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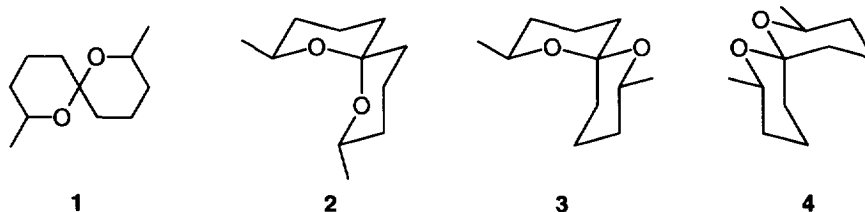
(2S,6S,8S)-2,8-Dimethyl-1,7-dioxaspiro[5.5]undecane: A Natural Spiroacetal Lacking Anomeric Stabilisation

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Abstract: The absolute stereochemistry of the non-anomerically stabilised spiroacetal, (Z,Z)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane, **4** which is a significant component of the pheromonal gland secretion of the cucumber fly (*Bactrocera cucumis* French) is shown to be (2S,6S,8S) by synthesis of its enantiomer, and chiral gas chromatographic analyses.

Diastereomers of 2,8-dimethyl-1,7-dioxaspiro[5.5]undecane **1** are the major components of the pheromonal gland secretion of the cucumber fly (*Bactrocera cucumis* French),¹ a significant pest of horticulture in parts of Queensland. Evaluation of these pheromonal secretions as insect control agents necessitated determination of both the relative and absolute stereochemistries of the diastereomers. The (E,E) diastereomer² (~60% of volatile secretion) was shown¹ to be the (2S,6R,8S) isomer **2** (>99% e.e.), which was accompanied by the racemic (E,Z) isomer **3** (~5%). A third diastereomer (~8%) suspected to be the previously uncharacterised (Z,Z) isomer **4** was confirmed¹ as such by synthesis, careful separation under non-isomerising conditions, and spectral analyses. This

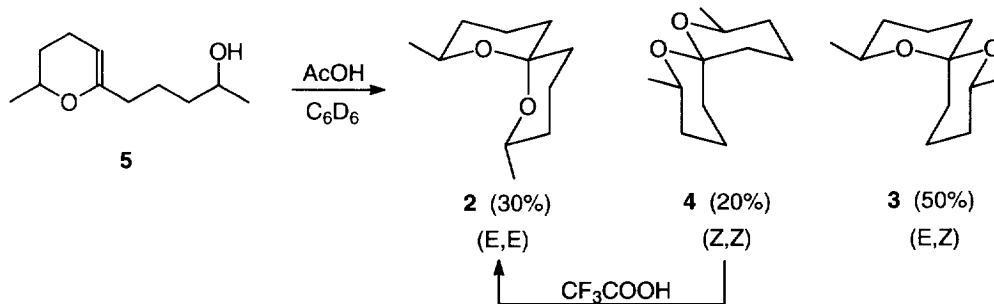


isomer **4** has been estimated to be 4.8 and 2.4 kcal/mole greater in free energy, than **2** and **3** respectively.³ Because of the interesting nature of this non-anomerically stabilised spiroacetal **4**, we undertook determination of its absolute stereochemistry to establish its relationship with the more abundant (2S,6R,8S)-**2**. On biosynthetic grounds we suspected that the natural (Z,Z) isomer **4** was the (2S,6S,8S) enantiomer (as drawn above), sharing

the same absolute configurations at C₂ and C₈ with the major (2*S*,6*R*,8*S*) isomer **2** but differing at the spiro-centre C₆, such change requiring only a formal acid catalysed epimerisation.

Chiral gas chromatographic analyses of the natural extract showed a single peak for the first eluting (E,E) diastereomer (2*S*,6*S*,8*S*)-**2**, two equally intense peaks for the (racemic) (E,Z) isomer **3**, and a sharp peak for the last eluting (Z,Z) isomer **4**. Analyses of the three racemic diastereomers (see later) showed that all three were separated into enantiomeric pairs, and consequently the natural (Z,Z) isomer was highly enantiomerically pure (>99% e.e.), just as the natural (E,E) was.¹ Treatment of the natural extract with dilute aqueous acid led to the disappearance of the (Z,Z) peak, and no new volatile component emerged. The only interpretation was that any spiroacetal resulting from isomerisation was coincident with the already present (2*S*,6*R*,8*S*) isomer **2**, and therefore the (Z,Z) isomer **4** was (2*S*,6*S*,8*S*). However, because of the disparity in the relative amounts of the (E,E) and (Z,Z) isomers (*ca.* 60:8), and other practical difficulties, a more direct demonstration of the chirality of the (Z,Z) isomer was required.

