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Synthesis and Absolute Stereochemistry of Hagen's-Gland Lactones in some Parasitic Wasps (Hymenoptera:Braconidae)

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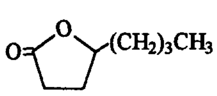
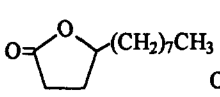
Abstract: Efficient syntheses and enantioselective gas chromatography have confirmed the structures and established the absolute stereochemistry of some novel bicyclic lactones (tetrahydrofurofuranones) in species of parasitic wasps (Hymenoptera:Braconidae). The co-occurring γ-lactones, octan-4-olide and dodecan-4-olide, have the (*R*)-configuration. © 1997 Elsevier Science Ltd.

Certain species of parasitic wasps (in the family Braconidae) exhibit potential as biological control agents, and there has been considerable interest in their morphology and taxonomy.[1] From a chemical perspective, Williams and co-workers[2] have reported that the Hagen's glands (located near the abdominal tips) of the braconid wasps, *Diachasmimorpha longicaudata* (Ashmead), *Diachasmimorpha tryoni* (Cameron) and *Fopius (Biosteres) arisanus*, are lactone rich, and possible roles for these secretions have been summarised.[2] In addition to octan-4-olide **1** and dodecan-4-olide **2**, Williams[2] suggested that the hitherto uncharacterized bicyclic lactones **3** and **4**, ((3aα, 5β, 6aα)-5-n-butyltetrahydrofuro-[3,2-b]furan-2(3H)-one and the 5-n-hexyl derivative, respectively) were also present. The structures and relative stereochemistry of **3** and **4** were based on nmr considerations.[2,3] In this report we wish to describe efficient syntheses of these lactones, in both racemic and enantiomeric forms, which confirm the structures of **3** and **4**, and the determination of the absolute configurations of the natural lactones. Information on the lactone mixture (including stereochemistry) from the previously unexamined indigenous Australian species, *Diachasmimorpha kraussii* (Fullaway) is also presented.



