,5,7-trioxaspiro[5.5]undecane (15) - **IR** 3065, 3031, 2958, 2928, 2876, 2837, 1603, 1496, 1454, 1378, 1306, 1255, 1220, 1165, 1131, 1074, 1040, 984 cm^{-1}; **^{1}H NMR** 7.42-7.15 (5H, m), 5.40 (1H, dd, J = 11.4, 2.7), 4.15 (1H, ddd, J = 13.5, 11, 2.6), 3.87-3.73 (2H, m), 2.08-1.91 (3H, m), 1.72 (1H, dm, J = 13.5), 1.63 (1H, dm, J = 13.5), 1.1-1.7 (2H, m), 1.28 (3H, d, J = 6.4), 0.94 (3H, d, J = 6.1); **^{13}C NMR** 142. 1 (0), 128.4 (1), 127.6 (1), 126.1 (1), 110.7 (0), 70.7 (1), 68.7 (1), 58.7 (2), 42.3 (2), 41.1 (1) 33.0 (2), 26.9 (1), 21.8 (3), 21. 4 (3); **LRMS** (EI mode) m/z 262 (M^+, 6%), 176 (21), 156 (24), 141 (10), 129 (14), 117 (100), 104 (55), 91 (8), 77 (11), 69 (9), 56 (9), 41 (14).

(2R, 6R, 8R, 10S)-4-Phenyl-8,10-dimethyl-1,5,7-trioxaspiro[5.5]undecane (16) - **IR** 2958, 2928,1453, 1388, 1375, 1317, 1256, 1218, 1198, 1171, 1132, 1085, 1052, 1034, 1007, 981, 922, 753, 699 cm^{-1}; **^{1}H NMR** 7.40-7.25 (5H, m),, 4.97 (1H, dd, J = 11.6, 2.6), 4.53 (1H, ddd, J = 10.8, 12.8, 2.4), 3.87 (1H, ddd, J = 11.0, 5.2, 1.35), 3.76 (1H, dq, 11.3, 2.3), 2.10-1.92 (3H, m), 1.75 (dm, J = 12.8), 1.59 (dm, J = 12.8), 1.24 (3H, d, J = 6.2), 1.22-1.14 (1H, m), 0.95-0.86 (1H, m), 0.91 (3H, d, J = 6.3); **^{13}C NMR** 141.9 (0). 128.5 (1), 127.7 (1), 125.9 (1), 110.6 (0), 69.3 (1), 68.7 (1), 59.9 (2), 42.1 (2), 41.1 (2), 32.5 (2), 26.7 (1), 21.7 (3), 21.4 (3); **LRMS** (EI mode) m/z 262 (M^+, 2%), 176 (21), 156 (41), 141 (21), 129 (17), 117 (100), 104 (29), 91 (12), 77 (14), 69 (15), 56 (16), 41 (18).

(4R, 6R, 9S)-4-Phenyl-9-ethyl-1,5,7-trioxaspiro[5.5]undecane (18) - **IR** 2960, 2874, 1451, 1380, 1258, 1218, 1196, 1159, 1061, 991, 943, 908, 880, 751, 699 cm^{-1}; **^{1}H NMR** 7.39-7.25 (5H, m), 5.27 (1H, dd, J = 11.4, 2.5), 4.18 (1H, ddd, J = 12.5, 11.4, 2.3), 3.80 (2H, apparent ddd, J = 11.4, 4.6, 2), 3.48 (1H, dd, J = 11.6, 11.0), 2.1-1.9 (2H, m), 1.85-1.1 (7H, m), 0.91 (3H, t, J = 7.3); **^{13}C NMR** 141.8 (0), 128.4 (1), 127.7 (1), 126.1 (1), 110.1 (0), 70.7 (1), 67.9 (2), 58.8 (2), 36.3 (1), 33.8 (2), 32.6 (2), 26.0 (2), 24.5 (2), 11.6 (3); **LRMS** (EI mode) m/z 262 (M^+, 6%), 232 (6), 176 (27), 156 (29), 118 (55), 117 (100), 115 (12), 105 (23), 104 (71), 103 (27), 78 (24), 77 (21), 70 (31), 69 (19), 56 (27), 55 (23), 51 (15), 41 (28).