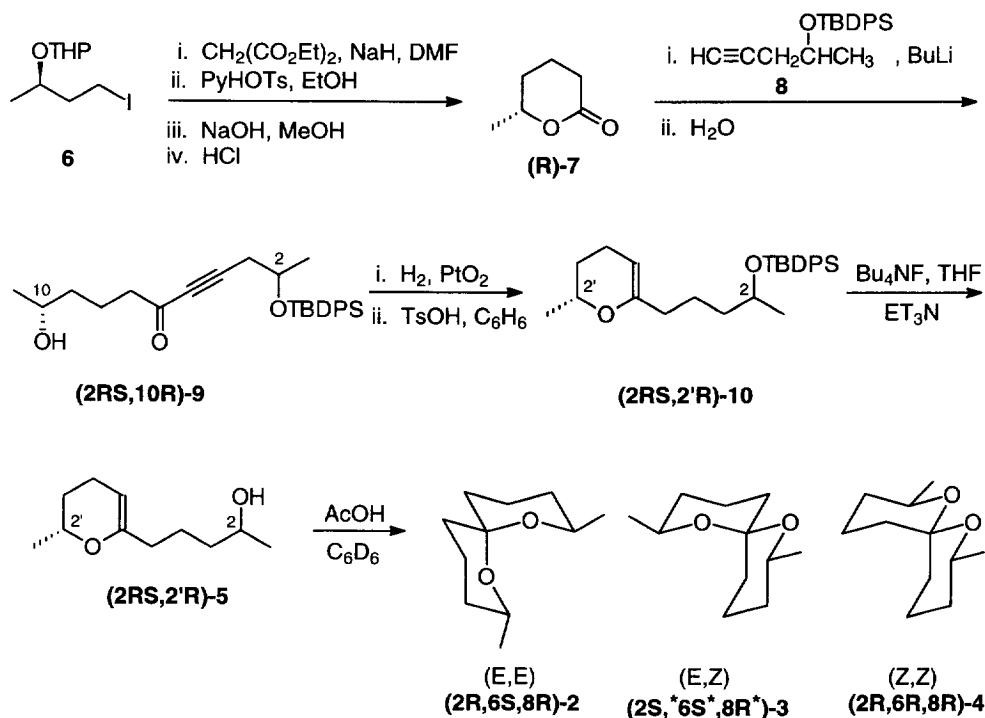
Recently Deslongchamps⁴ reported that acid induced cyclisation of racemic dihydropyran **5** could be regulated to provide different mixtures of the diastereomers **2**, **3** and **4**. In particular, use of acetic acid in benzene provided significant amounts of the (Z,Z) isomer **4** (kinetic control) which however, underwent conversion to the (E,E) isomer **2** on exposure to trifluoroacetic acid (thermodynamic control) (Scheme 1). (Isomerisation of either **2** or **4** to **3** would require a configurational change at one of the formal secondary alcohol centres.)



Scheme 1

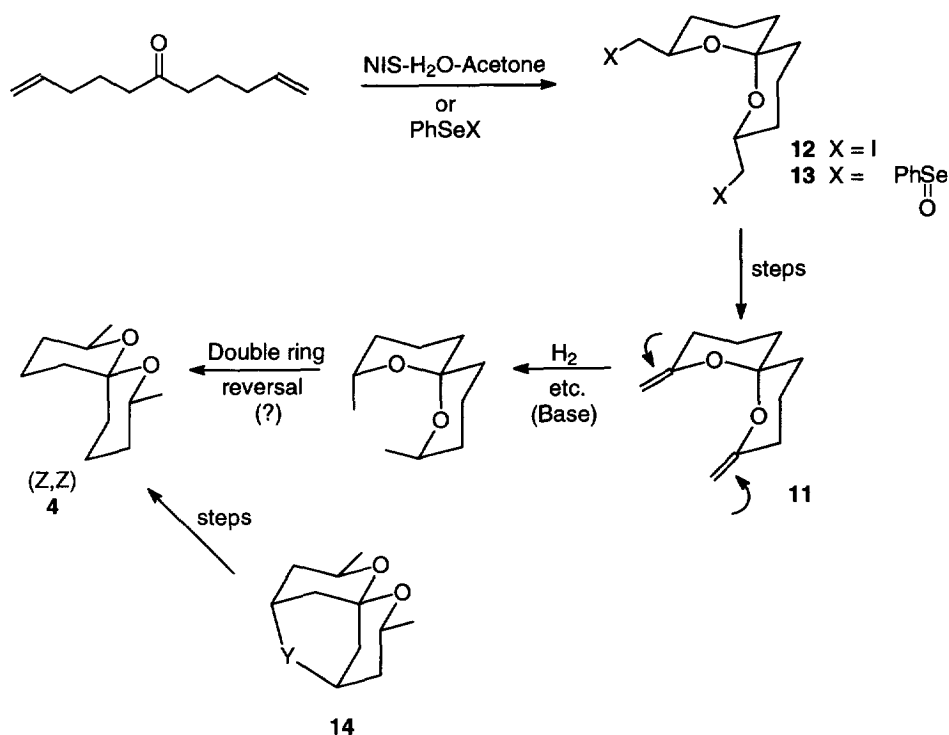
Repetition of this reaction, essentially as described,⁴ provided a mixture of the (E,E), (E,Z) and (Z,Z) diastereomers (**2**, **3** and **4** respectively) which were separated into enantiomeric pairs on a β -cyclodextrin column as described above. Consequently, utilisation of **5** with one homochiral centre, under kinetically controlled cyclisation conditions, would provide a single enantiomer of (Z,Z) isomer **4** (and also of (E,E) isomer **2**) along with racemic (E,Z) isomer **3**. This was accomplished⁵ as shown in Scheme 2, commencing with (R)-3-tetrahydropyran-2'-yloxy-1-iodobutane **6**, readily available from natural polyhydroxybutyrate.⁶ With the availability of the