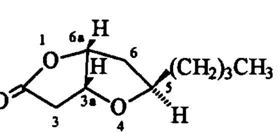
1

F.arisanus



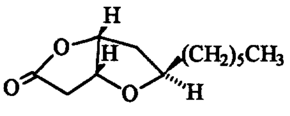
2

D.tryoni



3

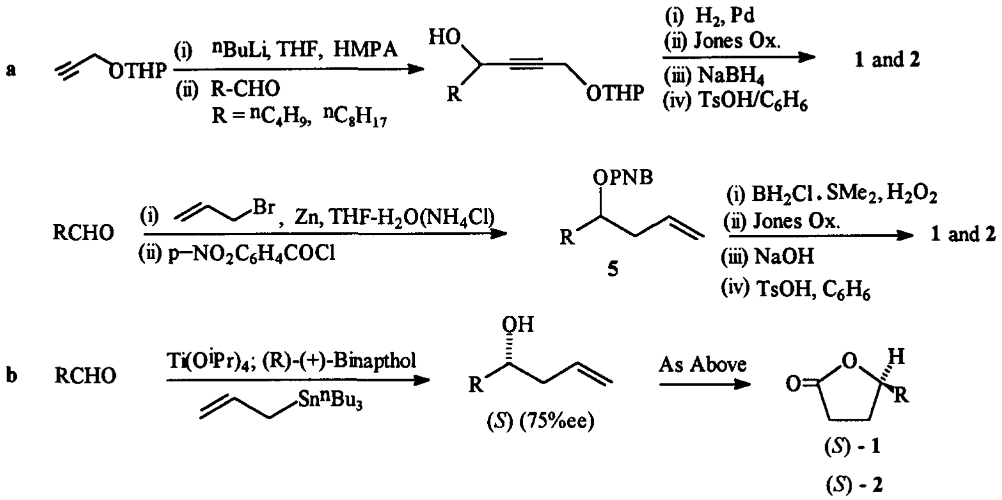
D.longicaudata



4

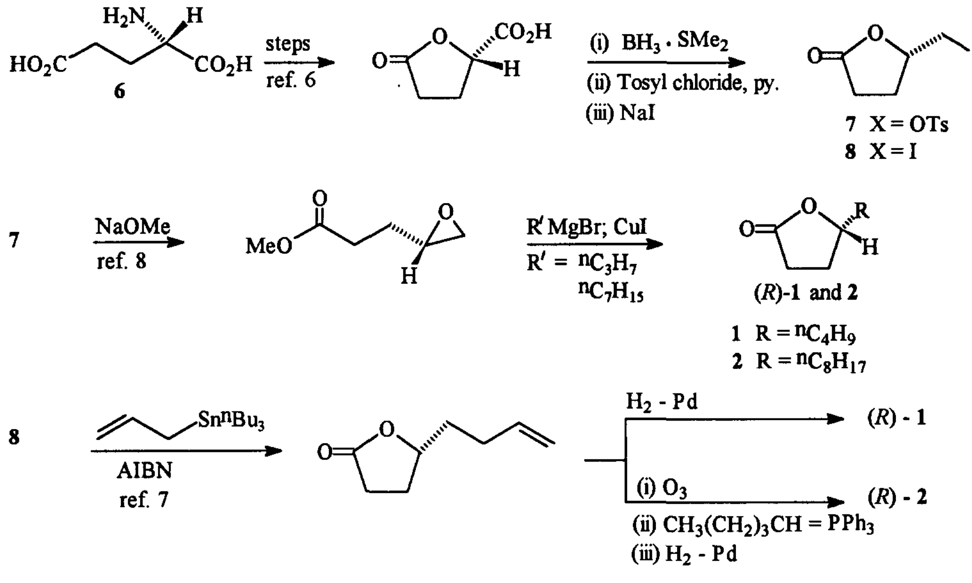
D.kraussii

Samples of **1** and **2**, as racemates, were obtained by several methods, two of which are summarised in Scheme 1**a**. The homoallylic alcohol corresponding to the p-nitrobenzoate, **5** (R = $^{n}C_4H_9$), was acquired in enantiomerically enriched form by asymmetric allylation[4] of pentanal, as shown in Scheme 1**b**, and (*S*)-**1** (75%ee) then resulted.[5] A similar sequence starting with nonanal produced (*S*)-**2**.



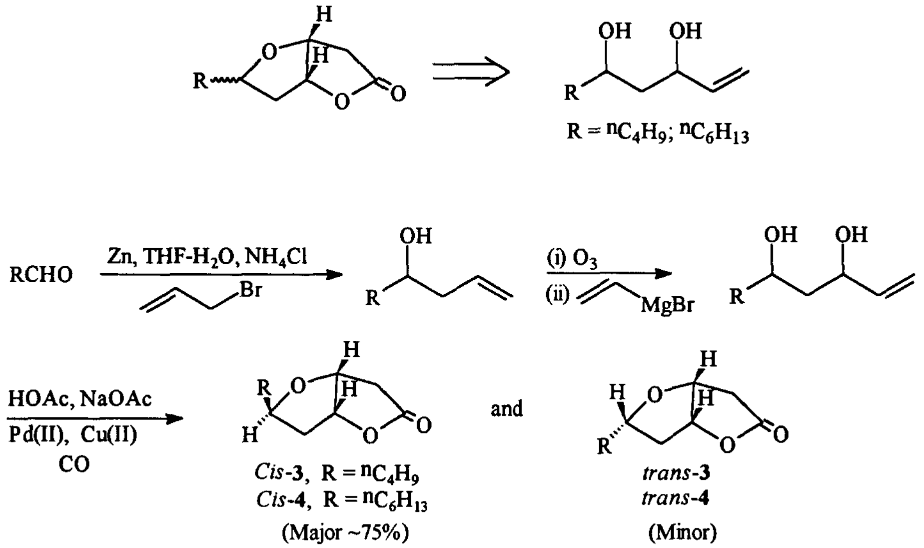
Scheme 1

Alternative approaches to enantiomers of **1** and **2** employed (*S*)-(+)-glutamic acid **6**, and these are summarised below in Scheme 2.



Scheme 2

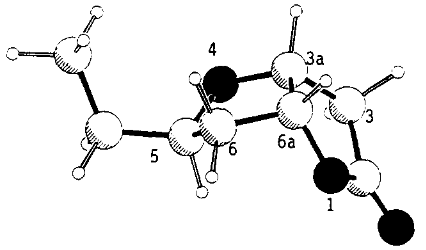
Access to the bicyclic lactones **3** and **4** appeared possible by utilisation of a palladium (II)-catalysed oxy-carbonylation-lactonisation sequence,[9] with an unsaturated 1,3-diol system, shown below in Scheme 3. This "one-pot" conversion of the enediol to the separable (flash chromatography) diastereomers *cis*-**3** and *trans*-**3** was very clean, and an analogous procedure starting with n-heptanal (Scheme 3) provided the diastereomers of **4**. The relative stereochemistry of *cis* and *trans* **3** and **4** was determined by NOE measurements, and comparisons of experimental and calculated ^1H–^1H coupling constants. The latter were calculated for the MM3- minimised structures for the analogues with an ethyl side-chain, and in each system the favoured structure has this group

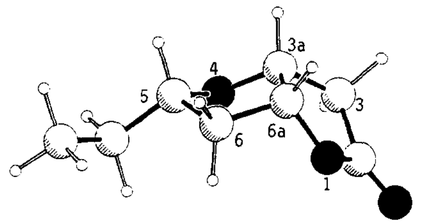


(*Cis* refers to the orientation of R relative to the ring-junction hydrogens)

Scheme 3

pseudo- equatorial (see below). The correspondence between calculated and experimental J-values for the ethyl system analogous to *cis*-**3** and *cis*-**4** is quite good, but only moderate for the *trans* isomers. From these data, and comparisons with the published spectra,[2] it follows that the major naturally occurring bicyclic lactones are the *cis*-**3** and *cis*-**4** isomers.

