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Structure Elucidation and Synthesis of Dioxolanes Emitted by Two *Triatoma* Species (Hemiptera: Reduviidae)

B. Bohman,[†,#] A. Tröger,[‡] S. Franke,[‡,△] M. G. Lorenzo,[§] W. Francke,[‡] and C. R. Unelius*[,†,⊥]

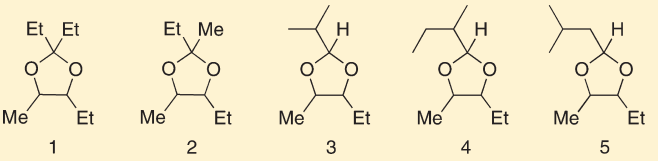
[†]School of Natural Sciences, Linnaeus University, SE-391 82 Kalmar, Sweden

[‡]Organic Chemistry, University of Hamburg, Martin-Luther-King-Platz 6, D-20146 Hamburg, Germany

[§]Laboratório de Triatomíneos e Epidemiologia da Doença de Chagas, Centro de Pesquisas René Rachou/FIOCRUZ, 30.190-002, Belo Horizonte, Minas Gerais, Brazil

Supporting Information

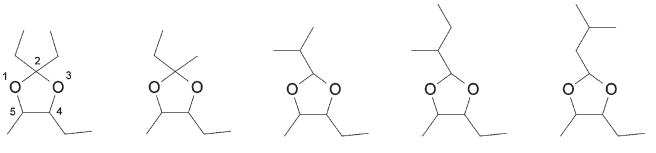
ABSTRACT: Volatiles from the metasternal glands of two species of true bugs of the Triatominae subfamily, *Triatoma brasiliensis* and *Triatoma infestans*, were analyzed by SPME-GC/MS. Two sets of new natural products were found: (4*S*,5*S*)- and (4*R*,5*R*)-2,2,4-triethyl-5-methyl-1,3-dioxolane (**1**) (major component) and (4*S**,5*S**)-2,4-diethyl-2,5-dimethyl-1,3-dioxolane (**2**) (trace component), (2*R*/*S*,4*S*,5*S*)- as well as (2*R*/*S*,4*R*,5*R*)-4-ethyl-5-methyl-2-(1-methylethyl)-1,3-dioxolane (**3**) (minor component), (2*R*/*S*,4*S**,5*S**)-4-ethyl-5-methyl-2-(1-methylpropyl)-1,3-dioxolane (**4**) (trace component), and (2*R*/*S*,4*S**,5*S**)-4-ethyl-5-methyl-2-(2-methylpropyl)-1,3-dioxolane (**5**) (trace component). Syntheses of optically active **1** and **3** were carried out by reacting pure enantiomers of 2,3-pentanediol with 3-pentanone or 2-methylpropanal. The preparation of pure stereoisomers of 2,3-pentanediol involved a novel key step for the synthesis of secondary alcohols: the reduction of a carboxylic ester by means of DIBAH and in situ alkylation of the intermediate by Grignard reaction at low temperature. Starting from the pure enantiomers of methyl lactate, all four stereoisomers of 2,3-pentanediol were synthesized and transformed to the corresponding isomers of **1** and **2**. Relative configurations of the natural products and enantiomeric compositions of naturally occurring **1** and **2** were determined by comparison of their mass spectra and gas chromatographic retention times (co-injection) with those of authentic reference samples.



In rural areas of the Southern Cone of South America and Northeastern Brazil, *Triatoma infestans* and *Triatoma brasiliensis* (Hemiptera: Reduviidae) are main vectors of Chagas disease, the principal health and socioeconomic burden caused by a parasitic infection in Latin America.[1−3] Triatomine bugs frequently invade human dwellings, where they develop colonies through blood-feeding on humans and domestic animals. In this context, the insects can transmit *Trypanosoma cruzi*, a parasite that acts as the etiological agent of Chagas disease. Since no vaccine is available for human immunization against *T. cruzi* and no effective treatment exists to cure chronic patients, the elimination of triatomine vectors is essential for Latin American national health programs.