(2R,6R,8R) isomer of **4** as part of the spiroacetal mixture (Scheme 2), chiral GC analyses, including co-elution studies, confirmed the natural (*Z,Z*) isomer was (2S,6S,8S) **4**, as we had suspected. The proportion of the (2S,6S,8S) isomer **4** relative to the (2S,6R,8S) isomer **2** in the natural secretion exceeds that expected on thermodynamic grounds ($\Delta\Delta F \cong 4.8$ kcal/mol)³ but lower than that reported⁴ for kinetically controlled cyclisation (EE:ZZ = 3:2) of dihydropyran **5** which therefore involves an early transition state in which the unfavourable features of **4** (relative to **2**) are not advanced.⁴



Scheme 2

Metal ion mediated cyclisation of the hydrate of **5** or the related open-chain keto-diol may be regulated in a similar way to provide a non-equilibrium level of the (*Z,Z*) isomer **4**. Rational approaches to the diastereomerically pure (*Z,Z*) isomer are being explored. For example, hydrogenation of the *bis-exo*-methylene spiroacetal **11** under basic conditions would appear to be a promising route to the (*Z,Z*) isomer (Scheme 3), but acquisition of **11**, by elimination from the diiodide **12** or *bis*-selenoxide **13** have not been straight-forward.⁷ Alternative approaches employing a structurally locked intermediate (e.g. **14**) from which Y may finally be removed, again under basic conditions, are being investigated.⁸



Scheme 3

We suggested¹ previously that the (Z,Z) diastereomer in *B. cucumis* glandular secretions may have served as a "clock" to indicate to conspecific fruit flies the age of the released chemical signal. This was based on an assumption that the isomerisation of the (Z,Z) diastereomer to the (E,E) isomer would be relatively facile, once it was released, but the current information on the acidic conditions necessary to induce this isomerisation indicates our suggestion is somewhat unlikely.

EXPERIMENTAL

(+)-5-Methyl- δ -valerolactone, (+)-7: 4-Acetylbutyric acid (2.6 g; 20 mmol) was reduced with NaBH_4 (378 mg, 10 mmol) and converted to the title lactone in the reported manner.⁹ Distillation afforded the title lactone (1.4 g, 70%) (Kugelrohr, oven temperature 120°C, 0.02 mBar). Lit.⁹ 112–113°C/21 mBar. $^1\text{H NMR}$ (CDCl_3 , 200 MHz) δ_{H} 1.37 (d, $J = 6$ Hz, 3H), 1.54 (m, 6H), 1.92 (m, 3H), 2.50 (m, 2H), 4.47 (m, 1H). $^{13}\text{C NMR}$ (CDCl_3 , 50 MHz) δ_{C} 17.7, 20.9, 28.4, 28.8, 76.2, 171.4. The $^1\text{H NMR}$ spectrum matched that reported for the (R)-isomer.¹⁰

