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Identification and synthesis of new bicyclic acetals from caddisflies (Trichoptera)

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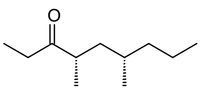
Dedicated to Prof. Dr. Axel Zeeck on the occasion of his 65th birthday

Abstract—As shown by synthesis and enantioselective gas chromatography, males and females of the caddisfly species *Potamophylax latipennis* and *Potamophylax cingulatus* produce (1*R*,3*S*,5*S*,7*S*)-1-ethyl-3,5,7-trimethyl-2,8-dioxabicyclo[3.2.1]octane, while *Glyphotaelius pellucidus* produces 1,3-diethyl-4,6-dimethyl-2,7-dioxabicyclo[2.2.1]heptane, having either the (1*S*,3*S*,4*R*,6*S*) or (1*R*,3*R*,4*S*,6*S*)-configuration. As shown by electrophysiological investigations, the compounds are perceived by the antennae of both sexes.

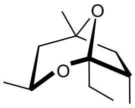
Volatile bicyclic acetals play an important role as intra- and interspecific signals in insect chemical communication. Structures identified so far include unbranched carbon skeletons, terpenoids and polyketides derived from propanoate and acetate units.[1] Here we describe the structure elucidation and synthesis of new biologically active polyketide bicyclic acetals from caddisflies.

Branched ketones have been identified as biologically active compounds from several species of caddisflies (Trichoptera): (*S*)-4-methyl-3-heptanone, (4*S*,6*S*)-4,6-dimethyl-3-octanone and (4*S*,6*S*)-4,6-dimethyl-3-nonanone (**1**) have been found in *Potamophylax latipennis*, *P. cingulatus* and *Glyphotaelius pellucidus*.[2] As a result of the present investigations, we identified two new bicyclic acetals showing the same carbon skeleton as **1**: (1*R*,3*S*,5*S*,7*S*)-1-ethyl-3,5,7-trimethyl-2,8-dioxabicyclo[3.2.1]octane (**2a**) was identified from the *Potamophylax* species, while 1,3-diethyl-4,6-dimethyl-2,7-dioxabicyclo[2.2.1]heptane, presumably showing (1*S*,3*S*,4*R*,6*S*) (**3a**) or (1*R*,3*R*,4*S*,6*S*)-configuration (**3b**) was found in the *Glyphotaelius* species.

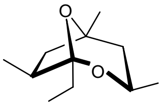
P. cingulatus and *P. latipennis* were collected either as adults or as pupae at locations near Lund, Sweden. Extracts were prepared by dissecting the 4th and 5th abdominal sternite and extracting them with dichloromethane. Gas chromatographic analyses of the extracts by using conventional flame ionization and simultaneously an antenna of *Potamophylax* as detectors (GC/EAD) revealed the presence of a relatively nonpolar component that was very well perceived by the antenna.[3] Investigations applying coupled gaschromatography/mass spectrometry (GC/MS), including high resolution GC/MS, showed the molecular weight of this active compound to be M = 184 ($C_{11}H_{20}O_2$).[4] During



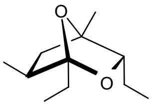
(4*S*,6*S*)-**1**



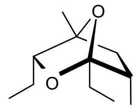
(1*R*,3*S*,5*S*,7*S*)-**2a**



(1*S*,3*R*,5*R*,7*S*)-**2b**



(1*S*,3*S*,4*R*,6*S*)-**3a**



(1*R*,3*R*,4*S*,6*S*)-**3b**

Keywords: Bicyclic acetals; Caddisflies; Trichoptera; Insects; Communication.