Volatile constituents of the metasternal glands (MGs) of *T. infestans*, *Rhodnius prolixus*, and *T. brasiliensis* have been suggested to be emitted during copulation and to play a role in sexual communication.[4−6] Manrique et al. identified five volatile compounds, predominantly 3-pentanone and short-chain alcohols, in the secretion produced by the MGs of *T. infestans*.[4] The second most abundant compound of this secretion was reported as unknown, although its mass spectrum was published. During studies on volatiles from MGs of *T. brasiliensis*,[6] 3-pentanone was again identified as a major component, as well as (*S*)-2-methyl-1-butanol, (*R*)-4-methyl-1-heptanol, and (*R*)-1-phenylethanol, together with the same unknown compound that was found in *T. infestans*. The ketone, chiral alcohols, and the unknown compound triggered electrophysiological responses, i.e., EAD deflections, in the antennae of male *T. brasiliensis*.[6] In a recent short communication we reported the identification of the unknown as 2,2,4-triethyl-5-methyl-1,3-dioxolane (**1**), which in *T. brasiliensis* is produced as a mixture of (4*S*,5*S*)-**1** and (4*R*,5*R*)-**1** in a ratio of about 4:1.[7]

Further investigations have now revealed that a number of additional acetals are produced in *T. brasiliensis*. Here we present the synthesis of highly pure stereoisomers of **1**, as well as the structure elucidation and synthesis of four new naturally occurring alkylated dioxolanes (**2**−**5**) found in the MGs of these triatomines.



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RESULTS AND DISCUSSION

All four stereoisomers of **1** were synthesized individually and were easily distinguished by enantioselective GC. The order of elution was (4*R*,5*R*); (4*S*,5*S*); (4*S*,5*R*); (4*R*,5*S*) with significant differences in α-values between the *cis*-/*trans*-isomers: α $tr_{4S,5S}/tr_{4R,5R}$ = 1.04, α $tr_{4S,5R}/tr_{4S,5S}$ = 1.54, and α $tr_{4R,5S}/tr_{4S,5R}$ = 1.05. The two *trans*-isomers (4*S*,5*S*)-**1** and (4*R*,5*R*)-**1** were found to be present in the glands in a ratio of about 4:1.

In addition to **1**, a trace of *trans*-2,4-diethyl-2,5-dimethyl-1,3-dioxolane (**2**) was identified. The mass spectrum of dioxolane **2** (Figure 1) showed the same principal fragmentation pattern as **1**.[7] Mass spectra and gas chromatographic retention times of synthetic samples of (4*S**,5*S**)-**1** and (2*R*/*S*,4*S**,5*S**)-**2** matched the data of the natural products.

During our investigation of volatile components of metasternal glands of *T. brasiliensis*, we identified an additional set of compounds with retention times (GC) and mass spectrometric fragmentation patterns very similar to those of **1** and **2**. On the achiral polar stationary phase, two peaks in a ratio of about 1:1 with virtually identical mass spectra, indicative of a pair of diastereomers, were found. On a polar column the Kovats indices were 1116 and 1120, respectively, even lower than that of **1**, which was 1156.[6] The 70 eV EI-mass spectrum (Figure 2) showed a base peak at *m*/*z* 115, while the highest visible fragment appeared at *m*/*z* 157. On the basis of the experience gained during our structure assignment of **1**, we postulated a 1,3-dioxolane structure for the target compound. Proposing a molecular mass of *M* = 158, the signal at *m*/*z* 157 = $(M - H)^+$ suggested a dioxolane formed from an aldehyde.[8] As a consequence, *m*/*z* 115 was assumed to be formed by loss of a propyl unit upon α-cleavage at C2. Thus, the parent carbonyl compound of the proposed dioxolane should be either butanal or 2-methylpropanal. Two less abundant but diagnostic signals, at *m*/*z* 114 ($M^+ - 44$) and *m*/*z* 100 ($M^+ - 58$), indicated the same substitution pattern at C4 and C5 as in **1**.[7,9] Since isobutyric acid is known as a volatile from Brindley's glands in *T. infestans*,[4] it was reasonable to assume that the corresponding aldehyde could be produced by this closely related species. Using synthetic compounds as reference samples, our hypothesis, that the target acetals were 4-ethyl-5-methyl-2-(1-methylethyl)-1,3-dioxolanes (**3**), proved to be correct.

