# A New Spiroketal Type from the Insect Kingdom

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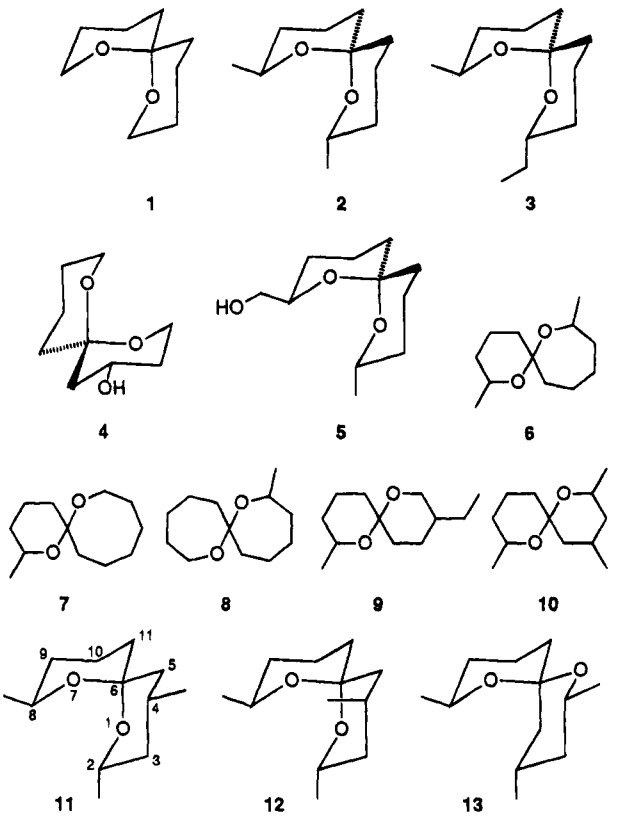
*Summary:* The major component of the male or female dorsal abdominal gland secretion of the aposematic shield bug, *Cantao parentum* (White) (Hemiptera: Scutelleridae), is (2*S*,4*R*,6*R*,8*S*)-2,4,8-trimethyl-1,7-dioxaspiro-[5.5]undecane (**23**), the first example from the insect kingdom of a branched carbon chain spiroketal and the first spiroketal of any type from Hemiptera or lower insect orders.

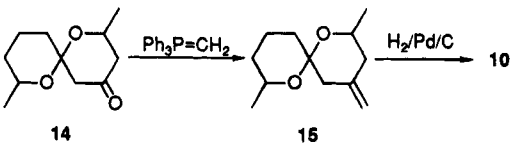
Spiroketals are important components of glandular secretions of higher insects, having been described from the orders Coleoptera (beetles), Diptera (flies), and Hymenoptera (bees and wasps).[1,2] The characterized spiroketals are very predominantly odd-numbered in carbon,[3] e.g., **1** and **2**, but even-carbon variants, e.g., **3**, are occasionally present.[2,4] Hydroxy derivatives, e.g., **4** and **5**, sometimes occur as very minor components.[5–7] Spiroketals were previously unknown from Hemiptera (an order which includes insects commonly known as bugs) and the other lower insect orders. Furthermore, no spiroketal with a branched carbon chain had, until now, been surrendered by the insect kingdom. We now report studies that substantially extend our knowledge of the type and origin of insect-generated spiroketals (Chart 1; Structures **2**–**5** as drawn correspond to the absolute configurations of the naturally occurring compounds, whereas **11**–**13** are used to indicate relative stereochemistry).

During the course of a general investigation of the scent-gland chemistry of true bugs, attention was directed to the shield bug *Cantao parentum* (White) (Hemiptera: Scutelleridae), the only Australian representative of the four member *Cantao* genus.[8] Adults of these aposematic insects, resplendent in an orange shield with contrasting black spots, possess an unusual dorsal abdominal gland (DAG) system,[9,10] the flap component

**Chart 1**




**Scheme 1**




of which can be rapidly opened and closed, exposing the inner glandular surface from which volatiles are released. GC–MS examination of the dichloromethane extract of excised DAG's of either male or female bugs showed that a minor component was the known (*E*,*E*)-2,8-dimethyl-1,7-dioxaspiro[5.5]undecane **22**, by comparison with an authentic sample.[4] The major gland component, with apparent $M$ = 198, also exhibited a fragmentation pattern indicative of a spiroketal, and GC–HRMS established the formula $C_{12}H_{22}O_2$ (calcd 198.1618, obsd 198.1629). One trace component of slightly longer retention time displayed a very similar mass spectrum, while two closely spaced minor components of still longer retention time exhibited related mass spectra, but with quite different relative abundances of common fragments.