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microchemical reactions,[5] the compound could neither be hydrogenated or silylated nor reduced with lithium aluminium hydride, suggesting the structure of a bicyclic diether or, more likely, a bicyclic acetal. Comparison of obtained mass spectra with those reported in the literature[1,6] showed the target compound to be 1-ethyl-3,5,7-trimethyl-2,8-dioxabicyclo[3.2.1]octane. The (1*S*,3*R*,5*R*,7*S*)-stereoisomer of this bicyclic acetal, sordidin (**2b**),[7,8] is the male aggregation pheromone of the banana weevil, *Cosmopolites sordidus*, however, the gas chromatographic retention time of our natural compound did not match that of sordidin.[9]

Starting from (*S*)-4-methyl-4-penten-2-ol,[10] our synthesis of (1*R*,3*S*,5*S*,7*S*)-**2a** and *ent*-**2b** generally followed that of Ndiege et al.[11] As a result, the bicyclic acetals (1*R*,3*S*,5*S*,7*S*)-**2a**, *ent*-**2b**, (1*S*,3*S*,5*R*,7*R*)-**2c** and (1*S*,3*S*,5*R*,7*S*)-**2d** were obtained in an overall yield of 25%. The stereoisomers (1*R*,3*S*,5*S*,7*S*)-**2a** and *ent*-**2b** could be isolated as a mixture, slightly contaminated with **2c** and **2d** [(**2a**+*ent*-**2b**): (**2c**+**2d**) ca 95:5],[12] showing enantiomeric purities of 81% and 96%, respectively.[13]

Analysis of the extracts proved the natural compound to show (1*R*,3*S*,5*S*,7*S*)-configuration. Upon storage of the extracts, the compound showed a strong tendency to epimerize to *ent*-**2b**, which we also found in some samples. Easy epimerization has also been described for 7-episordidin.[8]

Extracts of *G. pellucidus* specimen, collected in southern Sweden, were obtained as described for *Potamophylax* spp. GC/MS analyses of these extracts revealed an unknown compound with a molecular mass of $M^+ = 184$ ($C_{11}H_{20}O_2$ upon high resolution GC/MS) eluting between 4,6-dimethyl-3-octanone and 4,6-dimethyl-3-nonanone from both polar and nonpolar stationary phases. These two ketones had already been known from *Glyphotaelius*,[2] and in addition, an unsaturated ketone, 4,6-dimethyl-6-nonen-3-one, could be identified in the course of the present investigations. The prominent peaks at *m*/*z* 57 and 86 in the mass spectrum of the unknown compound (Fig. 1) pointed to close structural relationships to the branched aliphatic ketones.[1] Again, the compound could neither be hydrogenated or silylated nor reduced with lithium aluminium hydride, suggesting it to be an isomer of the new *Potamophylax* compound **2a**. Considering the presence of 4,6-dimethyl-6-nonen-3-one and the ability of insects to transform unsaturated ketones to bicyclic acetals,[1] the structure of the unknown compound was proposed to be 1,3-diethyl-4,6-dimethyl-2,7-dioxabicyclo[2.2.1]heptane (**3**).

Following an Enders approach, our synthesis of **3** started with the alkylation of the dimethylhydrazone of 3-pentanone (**4**) with 1-bromo-2-methyl-2-pentene (**5**) (Scheme 1). Deprotection of the reaction product yielded the unsaturated ketone **6**, which after treatment with *m*CPBA furnished a mixture of all isomers of **3** via the intermediate ketoepoxide **7**.[14] Partial separation of 3-*endo* (**3a** and **3b**) and 3-*exo* (**3c** and **3d**) diastereomers was achieved by column chromatography.[12]

On the basis of their NMR and mass spectra, 3-*endo* and 3-*exo* isomers could be easily distinguished. The ^1H NMR spectra of the 3-*endo* isomers show a ^4J coupling between H-3 and H-5, with a coupling constant of about

