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From (R)-(+)-Pulegone to (2S,4R,6R,8S)-2,4,8-Trimethyl-1,7-dioxaspiro[5.5]undecane - A Unique Spiroacetal from the Insect Kingdom

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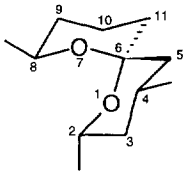
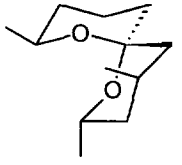
Abstract: Enantioselective syntheses of the unique, insect-derived spiroacetal, (2S,4R,6R,8S)-2,4,8-trimethyl-1,7-dioxaspiro[5.5]undecane and some diastereomers, utilising (R)-(+)-pulegone as chiral source-material, and asymmetric dihydroxylation as a key step, are described.

Recently, we reported[1] that the major component of the abdominal gland secretion of the shield bug, *Cantao parentum* (White) was (2S,4R,6R,8S)-2,4,8-trimethyl-1,7-dioxaspiro[5.5]undecane (**1**), the first example from the insect kingdom of a branched carbon-chain spiroacetal. Our synthesis[1] of (**1**) also led to its C-4 epimer (**2**), because the free radical addition of the (S)-(+)-lactate derived iodide (**3**) to ethyl crotonate to provide intermediate (**4**) was not diastereoselective.



(1)



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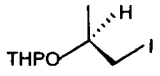

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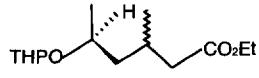
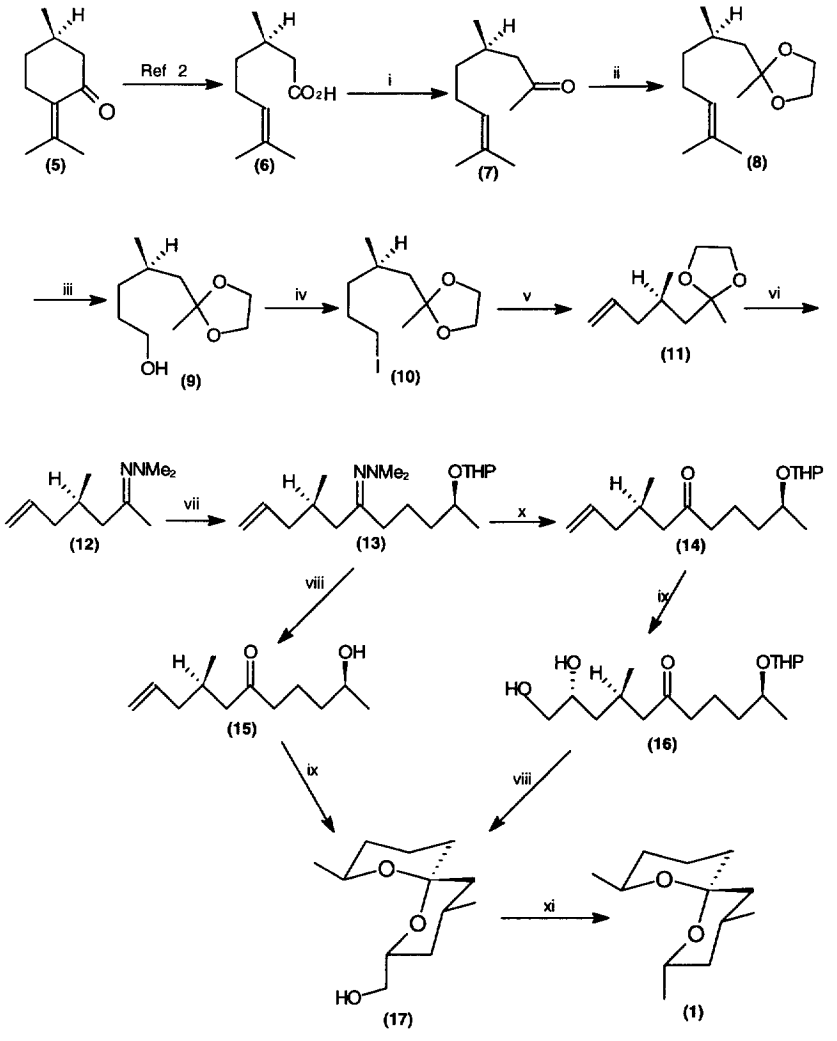


(4)