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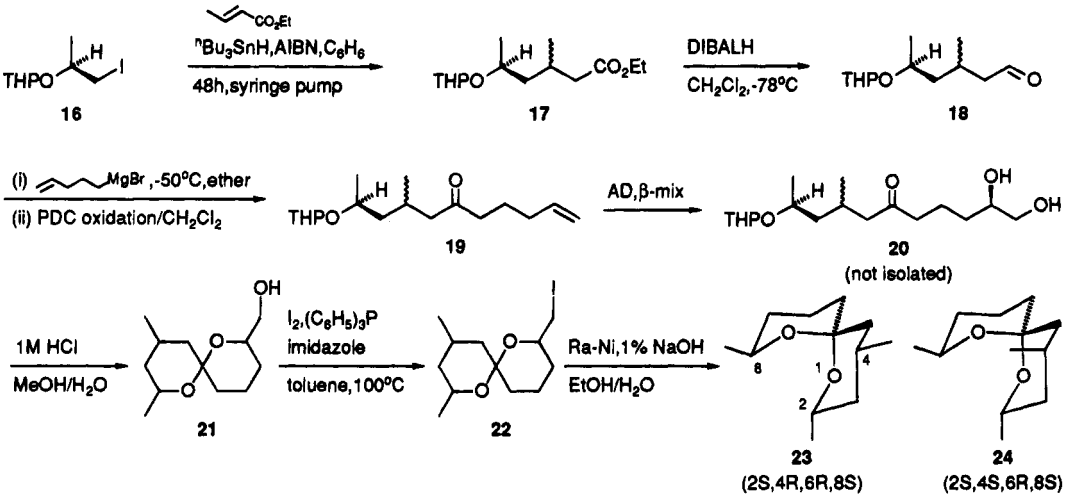
**Scheme 2**




The mass spectrum of the major natural product showed characteristic fragments at *m/z* 112 and 115 which indicated the presence of a methylated tetrahydropyran or an oxepane. The fragments with *m/z* 126 and 129 pointed to a homologous structure for the alternate ring, and the difference of 3 amu in the two sets of fragments demonstrated that methylene groups were adjacent to the spiro center.[11] Comparisons of mass spectra and retention times with those of known spiroketals **3**[4,5] and **6**–**8**,[12] eliminated these from consideration and left no feasible structural options consistent with the generalization that insect-derived spiroketals possess unbranched carbon skeletons.[2,3] The absence of a significant ion at *m/z* 169 (M − 29) indicated the absence of an ethyl group α to oxygen, although location β to oxygen could not be unequivocally dismissed, on the basis of the mass spectra of compounds related to the talaromycins.[13] Consequently, we synthesized the ethyl-substituted spiroketal **9** as a diastereomeric mixture,[14] but no isomer was identical with the major natural component (all diastereomers of **9** exhibited a discernible *m/z* 169 ion (M − $C_2H_5$)).[15]

A spiroketal system strongly supported by the mass spectral data is 2,4,8-trimethyl-1,7-dioxaspiro[5.5]undecane (**10**), and access to a diastereomeric mixture of **10** was gained by Wittig olefination of known ketone system **14**[7] followed by hydrogenation (Scheme 1).

This procedure provides the *E,E* ring-configured[2] spiroketals **11** and **12**, (with **12** predominating), together with three later eluting isomers each having at least one *Z*-configured ring,[2] e.g. **13**.[16] The various diastereomers were separated (HPLC) and characterized, with the relative stereochemistry shown in **11** and **12** being confirmed by correlated NMR spectroscopy at 500 MHz. Comparison of GC–MS behavior and coinjection studies demonstrated that the natural product was the all-equatorial *E,E*-isomer **11**.[17]

Two of the later eluting minor isomers in the synthetic mixture were identical (GC–MS, coinjection) with the two later eluting, minor natural spiroketals. The relative stereochemistry of these minor isomers is being determined. All five diastereomers of system **10** present in the synthetic mixture were nicely separated into enantiomeric pairs on a β-cyclodextrin column,[18] and examination of the natural extract showed that the major component **11** was of high enantiomeric excess (>98% ee). (The co-occurring 2,8-dimethyl-1,7-dioxaspiro[5.5]-undecane (**2**) was also of very high ee and has the 2*S*,6*R*,8*S* stereochemistry as drawn (Chart 1) on the basis of previous determinations of chirality in this system.[4,19])

Synthesis of the enantiomers of **11** and **12** was next undertaken, and stereoisomers **23** and **24** were acquired in eight steps and 7.1% overall combined yield by a route (Scheme 2) commencing with free radical addition of the ethyl (*S*)-(+)-lactate-derived iodide **16**[4] to ethyl crotonate. Asymmetric dihydroxylation[20] (AD) with commercial "β-mix" of protected hydroxy ketone **19** installs predominately *R* chirality at the newly created secondary alcohol center in monoprotected triol **20**, which was immediately deprotected and cyclized to the hydroxyspiroketal **21**. Conversion to the targets was achieved by iodide forma-