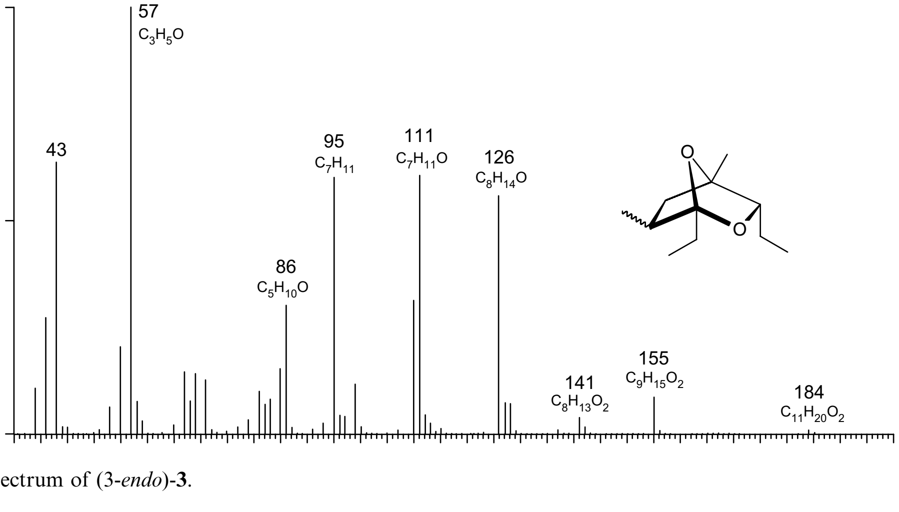
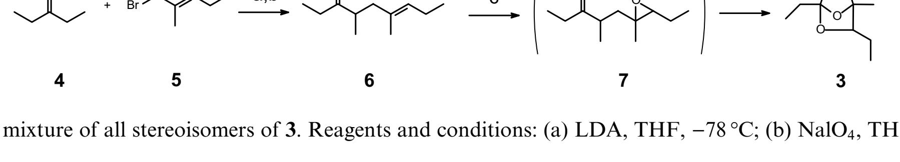


Figure 1. 70 eV Mass spectrum of (3-*endo*)-**3**.



Scheme 1. Synthesis of a mixture of all stereoisomers of **3**. Reagents and conditions: (a) LDA, THF, −78 °C; (b) $NaIO_4$, THF/H_2O, rt; (c) *m*CPBA, CH_2Cl_2, 0 °C.

1.6 Hz, producing, together with the ^3J coupling between H-3 and the methylene protons of the attached ethyl group, a ddd signal for H-3 (Fig. 2). In contrast, H-3 of the 3-*exo* isomers do not couple with H-5 and appear as a dd signal due to the ^3J coupling with the methylene protons of the ethyl group. The mass spectra of 3-*endo* and 3-*exo* isomers are quite similar, with the exception of an additional peak at m/z 128 in the spectra of the 3-*exo* isomers. Upon comparison of mass spectra and gas chromatographic retention times with the synthetic material, the natural product could be identified as a 3-*endo* isomer of **3**.

The absolute configuration of the natural compound could not be determined due to lack of material. However, we postulate the absolute configuration to be either (1*R*,3*R*,4*S*,6*S*) or (1*S*,3*S*,4*R*,6*S*). This assumption is based on known transformation mechanisms of unsaturated ketones to bicyclic acetals and on the principle of conservativity in nature. Actions of nonsubstrate specific monooxygenases upon unsaturated ketones have been shown to occur in various bark beetle species.[15] For *Dendroctonus ponderosae*, the conversion of (*Z*)-6-nonen-2-one to *exo*-brevicomin has been proven to proceed directly via the epoxide without prior transformation to a diol.[16] Methyl branching in insect volatiles similar to 4,6-dimethyl-3-nonanone (**1**) frequently shows (*S*)-configuration.[17] Hence, regarding (6*E*)-4,6-dimethyl-6-nonen-3-one, present in *G. pellucidus*, to be the actual precursor of **3** and showing (4*S*)-configuration as in **1**, the cyclization via an epoxide leads to either (1*S*,3*S*,4*R*,6*S*)-**3a** [(3-*endo*,6-*exo*)] or (1*R*,3*R*,4*S*,6*S*)-**3b** [(3-*endo*,6-*endo*)]. (*E*)-configuration of the double bond in the precursor defines the 3-*endo* configuration in the bicyclic acetal, while the (4*S*)-configuration in **1** is carried through to the 6 position in **3**.