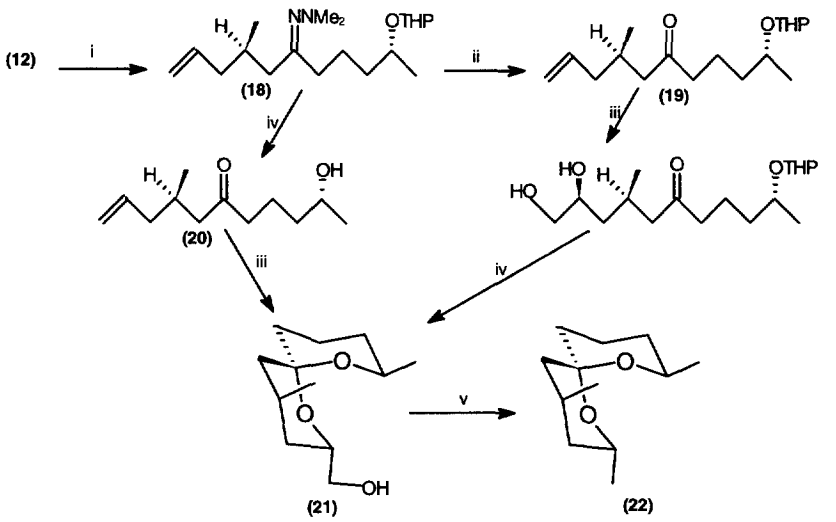
Control of the absolute stereochemistry at C-4 in (**1**) appeared possible utilising the chiral pool component (R)-(+)-pulegone (**5**) and the derived[2] (R)-(+)-citronellic acid (**6**). The methyl ketone (**7**)[3] derived from (**6**) (Scheme 1) was protected as the ethylene ketal (**8**) before ozonolysis and borohydride reduction to yield alcohol (**9**), which was converted to the iodide (**10**) via the tosylate. Treatment with $K^+ {}^-OBu^t$ smoothly provided alkene (**11**) which was deprotected, and transformation to the N,N-dimethylhydrazone (**12**) set the stage for alkylation with (S)-3-(tetrahydropyran-2′-yloxy)-1-iodobutane[4] to provide (**13**). Selective deprotection (silica) provided the intermediate (**14**), whereas fully deprotected (**15**), resulted from treatment of (**13**) with 10% aqueous HCl. The absolute stereochemistry at the positions that would become C-4 and C-8 in (**1**) were now installed. Creation of the correct chirality at C-2 (of (**1**)) was based on asymmetric



Scheme 1 i, MeLi/-78°C; ii, $HOCH_2CH_2OH$/TsOH; iii, O_3/-78°C, $NaBH_4$; iv, a) TsCl/-15°C, b)NaI; v, ^tBuOk; vi, a) 30%AcOH/80°C, b) $H_2NN(CH_3)_2$/AcOH; vii, LDA/-78°C, (*S*)-(Tetrahydropyranyl-oxy)-butyl iodide; viii,10%HCl; ix, AD-mix β/0°C; x, SiO_2; xi, a)TsCl/-15°C, b) $LiAlH_4$

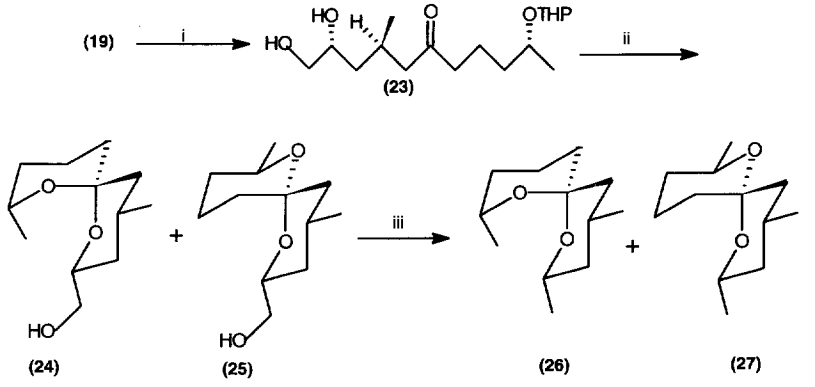
dihydroxylation,[5] with AD-mix β, of either (**14**) or (**15**), followed by spirocyclisation to provide the hydroxymethyl precursor (**17**) which on reduction (tosylation, $LiAlH_4$) led to (**1**) (ee ≈ 99.5%) whose ^1H, ^{13}C nmr and mass spectra matched those previously reported.[1]

Adaptation of the procedures in **Scheme 1** permitted acquisition of diastereomers of (**1**), several of which appeared to be minor components of the insect secretion. For example, alkylation of hydrazone (**12**) with (R)-3-(tetrahydropyran-2′-yloxy)-1-iodobutane[4] yielded (**18**), (the epimer of (**14**)) which could again be selectively or fully deprotected to furnish (**19**) and (**20**) respectively. Treatment of either with AD-Mix-α, and cyclisation provided predominantly the hydroxymethyl compound (**21**), although use of (**19**) appeared more efficient. Reduction of (**21**) provided (**22**), the enantiomer of (**2**), with ee ≈ 99.5%, $[\alpha]_D^{23} = +71$ (**Scheme 2**).



Scheme 2 i, LDA/-78°C, (R)-3(Tetrahydropyranyloxy)-butyl iodide; ii, SiO_2; iii, AD-mix a/0°C; iv, 10%HCl; v, a) TsCl/-15°C, b)$LiAlH_4$

Intermediates (**19**) and (**20**) were also treated with AD-mix-β to provide (**23**) (**Scheme 3**) and then the hydroxymethyl-isomers (**24**) and (**25**), reduction of which yielded the spiroacetals (**26**) and (**27**) (*ca* 55:45), which are epimeric at the spiro-centre. Relief of the 1,3-diaxial CH_3-O interaction in (**26**) requires loss of one anomeric stabilisation in the epimer (**27**), so that the free energies of (**26**) and (**27**) are similar and this is reflected in their relative proportions.



Scheme 3 i, AD-mix β/0°C; ii, 10%HCl; iii, a) TsCl/-15°C, b)$LiAlH_4$

In summary, a series of stereoisomers of the unique 2,4,8-trimethyl-1,7-dioxaspiro[5.5]undecane system has been acquired in enantioselective ways using (R)-(+)-pulegone as a basic building block and employing asymmetric dihydroxylation to introduce additional chirality.

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References and notes:

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