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(15) New compounds have been characterized by high field (400 or 500 MHz) $^1H$, $^{13}C$, and correlated NMR spectroscopy, combined gas chromatography–mass spectrometry, "chiral" gas chromatography, and high-resolution mass spectrometry as appropriate.
(16) Our experience has been that *E,Z*-configured[2] 1,7-dioxaspiro-[5.5]undecanes elute (from a nonpolar column) after the *E,E* isomers and show surprisingly different relative intensities of common ions in their mass spectra. This aspect is currently being investigated.
(17) Important spectral data for spiroketals **11** and **12** **Spiroketal 11**: $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.78 (1H, app q, *J* = 12.1, H3a), 0.67 (3H, d, *J* = 6.7 Hz, CH3 at C-4), 0.95 (1H, t, *J* = 12.6 Hz, H5a), 1.09 (3H, d, *J* = 6.4 Hz, CH3), 1.12 (3H, d, *J* = 6.2 Hz, CH3), 1.15 (1H, m, H9a), 1.35 (1H, td, *J* = 13.3, 4.6 Hz, H11a), 1.47–1.52 (5H, m, H10e, H9e, H11e, H3e, H5e), 1.86 (1H, tt, *J* = 13.3, 3.5 Hz, H10a), 2.00 (1H, m, H4a), 3.67 (2H, m, H2, H8); $^{13}C$ NMR (50 MHz, $CDCl_3$) 19.01 (C10), 21.68, 21.86, 22.02 (3 × CH3), 25.07 (C4), 32.77 (C9), 35.09 (C11), 41.58 (C3), 43.90 (C5), 64.96, 65.07 (C2,C8), 96.51 (C6); mass spectrum (EIMS) *m/z* 198 (10), 154 (8), 139 (17), 129 (100), 128 (42), 126 (53), 115 (96), 114 (15), 112 (74), 111 (51), 98 (10), 97 (34), 83 (17), 69 (33), 55 (31); HRMS calcd for $C_{12}H_{22}O_2$ 198.1618, obsd 198.1617. **Spiroketal 12**: $^1H$ NMR (500 MHz, $CDCl_3$) δ 1.04–1.6 (18H, m, including 3 × CH3 at 1.12, d, *J* = 6.4, 1.15 Hz, d, *J* = 6.4, 1.19 Hz, d, *J* = 7.3 Hz), 1.89 (1H, app qt, *J* = 13.3, 4.0 Hz, H10a), 1.96 (1H, m, H4e), 3.72 (1H, m, H8), 3.88 (1H, m, H2); $^{13}C$ NMR (125 MHz, $CDCl_3$) 19.05 (C10), 20.72, 21.87, 21.95 (3 × CH3), 25.44 (C4), 32.52 (C9), 35.43 (C11), 38.60 (C3), 40.13 (C5), 60.18 (C2), 65.19 (C8), 97.45 (C6); mass spectrum (EIMS) *m/z* 198 (8), 154 (8), 139 (19), 129 (70), 128 (35), 126 (45), 115 (78), 114 (21), 112 (62), 111 (49), 98 (9), 97 (43), 87 (20), 83 (50), 69 (100), 55 (64); HRMS calcd for $C_{12}H_{22}O_2$ 198.1618, obsd 198.1612.
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tion **22** and Raney-nickel reduction,[21] and the preponderance (90%) of the *E,E* [2] ring configured spiroketals **23** ($[\alpha]^{23}_D$ −66.4° ($CHCl_3$)) and **24** ($[\alpha]^{23}_D$ −69.0° ($CHCl_3$)) reflects the level of chiral induction in the AD reaction.[22] (Note the descriptor change at C-8 accompanying the **22** to **23**, **24** transformation). *ent*-**23** and *ent*-**24** were obtained from (2*R*,6*S*,8*R*)-2,8-dimethyl-1,7-dioxaspiro-[5.5]undecan-4-one[7] following the sequence outlined in Scheme 1.

With the availability of **23**, **24**, *ent*-**23**, *ent*-**24**, and the racemates, elution and coinjection studies using a β-cyclodextrin column established that the major natural component was (2*S*,4*R*,6*R*,8*S*)-2,4,8-trimethyl-1,7-dioxaspiro[5.5]undecane (**23**), with no detectable level of *ent*-**23**. Compound **23** is the first example from the insect kingdom of a branched carbon chain spiroketal and the first spiroketal of any type from Hemiptera or lower insect orders. Interesting questions arise concerning its biosynthesis and biological role. The compound is not sex-specific, and an aggregation role may be indicated by the presence of a single large colony in a host tree (*Mallotus philippensis* (Lam.) (Euphorbiaceae)) at certain stages of insect development. Studies of the other *Cantao* species are being planned to provide a complete profile of this genus.

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(22) Absolute stereochemical control at the methyl-bearing C-4 is possible by utilizing (*R*)-(+)-citronellic acid as starting material. (Tu, Y. Q. Work in progress.)

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**Supplementary Material Available:** Experimental procedures for **15**, **10**, **17**, **18**, **19**, **21**, **22**, and **23/24** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.