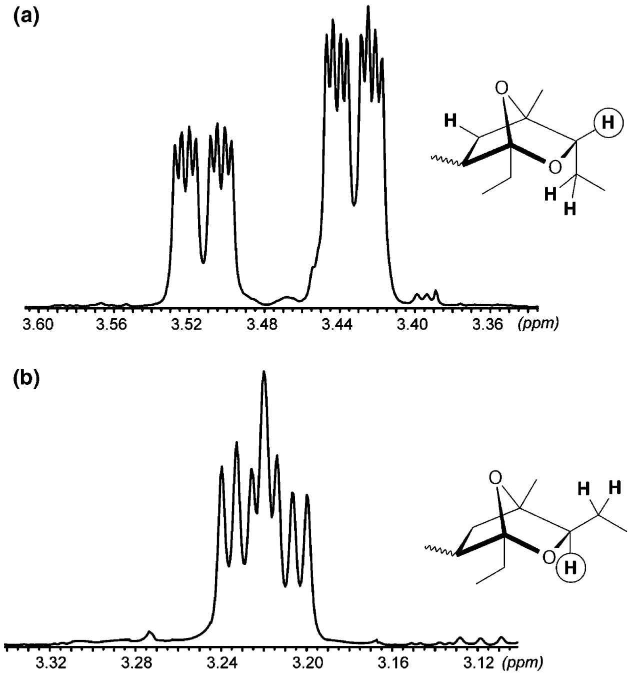


Figure 2. ^{1}H NMR signals of H-3 of 3-*endo* isomers (a) and 3-*exo* isomers (b) of **3**.