(2R, 6R, 9R)-4-Phenyl-9-ethyl-1,5,7-trioxaspiro[5.5]undecane (19) - **IR** 2961, 2874, 1451, 1382, 1371, 1259, 1215, 1161, 1127, 1063, 1012, 987, 945, 918, 880, 752, 699 cm^{-1}; **^{1}H NMR** 7.40-7.27 (5H, m), 5.03 (1H, dd, J = 11.7, 2.7), 4.46 (1H, ddd, J = 12.7, 11.0, 2.7), 3.90-3.79 (2H, m), 3.35 (1H, dd, J = 10.4, 10.6), 2.1-1.9 (2H, m), 1.8-1.4 (4H, m), 1.3-1.05

(3H, m), 0.88 (3H, t, J = 7.3); **^{13}C NMR** 142.0 (0), 128.5 (1), 127.7 (1), 126.0 (1), 110.1 (0), 69.5 (1), 68.1 (2), 59.9 (2), 36.5 (1), 34.0 (2), 32.5 (2), 26.1 (2), 24.5 (2), 11.6 (3); **LRMS** (EI mode) m/z 262 (M^+, 4%), 232 (8), 176 (26), 156 (36), 118 (55), 117 (100), 115 (11), 105 (20), 104 (65), 103 (25), 78 (23), 77 (19), 70 (32), 69 (19), 56 (27), 55 (23), 51 (13), 41 (29).

(4R, 6R, 10S)-4-Phenyl-10-ethyl-1,5,7-trioxaspiro[5.5]undecane (21) – **IR** 3064, 3031, 2960, 2930, 2878, 1456, 1383, 1280, 1218, 1152, 1070, 1037, 984, 937, 873, 812, 753, and 699 cm^{-1}; **^{1}H NMR** 7.4-7.2 (5H, m), 5.33 (1H, dd, J = 11.8, 2.9), 4.17 (1H, ddd, J = 12.5, 11.0, 2.5), 3.89 (1H, ddd, J = 15.4, 6.5, 2.4), 3.81 (1H, ddd, J = 15.4, 7.1, 1.8), 3.69 (1H, ddd, J = 17.8, 15.4, 3.5); 2.1-1.9 (2H, m), 1.86-1.6 (4H, m), 1.4-1.2 (3H, m), 0.9 (3H, t, J = 7.5); **^{13}C NMR** 143.1 (0), 130.0 (1), 129.5 (1), 128.0 (1), 112.0 (0), 72.4 (1), 64.5 (2), 60.3 (2), 42.3 (2), 35.0 (1), 34.2 (2), 32.8 (2), 30.9 (2), 12.3 (3); **LRMS** (CI mode, NH_3) m/z 264 (M^++2, 26%), 263 (M^++1, 100%), 156 (7), 146 (22), 117 (14).

(2R, 6S, 10R)-4-Phenyl-10-ethyl-1,5,7-trioxaspiro[5.5]undecane (22) – **IR** 3064, 3031, 2960, 2927, 2872, 1605, 1497, 1454, 1384, 1278, 1214, 1152, 1071, 981, 939, 872, 816, 752, and 698 cm^{-1}; **^{1}H NMR** 7.43-7.27 (5H, m), 5.01 (1H, dd, J = 11.8, 2.9), 4.48 (1H, ddd, J = 17.8, 15.4, 3.5), 3.94-3.84 (2H, m), 3.66 (1H, ddd, J = 10.6, 9.2, 2.1), 2.10-1.92 (2H, m), 1.9-1.68 (2H, m), 1.34-1.16 (5H, m), 0.88 (3H, t, J = 7.4); **^{13}C NMR** 142.0 (0), 128.7 (1), 126.8 (1), 125.6 (1), 111.0 (0), 68.7 (1), 62.5 (2), 60.5 (2), 41.0 (2), 32.5 (1), 32.0 (2), 31.0 (2), 29.5 (2), 11.5 (3); **LRMS** (CI mode, NH_3) 264 (M^++2, 26%), 263 (M^++1, 100%), 156 (9), 146 (13), 117 (9).