Of the eight possible stereoisomers of **3**, only those showing *trans*-configuration at positions 4/5 were found in the MGs. Ratios varied between the samples, but all contained mixtures of C2-epimers, and (2*R*/*S*,4*S*,5*S*)-**3** and (2*R*/*S*,4*R*,5*R*)-**3** were the most abundant ones in the glands. Due to very similar retention times and coelution with other compounds in the biological samples, the assignment of absolute configuration of the *trans*-isomers is tentative, but a general excess of (2*R*/*S*,4*S*,5*S*)-**3** was observed, which is in line with the established configuration of **1**.

In addition to **3**, trace amounts of 4-ethyl-5-methyl-2-(1-methylpropyl)-1,3-dioxolane (**4**) and 4-ethyl-5-methyl-2-(2-methylpropyl)-1,3-dioxolane (**5**) were identified. Again, as the substances showed *trans*-configuration at C4/C5, the general motif of *syn*-2,3-pentanediol as a substructure in all acetals was repeated. The mass spectrometric fragmentation patterns of **4** and **5** resembled that of **3**. Mass spectra and gas chromatographic retention times of synthetic samples corresponded well with data of the natural products. Due to the minute amounts of the natural products, the absolute configuration of these acetals could not be unambigously determined, although it is most likely that the

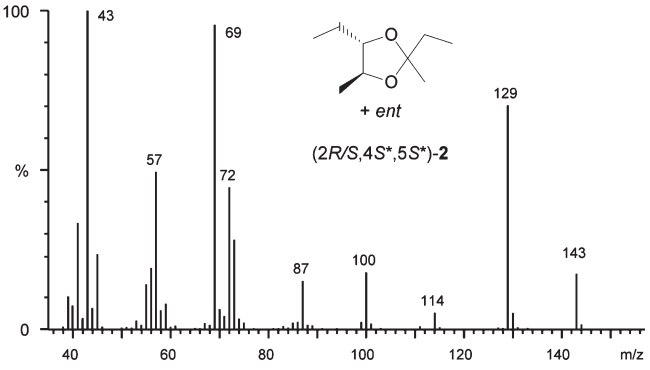

Figure 1. EI-mass spectrum (70 eV) of (2*R*/*S*,4*S**,5*S**)-2,4-diethyl-2,5-dimethyl-1,3-dioxolane (**2**).

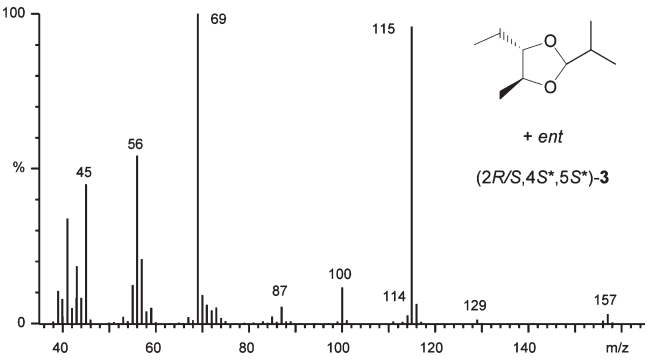

Figure 2. EI-mass spectrum (70 eV) of (2*R*/*S*,4*S**,5*S**)-4-ethyl-5-methyl-2-(1-methylethyl-1,3-dioxolane (**3**).

configuration at the diol part of the acetals follows the general pattern (major isomer showing (*S*,*S*)-configuration).

The absolute configuration of the acetals **1** and **3**, found in the glands, was determined by synthesis and co-injections of pure stereoisomers. These dioxolanes were prepared from the pure enantiomers of methyl lactate by a modified method of Lacey et al.[10] The decisive novelty in our approach, which reduced the number of steps, was the Grignard reaction carried out in situ on the intermediate formed upon DIBAH-mediated reduction at low temperature, with some similarity to the known procedure for the transformation of carboxylic esters to alkenes.[11]

The target compounds were prepared from the two enantiomers of methyl lactate, which were protected using 3,4-dihydro-2*H*-pyran in CH_2Cl_2 and catalytic amounts of *p*-TsOH (Figure 4).[12]

Using DIBAH in toluene,[13,14] the resulting tetrahydropyranyl derivatives were reduced to the corresponding aldehyde equivalents, which were alkylated in situ at low temperature by Grignard reactions with ethyl magnesium bromide. The THP-protected 2,3-pentanediols were deprotected to the corresponding 2,3-pentanediols (Figure 3).[12]

The two diastereomers of 2,3-pentanediol were separated on silica gel[10] and distinguished by their significantly different NMR spectra.[15] Each of the four stereoisomers of 2,3-pentanediol was transformed to the corresponding dioxolane via standard acid-catalyzed acetalization,[16] yielding pure stereoisomers of **1** and **3** in >95% isomeric purity (Figure 4).