(R)-5-Methyl- δ -valerolactone, (R)-7: Diethylmalonate (608 mg, 3.8 mmol) in dry DMF (2.5 ml) was slowly

added to a stirred suspension of NaH (91 mg, 3.8 mmol) in a dry benzene-DMF mixture (4 ml: 5 ml), under N₂. After 0.5 h, (R)-3-tetrahydropyran-2'-yloxy-1-iodobutane **6** (713 mg, 3.8 mmol) in dry DMF (2.5 ml) was added. The mixture was heated at 100°C for 8 h, and after cooling to 20°C, was treated with saturated aqueous NH₄Cl and then extracted with ethyl acetate. The organic phase was dried and the solvent removed (rotary evaporator) to provide a yellowish oil (640 mg, 80%) which was dissolved in ethanol (30 ml) containing pyridinium p-toluene-sulfonate (~30 mg), and then heated at 55°C for 4 h. The mixture was diluted with ethyl acetate (20 ml) and then washed with 1 M aqueous NaOH. The organic phase was evaporated to yield an oil (450 mg, 97%) which was not characterised (other than by GC-MS) but added to MeOH (5 ml) containing NaOH (757 mg, 19 mmol) and heated under reflux for 2 h. After cooling, the reaction mixture was diluted with water and acidified with HCl to pH 2, and then stirred for 19 h at 20°C. Saturated aqueous NaCl was added, and the whole extracted with ether which was separated and the residue purified by column chromatography (EtOAc-hexane, silica) to yield (R)-**7** (196 mg, 89%). This product had identical spectroscopic properties to the racemate described above, which was not separable into enantiomers on a Lipodex A column. Consequently the e.e. of this lactone was not determined directly, but was >99% as judged by the e.e. of the spiroacetals derived from it. An optical rotation of $[\alpha]_D^{20} +37.2$ (c = 1.825, EtOH) has been reported¹⁰ for the (R)-isomer obtained by a very similar route. The (R)-isomer (R)-**7** and its racemate (+)-**7** were transformed to spiroacetal mixtures by the route shown in Scheme 2 for the (R)-isomer and described below for the racemate.

4-[(t-Butyl)diphenylsilyloxy]pent-1-yne, 8, was synthesised in the reported fashion,⁴ and converted to its lithio derivative and reacted with the racemic 5-methyl- δ -valerolactone **7** in the described way.⁴ The resulting **2-[(t-Butyl)diphenylsilyloxy]-10-hydroxydec-4yn-6-one, 9**, had ¹H NMR spectra as reported.⁴ ¹³C NMR (CDCl₃, 50 MHz) δ_c 19.1, 20.0, 23.0, 23.4, 26.8, 29.4, 38.2, 45.1, 67.2, 67.4, 82.2, 91.2, 127.6, 129.7, 133.7, 135.7, 187.9. **5-(3',4'-Dihydro-2'-methyl-2H-pyran-6'-yl)pentane-2-ol, 5**: Hydrogenation of the ynone **9** and acid catalysed dihydropyran formation to yield **10** were conducted as described.⁴ Removal of the silyl protection group was achieved using 1M ⁿBu₄NF in dry THF containing Et₃N and after chromatography, **5** was obtained, and its ¹H NMR spectrum matched that reported.⁴ ¹³C NMR (CDCl₃, 50 MHz) δ_c 20.8, 21.2, 23.7, 29.5, 34.7, 39.0, 67.5, 71.5, 94.7, 154.5. LRMS (GC-MS): 184 (M⁺, 6.6%), 169 (M-CH₃, 6.3), 166 (M-H₂O, 5.8), 151 (7.2), 125 (17.2), 115 (61.7), 112 (37.0), 99 (13.8), 97 (91.7), 83 (20.9).

(E,E)-, (E,Z)- and (Z,Z)-2,8-Dimethyl-1,7-dioxaspiro[5.5]undecane, 2, 3 and 4: A solution of the above dihydropyran, **5** (184 mg, 1 mmol) in benzene-d₆ (2 ml) was treated with AcOH (~3 drops) and the cyclisation was monitored by capillary GC, GC-MS and NMR spectroscopy. After ca. 10 h, a diastereomeric ratio of (E,E):(Z,Z):(E,Z) = 3:2:5 was measured and agreed with that reported.⁴ The ¹H, ¹³C NMR spectra and GC-MS data for these diastereomers have been discussed previously,¹ and agree with the data recently reported⁴ and obtained in the present work. The enantiomeric pairs of each of the diastereomers were separated by chiral gas chromatography analysis conducted on a 50 metre CP- β -cyclodextrin-2,3,6-M-19 fused silica column. The

diastereomeric mixture obtained by acid cyclisation of the dihydropyran, (R)-**5**, derived from (R)-5-methyl- δ -valerolactone (R)-**7**, furnished the (2R,6S,8R) and (2R,6R,8R) enantiomers (>99% e.e., chiral GC analysis) of the (E,E) and (Z,Z) systems respectively, thus permitting determination of elution orders. The natural (Z,Z) isomer, (2S,6S,8S)-**4** elutes before its enantiomer, while (2S,6R,8S)-**2** (previously shown¹ to be the natural (E,E) isomer) elutes after its enantiomer.

Fruit-Fly Glandular Extract: Dissection of sexually mature male cucumber flies (*B. cucumis* French) was conducted as previously described.¹

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