(4R, 6R, 8S)-4-Phenyl-8-*n*-hexyl-1,5,7-trioxaspiro[5.5]undecane (24) – **IR** 2931, 2857, 1455, 1379, 1260, 1218, 1203, 1062, 1027, 975, 699 cm^{-1}; **^{1}H NMR** 7.42-7.22 (5H, m), 5.37 (1H, dd, J = 11.7, 2.7), 4.13 (1H, ddd, J = 12.6, 10.8, 2.7), 3.78 (1H, ddd, J = 10.8, 4.7, 1.0), 3.68-3.56 (1H, m), 2.1-1.2 (18H, m), 0.91 (3H, distorted t, J = 6.7); **^{13}C NMR** 142 (0), 128.4 (1), 127.6 (1), 126.2 (1), 110.4 (0), 73.2 (1), 70.7 (1), 58.6 (2), 36.2 (2), 34.3 (2), 33.0 (2), 32.0 (2), 30.1 (2), 29.6 (2), 26.0 (2), 22.8 (2), 20.3 (2), 14.3 (3); **LRMS** (EI mode) m/z 318 (M^+, 2%), 233 (6), 212 (4), 176 (10), 118 (22), 117 (100), 105 (15), 104 (60), 103 (20), 99 (55), 78 (18), 77 (13), 71 (26), 70 (16), 55 (20), 43 (25), 41 (26).

(2R, 6R, 8R)-4-Phenyl-8-*n*-hexyl-1,5,7-trioxaspiro[5.5]undecane (25) - **IR** 2931, 2857, 1454, 1379, 1262, 1249, 1202, 1119, 1040, 970. 912, 734, 698 cm^{-1}; **^{1}H NMR** 7.45-7.2 (5H, m), 4.96 (1H, dd, J = 12, 3), 4.52 (1H, ddd, J = 12.5, 12, 3), 3.85 (1H, ddd, J = 11, 5, 1), 3.70-3.55 (1H, m), 2.10-1.90 (2H, m), 1.90-1.20 (16H), 0.89 (3H, distorted t, J = 6.9); **^{13}C NMR** 141.9 (0), 128.4 (1), 127.7 (1), 125.9 (1), 110.3 (0), 73.0 (1), 69.4 (1), 59.8 (2), 36.1 (2), 34.1 (2), 32.4 (2), 32.0 (2), 30.9 (2), 29.5 (2), 25.9 (2), 22.8 (2), 20.1 (2), 14.2 (3); **LRMS** (EI mode) m/z 318 (M^+, 1%), 233 (6), 212 (12), 176 (13), 118 (25), 117 (100), 105 (13), 104 (37), 103 (15), 99 (41), 78 (13), 77 (12), 71 (20), 70 (13), 55 (16), 41 (22).

HYDROLYSIS OF SPIROCYCLIC ORTHOLACTONES

The hydrolysis of the spirocyclic ortholactone **8** exemplifies the general procedure used throughout. In all cases the yields in the hydrolysis step were 90±5% of distilled product.