The stereoisomers of **2**, **4**, and **5** were produced from *cis*-2-ethyl-3-methyloxirane and the corresponding carbonyl compound following the procedure of Blackett et al.[7,17]

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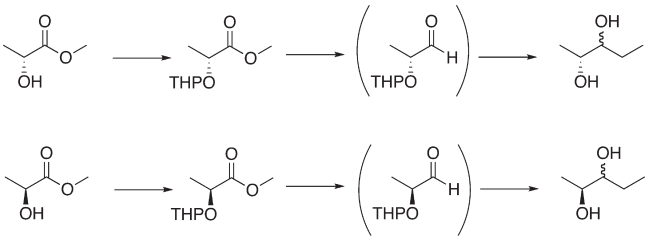

Figure 3. Diastereoselective syntheses of 2,3-pentanediol.

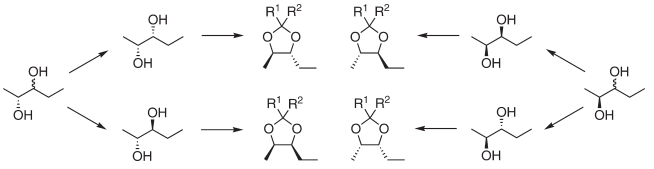

Figure 4. Syntheses of dioxolanes.

Gas chromatographic analyses and NMR investigations showed that the reaction of *syn*-2,3-pentanediol with 2-methylpropanol yielded a 1:1-mixture of the C2-epimers of the C4/C5-*trans*-configured dioxolane **3**. In contrast, *erythro*-2,3-pentanediol produced almost exclusively one stereoisomer. These results may be due to differences in the geometry of the transition state of the condensation step (alkyl group versus aldehyde proton; data not shown).

Vitta et al. have shown that adult *T. brasiliensis* produce a complex blend of volatile compounds in their metasternal glands and also that the odor blend produced by female MGs induces males to orientate toward associated airstreams.[6] Similar results have been presented from the related species *R. prolixus* in two recent reports,[5,18] reinforcing the idea that MG volatiles act as semiochemicals mediating triatomine sexual behavior. Furthermore, Vitta et al. showed that the attractiveness of female *T. brasiliensis* was lost when their MGs were mechanically blocked, that only males responded to female MG secretions, and that at least some of the dioxolanes described in this report triggered antennal responses in males.[6] The combination of the results from behavioral bioassays and EADs suggests the dioxolanes to be semiochemicals in triatomine bugs.

Interestingly, in contrast to pheromones with structures of bicyclic acetals[19] or spiroacetals[20] originating from intramolecular cyclization of corresponding ketodiols, the new 1,3-dioxolanes are probably products of intermolecular condensations. If these compounds, which are detected by the bugs,[6] play a role in the chemical communication of adult triatomines, they could be used in chemical baits in traps for monitoring or controlling Chagas disease vectors. Investigations on behavior-mediating activities of the new 1,3-dioxolanes will be a subject of further studies.

EXPERIMENTAL SECTION

General Experimental Procedures. For synthesized compounds ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 and 125 MHz, using a Varian Unity spectrometer. Alternatively, Bruker AV 400 and DRX 500 instruments were used. Tetramethylsilane served as the internal standard. Mass spectra (70 eV, EI) of synthetic compounds were obtained with an HP 6890 GC interfaced to an HP 5973 mass selective detector (Hewlett-Packard, Palo Alto, CA, USA), using helium as the carrier gas. The GC was equipped with a BPX-70 column (30 m × 0.25 mm i.d., 0.25 μm film, SGE Australia). Enantioselective GC of synthetic compounds was performed with an HP 5890 GC (Hewlett-Packard, Palo Alto, CA, USA) equipped with a CYCLOSILB column (30 m × 0.25 mm i.d., 0.25 μm film, J & W Scientific, USA).