Acknowledgements

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References and notes

1. Francke, W.; Schröder, W. *Curr. Org. Chem.* **1999**, *3*, 407–443.
2. Bergmann, J.; Löfstedt, C.; Ivanov, V. D.; Francke, W. *Eur. J. Org. Chem.* **2001**, 3175–3179.
3. Arn, H.; Städler, E.; Rauscher, S. *Z. Naturforsch.* **1975**, *30c*, 722–725, For details, see: Bergmann, J.; Löfstedt, C.; Ivanov, V.D.; Francke, W. Proc. 10th Int. Symp. Trichoptera—Nova Suppl. Ent., Keltern, **2002**, *15*, 37–46.
4. GC/MS analysis was carried out on a 30 m × 0.25 mm fused silica column coated with DB5, programmed from 60 to 300 °C at 5 °C/min, using the combination HP 5890 (Hewlett Packard)–VG 70/250E (Vacuum Generators, Manchester, UK).
5. Attygalle, A. In *Methods in Chemical Ecology*; Millar, J. G., Haynes, K. G., Eds.; Chapman & Hall: New York, 1998; pp 207–294.
6. Jayaraman, S.; Ndiege, I. O.; Oehlschlager, A. C.; Gonzalez, L. M.; Alpizar, D.; Falles, M.; Budenberg, W. J.; Ahuya, P. *J. Chem. Ecol.* **1997**, *23*, 1145–1161.
7. Beauhaire, J.; Ducrot, P.-H.; Malosse, C.; Rochat, D.; Ndiege, I. O.; Otieno, D. O. *Tetrahedron Lett.* **1995**, *36*, 1043–1046.
8. Mori, K.; Nakayama, T.; Takikawa, H. *Tetrahedron Lett.* **1996**, *37*, 3741–3744.
9. We like to thank Prof. Kenji Mori, Fuji Flavour, Tokyo, Japan, for a generous gift of a sample of sordidin.
10. Fletcher, M. T.; Moore, C. J.; Kitching, W. *Tetrahedron Lett.* **1997**, *38*, 3475–3476.
11. Ndiege, I. O.; Jayaraman, S.; Oehlschlager, A. C.; Gonzalez, L.; Alpizar, D.; Fallas, M. *Naturwissenschaften* **1996**, *83*, 280–282.
12. Column chromatography on silica (ICN pore size 60 Å, particle size 32–63 μm) with hexane–ethyl acetate (20:1). NMR data of **2** were in accord with those reported in the literature (see Ref. 11).
13. Separation of stereoisomers was achieved by using a 30 m × 0.25 mm fused silica column coated with a 1:1 mixture of heptakis-(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin and OV1701 (Macherey and Nagel, Düren, Germany), kept at 50 °C for 10 min, then programmed to 130 °C at 3 °C/min.
14. NMR spectra were recorded on a Bruker DRX500 (Karlsruhe, Germany) at 500 MHz, chemical shifts δ are given in ppm relative to tetramethylsilane (internal standard, 0 ppm). Spectroscopic data of the mixture (index 1 and 2: data for 3-*endo* isomers [28% and 46% in the mixture], index 3 and 4: data for 3-*exo* isomers [both 13% in the mixture]): ^{1}H NMR (500 MHz, C_6D_6): $\delta = 3.51$ (ddd, $J = 9.4$, 3.8, 1.6 Hz, 0.28H, H-3_1), 3.43 (ddd, $J = 9.1$, 3.8, 1.8 Hz, 0.46H, H-3_2), 3.23 (dd, $J = 9.1$, 3.3 Hz, 0.13H, H-3_3), 3.21 (dd, $J = 9.7$, 3.3 Hz, 0.13H, H-3_4), 2.14–2.08 (m, 0.26 H, H-$1'a_3$, H-6_4), 2.06–2.00 (m, 0.87H, H-$6_{1,2,3}$), 2.00–1.85 (m, 1.33 H, H-$1'a_{1,2,4}$, H-$5a_2$), 1.80–1.65 (m, 1.26H, H-$1'b_{all}$, H-$5a_3$, H-$5a_4$), 1.57 (dd, $J = 12.0$, 0.9 Hz, 0.28 H, H-$5a_1$), 1.56–1.47 (m, 0.28H, H-$3'a_1$), 1.42–1.32 (m, 0.72H, H-$3'a_{2,3,4}$), 1.30 (dd, $J = 12.0$, 4.4 Hz, 0.28H, H-$5b_1$), 1.21–1.11 (m, 7H, H-$3'b_{all}$, H-$1''_{all}$, H-$4'_{all}$), 1.02–0.94 (m, 4.36H, H-$3''_{all}$, H-$6'_{1,3}$, H-$5b_3$), 0.89 (dd, $J = 11.6$, 4.4 Hz, 0.13 H, H-$5b_4$), 0.81–0.75 (m, 2.23H,

$H\text{-}6'_{2,4}$, H-5b$_2$) ppm. ^{13}C NMR (125 MHz, C_6D_6): $\delta = 120.0$ (C-1), 112.0 (C-1), 111.5 (C-1), 87.6, 86.2, 86.0, 85.8, 84.5 (C-3$_{3,4}$), 46.2 (C-5$_4$), 45.1 (C-5$_3$), 42.6 (C-6$_4$), 42.2 (C-6^{1,2,3}), 39.3 (C-5$_2$), 37.5 (C-5$_1$), 25.5 (C-3′), 24.6 (C-3′), 24.0 (C-3′), 23.8 (C-1′), 19.6 (C-6′), 17.0 (C-4′), 12.2 (C-3″), 10.1 (C-3″), 8.6 (C-1″) ppm. HR-MS: found 184.1467, calcd for $C_{11}H_{20}O_2$ 184.1463.

15. Perez, A. L.; Gries, R.; Gries, G.; Oehlschlager, A. C. *Bioorg. Med. Chem.* **1996**, *4*, 445–450.
16. Vanderwel, D.; Oehlschlager, A. C. *J. Am. Chem. Soc.* **1992**, *114*, 5081–5086.
17. Francke, W.; Schulz, S. In *Comprehensive Natural Products Chemistry*; Barton, D., Nakanishi, K., Eds.; Elsevier Science: Dordrecht, The Netherlands, 1999; Vol. 8, pp 197–261.