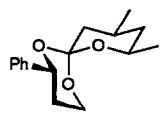
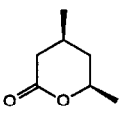
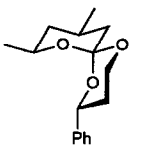
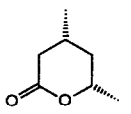
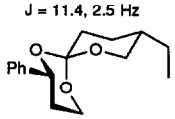
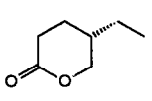
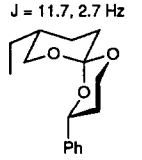
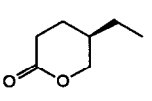
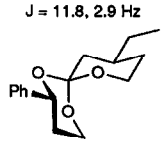
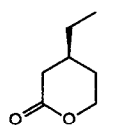
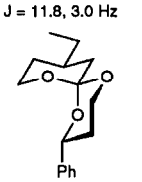
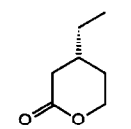
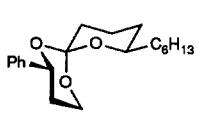
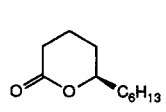
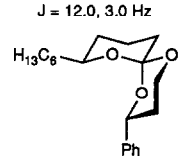
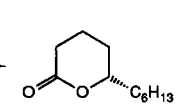
The spirocyclic ortholactone **8** (79 mg, 0.30 mmol) in THF (4 ml) containing one drop of 2M HCl was allowed to stand at room temperature until TLC analysis indicated complete consumption of starting material (*ca.* 1 h). Excess solid potassium carbonate was then added and the mixture stirred for a further 30 min whereupon the mixture was filtered and concentrated. The residue was chromatographed on a short column of silica gel eluting with 50% ether in petroleum ether to give lactone (5S, 6R)-**5** (30 mg, 0.27 mmol, 90% yield after kugelrohr distillation) followed by recovered diol **7**. After one recrystallisation the recovered diol **7** (90%) gave the same m. p. and optical rotation as that prepared from the epoxide as desribed above. The resolved lactone (5S, 6R)-**5**, $[\alpha]_D$ (20°C) +12.9° (*c.* 1.5 in $CHCl_3$); lit.[1,7] $[\alpha]_D$ +13.1° (*c.* 4.86 in $CHCl_3$), gave identical high field ^{1}H NMR and IR spectra as those recorded on racemic **5**.

Hydrolysis of spirocyclic ortholactone **9** - Hydrolysis of **9** (107 mg, 0.41mmol) as desribed above gave (5R, 6S)-**5** (41 mg, 0.37 mmol. 91%) identical with the (5S, 6R)-isomer by NMR and IR spectroscopy but with opposite sign of rotation: $[\alpha]_D$ (20°C) -12.3° (*c.* 0.85 in $CHCl_3$).

Optical rotation data for the resolved lactones are given in the Table.

TABLE

Optical rotation and selected NMR data for chromatographically resolved spirocyclic ortholactones and their corresponding hydrolysis products

Less Polar Diastereoisomer[a]		More Polar Diastereoisomer[a]	
Ph-CH δ 5.40, dd J = 11.4, 2.7 Hz 	 (4S, 6R)-**14** Lit.[b] $[\alpha]_D$ +6.15° (c. 0.521 MeOH) Found $[\alpha]_D$ +6.82° (c. 0.4 MeOH)	Ph-CH δ 4.97, dd J = 11.6, 2.6 Hz 	 (4R, 6S)-**14** Lit.[b] $[\alpha]_D$ -6.18° (c. 0.534 MeOH) Found $[\alpha]_D$ -6.68° (c. 0.627 MeOH)
(4R, 6R, 8R, 10S)-**15** $[\alpha]_D$ +60.5° (c. 3.8 $CHCl_3$)		(2R, 6R, 8S, 10R)-**16** $[\alpha]_D$ +22.5° (c. 2.0 $CHCl_3$)	
Ph-CH δ 5.27, dd J = 11.4, 2.5 Hz 	 (5S)-**17** $[\alpha]_D$ -3.3° (c. 2.0 $CHCl_3$)	Ph-CH δ 5.03, dd J = 11.7, 2.7 Hz 	 (5R)-**17** Lit.[c] $[\alpha]_D$ +3.7° (c. 3.4 $CHCl_3$) Found $[\alpha]_D$ +3.3° (c. 3.6 $CHCl_3$)
(4R, 6R, 9S)-**18** $[\alpha]_D$ +77.5° (c. 3.6 $CHCi_3$)		(2R, 6R, 9R)-**19** $[\alpha]_D$ +34.0° (c. 3.6 $CHCl_3$)	
Ph-CH δ 5.35, dd J = 11.8, 2.9 Hz 	 (4S)-**20** Lit.[d] $[\alpha]_D$ -28.6° (c. 8.3 $CHCl_3$) Found $[\alpha]_D$ -27.2° (c. 8.2 $CHCl_3$)	Ph-CH δ 5.01, dd J = 11.8, 3.0 Hz 	 (4R)-**20** $[\alpha]_D$ +27.8° (c. 8.1 $CHCl_3$)
(4R, 6R, 10S)-**21** $[\alpha]_D$ +73.3° (c. 2.5 $CHCl_3$)		(2R, 6R, 10R)-**22** $[\alpha]_D$ +37.2° (c. 2.8 $CHCl_3$)	
Ph-CH δ 5.37, dd J = 11.7, 2.7 Hz 	 (6R)-**23** $[\alpha]_D$ +40.5° (c. 0.02 $CHCl_3$)	Ph-CH δ 4.96, dd J = 12.0, 3.0 Hz 	 (6S)-**23** $[\alpha]_D$ -39.5° (c. 0.012 $CHCl_3$)[e]
(4R, 6R, 8R)-**24** $[\alpha]_D$ +98.6° (c. 0.8 $CHCl_3$)		(2R, 6R, 8S)-**25** $[\alpha]_D$ +49.5° (c. 1.5 $CHCl_3$)	