All chemicals used for the syntheses were purchased from Sigma-Aldrich (Sweden or Germany), Alfa Aesar (Germany), and Merck (Germany). Anhydrous solvents were employed when appropriate, and reactions were carried out under nitrogen when required. Preparation and analysis of metasternal glands as well as co-injection with peak enhancement, including the corresponding instrumental setup, were described earlier.[4] Column chromatography (CC) on silica gel was carried out using a medium-pressure liquid chromatography (MPLC) system from Separo.[21]

Coupled gas chromatography/mass spectrometry GC/MS was carried out according to Vitta et al.[6] or the following protocol: A SPME fiber (Carboxen/PDMS Supelco, USA) was preheated for 30 min at 140 °C in the injection port of the GC and subsequently held for 30 min at 50 °C in the vial with the sample of metasternal glands. The fiber was desorbed in the injection port for 50 s. Mass spectra were obtained with an HP 5890 GC (Hewlett-Packard, Palo Alto, CA, USA) linked to a VG 70-250 SE double-focusing mass spectrometer (Vacuum Generators, Manchester, UK). GC-conditions: 50 m Optima FFAP (0.25 mm i.d., 0.25 μm film), 1 min 50 °C, then programmed to 75 °C at a rate of 10 °C/min, then programmed to 240 °C at a rate of 15 °C/min, 1 min splitless injection. High-resolution GC/MS analyses, GC/HR-EI-MS (RP:5000) and GC/CI-MS (isobutane, TP:600), respectively, were carried out under the same conditions.

All stereoisomers of 1,3-dioxolanes were formed by reaction of 2,3-pentanediol with 3-pentanone, butanone, 2-methylpropanal, 2-methylbutanal, and 3-methylbutanal, as described below.

Methyl (*R*)-2-(Tetrahydropyran-2-yloxy)propanoate. (*R*)-Methyl lactate (4.40 g, 42.3 mmol, 96% ee) was dissolved in DCM (15 mL), and *p*-TsOH (10 mg) was added. At 0 °C, DHP (5.34 g, 63.5 mmol, 5.77 mL) was added dropwise by syringe while stirring. The reaction mixture was allowed to warm to rt under continuous stirring. After 3 h at rt the mixture was washed with saturated aqueous solutions of $NaHCO_3$ and brine, dried over magnesium sulfate, and concentrated in vacuo. The crude product (9.77 g) was purified by MPLC, yielding 7.7 g of a mixture of diastereomers in a ratio of 2:1 and 90% purity, which was used for the next step. EIMS *m/z* 129 (7), 101 (32), 88 (8), 87 (7), 85 (100), 71 (7), 67 (10), 59 (7), 57 (10), 56 (8), 55 (12), 45 (9), 43 (9), 41 (10). NMR data corresponded to published data.[22,23]

Methyl (*S*)-2-(Tetrahydropyran-2-yloxy)propanoate. (*S*)-Methyl lactate (8.80 g, 84.6 mmol, 97% ee) was protected in the same manner as described for methyl (*R*)-2-(tetrahydropyran-2-yloxy) propanoate. After MPLC, 9.40 g of product of 84% purity was used for the next step. For analytical data see methyl (*R*)-2-(tetrahydropyran-2-yloxy)propanoate.

(*R*)-2-(Tetrahydropyran-2-yloxy)-3-pentanol. Magnesium (6.9 g, 0.29 mol) and some crystals of iodine were added to a round-bottom flask, which was heated until iodine vapors were formed. After cooling, THF (100 mL) was added, followed by ethyl bromide (28.5 g, 19.5 mL, 0.27 mol, dropwise addition via syringe) while maintaining spontaneous reflux to form the Grignard reagent. Subsequently, reflux was continued for 30 min before the mixture was allowed to cool to rt.

Methyl (*R*)-2-(tetrahydropyran-2-yloxy)propanoate (7.05 g, 0.034 mol (calcd on 90% purity)) was dissolved in toluene (30 mL), and the mixture was cooled to −75 °C. DIBAH (1.5 M in toluene, 28 mL, 0.042 mol) was added dropwise by syringe to the stirred solution, maintaining the temperature of the reaction mixture at −70 °C. Stirring was continued at this temperature for 30 min.