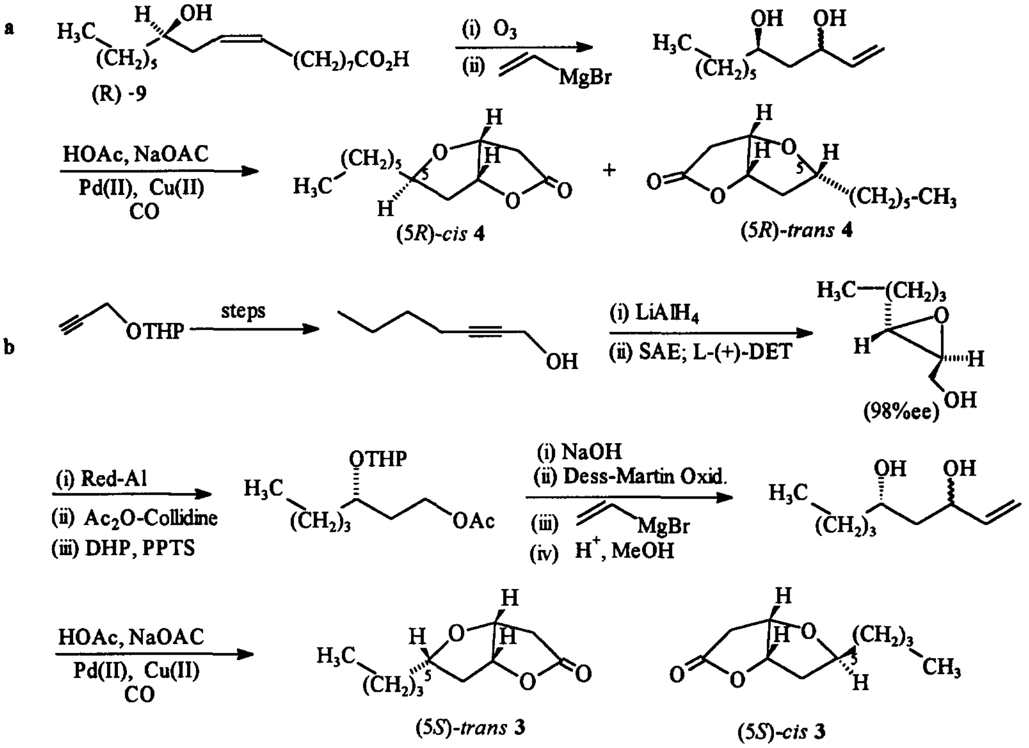




Calculated(Hz)	Dihedral Angle	Experimental
J 3α, 3a = 1.2	96°	~0
J 3β, 3a = 6.7	27°	6.7
J 3a, 6a = 4.8	24°	4.7
J 6a, 6α = 1.6	80°	~0
J 6a, 6β = 4.5	41°	4.7
J 5, 6α = 4.3	44°	4.8
J 5, 6β = 11.6	168°	10.3

Calculated(Hz)	Dihedral Angle	Experimental
J 3α, 3a = 1.2	94°	~3.5
J 3β, 3a = 6.4	29°	~3.5
J 3a, 6a = 4.4	27°	~4.5
J 6a, 6α = 3.3	121°	2.3
J 6a, 6β = 9.5	1°	6.7
J 5,6α = 10.7	155°	7.9
J 5, 6β = 6.0	33°	7.1

The racemic lactones **1** - **4** were separated into their enantiomers using enantioselective gas chromatography with heptakis (6-O-TBDMS-2,3-di,O-methyl)-beta-cyclodextrin, and enantiomers of **3** and **4** were therefore required for the determination of the absolute stereochemistry of the natural lactones. The readily available (*R*)-(+)- ricinoleic acid **9** was transformed as shown in Scheme 4**a** to provide (5*R*)-*cis* **4** and (5*R*)-*trans* **4**. Acquisition of an enantiomer of *cis*-**3** was based on Sharpless asymmetric epoxidation (SAE) methodology as shown in Scheme 4**b**.[10]



Scheme 4

With the availability of the racemates and certain enantiomers of **1** - **4**, enantioselective gas chromatographic analyses established that (*R*)-**1** and (*R*)-**2**, each >99%ee, were present in *F.arisanus* and *D.tryoni*, respectively.[11] Bicyclic lactone, (5*R*)-*cis*-**4** (>99%ee) was identified in D.kraussii and *D.longicaudata*, with the latter species containing (5*R*)-*cis*-**3** and racemic *trans*-**3** as minor components (*ca* 7% together) of the lactone mixture. The role of these lactones is being examined, and the "one-pot" synthesis of the bicyclic lactone core is being utilised to acquire other natural products incorporating this sub-structure.

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