[a] Relative polarity by t.l.c. analysis on silica gel eluting with 5% Et_2O in hexane.

[b] Carroll, F. I.; Mitchell, G. N.; Blackwell, J. T.; Sobti, A.; Meck, R. *J. Org. Chem.*, **1974**, *39*, 3890 [90% ee].

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[e] The $[\alpha]_D$ for 6-*n*-hexyl-valerolactone has not been recorded. The (6S)-*n*-heptyl and *n*-pentyl analogues gave $[\alpha]_D$ of -46° and -61° respectively (c. 1.0-1.3 MeOH): Mosandl, A.; Gessner, M. Z. *Lebensm. Unters. Forsch.*,**1988**, *187*, 40; [*Chem. Abs.*, *101*:133860s].

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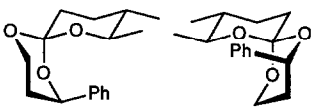
2. Graphical depiction of stereochemistry follows the convention proposed by Maehr: solid and broken *wedges* denote absolute configuration; solid and broken *lines* denote relative configuration in racemates. H. Maehr *J. Chem. Ed.*, **1985**, *62*, 14.

3. The homochiral diol **7** was chosen as the resolving agent because it was readily purified by crystallisation (m. p. 64-66°C) and therefore easily recovered; and because it contained a UV chromophore to facilitate HPLC analysis. It was easily prepared on a substantial scale by regioselective reductive cleavage of the oxiran ring of (1R, 2S)-1-phenyl-2-(hydroxymethyl)oxiran (**6**) [procedure: Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B. *J. Org. Chem.*, **1982**, *47*, 1378] derived from Sharpless asymmetric epoxidation of cheap cinnamyl alcohol [Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.*, **1987**, *109*, 5765]. Oxiran **6** and its antipode are both commercially available (Fluka) but expensive.

4. For a monograph on the preparation and synthetic applications of orthoesters and ortholactones see De Wolfe, R. H. *Carboxylic Ortho Acid Derivatives*; Academic Press, New York, 1970.

5. The reaction of (1R)-**7** and (5S*, 6R*)-**1** is a thermodynamically controlled process which can, in principle, give rise to four spirocyclic ortholactones: the observed products **8** and **9** as well as the two diastereoisomers **i** and **ii**. The absence of **i** and **ii** reflects the penalty incurred by axial disposition of the aryl ring. See reference 6 for an analysis of substiuent effects on spiroacetal conformation and configuration.



I II

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