To the stirred solution of the product, obtained from the reaction of methyl (*R*)-2-(tetrahydropyran-2-yloxy)propanoate and DIBAH, ethyl magnesium bromide (60 mL, ca. 0.16 mol) was added dropwise

at −70 °C. The mixture was stirred continuously for 20 min and during the following 40 min slowly warmed to rt. Subsequently, the mixture was poured into ice−water, and HCl (aq, 10%) was added until all precipitate was dissolved. The aqueous phase was extracted with THF/toluene, and the combined organic layers were washed with NaOH (1 M), NaOH (2 M), and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was distilled under reduced pressure (bp 22 °C at 32 Torr). The crude product, a slightly yellow oil with a purity of 87% (7.55 g) containing traces of solvents, was used for the next step. EIMS *m/z* 129 (3), 101 (3), 87 (11), 86 (8), 85 (100), 84 (8), 69 (5), 67 (8), 57 (11), 56 (7), 55 (5), 45 (9), 43 (6), 41 (8).

(*S*)-2-(Tetrahydropyran-2-yloxy)-3-pentanol. In the same manner as described above, methyl (*S*)-2-(tetrahydropyran-2-yloxy) propanoate (9.4 g, 0.042 mol (calcd on 84% purity) was converted to a product of ca. 70% purity (5.06 g), which was immediately used for the next step. For MS data see (*R*)-2-(tetrahydropyran-2-yloxy)-3-pentanol.

(2*R*,3*R*)- and (2*R*,3*S*)-Pentanediol. A stirred solution of (*R*)-2-(tetrahydropyran-2-yloxy)-3-pentanol (7.55 g, 87% purity) in MeOH (100 mL) was kept at 45 °C while Amberlyst 15 (3.0 g) was added. After 2 h the reaction mixture was filtered through cotton, and the solvent was removed in vacuo. The crude product (3.10 g) was purified, and the obtained diastereomers of 2,3-pentanediol were separated by repetitive MPLC (2 times). In total 522 mg of (2*R*,3*R*)-pentanediol (99% chemical purity and 98% enantiomeric purity as checked by enantioselective GC) and 707 mg of (2*R*,3*S*)-pentanediol were obtained (99% chemical purity and 96% enantiomeric purity as checked by enantioselective GC). EIMS *m/z* 89 (1), 75 (10), 71 (4), 60 (4), 59 (100), 58 (37), 57 (21), 55 (2), 47 (2), 46 (2), 45 (44), 44 (2), 43 (14), 42 (5), 41 (18), 40 (1), 39 (4).

(2*S*,3*S*)- and (2*S*,3*R*)-Pentanediol. In the same manner as above, 5.06 g of (*S*)-2-(tetrahydropyran-2-yloxy)-3-pentanol (70% purity) were deprotected. The crude diol (2.79 g) was obtained in 47% purity. The diastereomers were separated by repetitive MPLC (3 times). In total, 491 mg of (2*S*,3*S*)-pentanediol (98% chemical purity and 96% enantiomeric purity) and 473 mg of (2*S*,3*R*)-pentanediol were obtained (99% chemical purity and 95% enantiomeric purity). Spectroscopic data were in accord with the corresponding isomers derived from (*R*)-2-(tetrahydropyran-2-yloxy)-3-pentanol and with literature data.[15]

(4*R*,5*S*)-2,2,4-Triethyl-5-methyl-1,3-dioxolane, (4*R*,5*S*)-1. To a solution of 324 mg (3.8 mmol) of 3-pentanone in 25 mL of pentane were added 10 mg of *p*-TsOH, 100 mg of 4 Å molecular sieves (powdered), and 200 mg of (2*S*,3*R*)-pentanediol (1.92 mmol). The mixture was stirred at rt. Over the next 6 days, additional 3-pentanone was added (200 mg/d). The product was isolated by MPLC to yield a colorless oil (138 mg, 42%) of 99% isomeric purity and 96% chemical purity. EIMS *m/z* 144 (5), 143 (52), 128 (1), 114 (5), 87 (12), 86 (14), 75 (3), 70 (4), 69 (39), 58 (4), 57 (100), 56 (4), 55 (9), 45 (7), 43 (5), 42 (4), 41 (13), 39 (4); TOF-MS $(M + H)^+$ *m/z* 173.1529 (calcd for $C_{10}H_{21}O_2$, 173.1542); NMR data matched those reported earlier.[7]

(4*S*,5*R*)-2,2,4-Triethyl-5-methyl-1,3-dioxolane, (4*S*,5*R*)-1: colorless oil from 3-pentanone and (2*R*,3*S*)-pentanediol; same procedure as for (4*R*,5*S*)-**1**; for MS see (4*R*,5*S*)-**1**; NMR data matched those reported earlier.[7]

(4*R*,5*R*)-2,2,4-Triethyl-5-methyl-1,3-dioxolane, (4*R*,5*R*)-1: colorless oil from 3-pentanone and (2*R*,3*R*)-pentanediol; same procedure as for (4*R*,5*S*)-**1**. EIMS *m/z* 144 (5), 143 (57), 128 (2), 114 (10), 87 (11), 86 (22), 75 (3), 70 (7), 69 (65), 58 (4), 57 (100), 56 (5), 55 (14), 45 (8), 43 (6), 42 (6), 41 (18), 39(5); NMR data matched those reported earlier.[7]

(4*S*,5*S*)-2,2,4-Triethyl-5-methyl-1,3-dioxolane, (4*S*,5*S*)-1: colorless oil from 3-pentanone and (2*S*,3*S*)-pentanediol; same procedure as for (4*R*,5*S*)-**1**; for MS see (4*R*,5*R*)-**1**; NMR data matched those reported earlier.[7]

(2*R/S*,4*S,5*S**)-2,4-Diethyl-2,5-dimethyl-1,3-dioxolane, (2*R/S*,4*S**,5*S**)-2.** A solution of 100 mg (1.43 mmol) of (*Z*)-2-pentene in 5 mL of dry CH_2Cl_2 was cooled to 0 °C. After the addition of a dried solution of 398 mg (77%, 1.77 mmol) of *m*-CPBA in 5 mL of DCM the mixture was stirred at rt for 16 h. Subsequently, 10 mL of hexane was added, and the solution was condensed into a cooled receiver under reduced pressure. The DCM/hexane solution of the crude (2*R**,3*S**)-2-ethyl-3-methyloxirane was used in the next step without purification.

The whole amount of (2*R**,3*S**)-2-ethyl-3-methyloxirane obtained in the previous step was dissolved in 20 mL of a dry 1:1 mixture of DCM and hexane and cooled to 0 °C, and 50 μL (57 mg, 0.40 mmol) of $BF_3 \cdot Et_2O$ was added. After the addition of 113 mg (1.57 mmol) of freshly destilled 2-butanone, the solution was stirred at rt for 12 h. Subsequently, 2 mL of a saturated aqueous solution of $NaHCO_3$ was added. After stirring for 15 min the organic layer was dried over magnesium sulfate, filtered, and concentrated. The residue was chromatographed on silica gel using pentane/diethyl ether (10:1) as the eluent, to give 129 mg (0.82 mmol, 57% over two steps) of (2*R/S*,4*S**,5*S**)-**2** as a colorless oil. The chemical purity of the product was 97%, and the diastereomeric purity 96%. EIMS *m/z* 143 (17), 130 (5), 129 (70), 114 (5), 100 (18), 87 (15), 74 (3), 73 (28), 72 (45), 71 (4), 70 (6), 69 (96), 59 (8), 58 (6), 57 (49), 56 (19), 55 (14), 53 (3), 45 (23), 43 (100), 42 (3), 41 (33), 39(10); HR-GC/MS $(M + H)^+$ *m/z* 159.1382 (calcd for $C_9H_{19}O_2$, 159.1385). Although the C2-epimers could not be separated chromatographically, NMR assignments were made to the two different stereoisomers on the basis of two-dimensional NMR experiments.

(2*R/S*,4*S*,5*S*)-4-Ethyl-5-methyl-2-(1-methylethyl)-1,3-dioxolane, (2*R/S*,4*S*,5*S*)-3. To a solution of 2-methylpropanal (163 mg, 2.3 mmol) in diethyl ether (25 mL) were added *p*-TsOH (ca. 10 mg), 4 Å molecular sieves (powdered, ca. 100 mg), and (2*S*,3*S*)-pentanediol (200 mg, 1.92 mmol). The mixture was stirred at rt overnight and then filtered through cotton. The product was washed twice with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated in vacuo to yield a slightly yellow oil (201 mg, 66%). The chemical purity was 99%, and the diastereomeric purity 96%, while the C2-epimers were present in a ratio of 1:1. EIMS *m/z* 157 (4), 116 (7), 115 (100), 114 (4), 100 (7), 87 (3), 73 (3), 72 (3), 71 (4), 70 (6), 69 (80), 57 (13), 56 (33), 55 (8), 45 (23), 43(14), 41 (17), 39 (5); TOFMS $(M + H)^+$ *m/z* 159.1349 (calcd for $C_9H_{19}O_2$, 159.1385). Although the C2-epimers could not be separated chromatographically, NMR assignments were made to two different stereoisomers on the basis of two-dimensional NMR experiments.

(2*R/S*,4*R*,5*R*)-4-Ethyl-5-methyl-2-(1-methylethyl)-1,3-dioxolane, (2*R/S*,4*R*,5*R*)-3: colorless oil from 2-methylpropanal and (2*R*,3*R*)-pentanediol; same procedure as for (2*R/S*,4*S*,5*S*)-**3**; for spectroscopic data see (2*R/S*,4*S*,5*S*)-**3**.

(2*S,4*S**,5*S**,1′*R/S*)- and (2*R**,4*S**,5*S**,1′*R/S*)-4-Ethyl-5-methyl-2-(1-methylpropyl)-1,3-dioxolane, (2*S**,4*S**,5*S**,1′*R/S*)-4 and (2*R**,4*S**,5*S**,1′*R/S*)-4.** Following the procedure described for the synthesis of (2*R/S*,4*S**,5*S**)-**2**, 100 mg (1.43 mmol) of (*E*)-2-pentene dissolved in 5 mL of dry DCM was transformed to the epoxide and subsequently reacted with 135 mg (1.57 mmol) of freshly distilled *rac*-2-methylbutanal to give 92 mg (0.53 mmol, 37% over two steps) of a mixture of (2*S**,4*S**,5*S**,1′*R/S*)-**4** and (2*R**,4*S**,5*S**,1′*R/S*)-**4** as a colorless oil: EIMS *m/z* 171 (3), 128 (5), 116 (7), 115 (100), 114 (3), 99 (2), 87 (5), 86 (4), 85 (3), 71 (6), 70 (27), 69 (85), 59 (3), 58 (3), 57 (14), 55 (13), 45 (30), 43 (5), 42 (6), 41 (23), 39 (7); HR-GC/MS $(M + H)^+$ *m/z* 173.1539 (calcd for $C_{21}H_{19}O_2$, 173.1542). Although the C2-epimers could not be separated chromatographically, NMR data could be assigned on the basis of NOESY experiments including the protons at C2, C4, and C5 and on two-dimensional NMR experiments.

(2*S,4*S**,5*S**)- and (2*R**,4*S**,5*S**)-4-Ethyl-5-methyl-2-(2-methylpropyl)-1,3-dioxolane, (2*S**,4*S**,5*S**)-5 and (2*R**,4*S**,5*S**)-5.** Following the procedure described for the synthesis of (2*R/S*,4*S**,5*S**)-**2**, 100 mg (1.43 mmol) of (*E*)-2-pentene dissolved in 5 mL of dry CH_2Cl_2 was transformed to the epoxide and subsequently reacted with 135 mg (1.57 mmol) of freshly distilled 3-methylbutanal to give 107 mg

(0.62 mmol, 43% over two steps) of a mixture of (2*S**,4*S**,5*S**)-**5** and (2*R**,4*S**,5*S**)-**5**. EIMS *m*/*z* 171 (4), 128 (2), 116 (6), 115 (100), 114 (4), 113 (7), 99 (15), 87 (5), 85 (8), 71 (12), 70 (6), 69 (81), 68 (3), 59 (2), 58 (2), 57 (11), 55 (6), 45 (27), 43 (12), 42 (4), 41 (23), 39 (7); HR-GC/MS $(M + H)^+$ *m*/*z* 173.1537 (calcd for $C_{10}H_{21}O_2$, 73.1542). Although the C2-epimers could not be separated chromatographically, NMR data were assigned on the basis of NOESY experiments including the protons at C2, C4, and C5 and upon two-dimensional NMR experiments.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. NMR and mass spectra of all new compounds are available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +46 480 446271. Fax: +46 480 446262. E-mail: rikard.unelius@lnu.se.

Notes

△Stephan Franke passed away in December 2010; his scientific achivements keep him among us.

Present Addresses

#Research School of Chemistry and Research School of Biology, The Australian National University, Canberra, ACT 0200, Australia.

⊥The Plant & Food Research Institute of New Zealand, P.O. 51 Lincoln, New Zealand.

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