Synthesis and Stereochemistry of Chrysomelidial and Plagiolactone[1,2]

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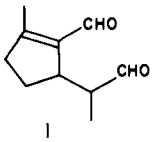
Abstract: Syntheses of chrysomelidial and plagiolactone, two recently characterized insect defensive terpenoids, are described. The absolute configuration of plagiolactone is established, and a probable absolute configuration is assigned to chrysomelidial. Autoxidation of chrysomelidial was found to give plagiolactone in low yield, accompanied by the corresponding cyclic acid anhydride.

The recent characterization of chrysomelidial (**1**) and plagiolactone (**2**) from the larvae of certain chrysomelid beetles[3,4] has added two new representatives to the list of physiologically active and biosynthetically important cyclopentanoid monoterpenes.[5] While qualitative evidence for the defensive role of these two insect secretions has already been presented,[3,4] the amounts of **1** and **2** available from natural sources for any more



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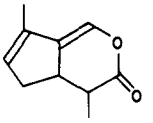


2

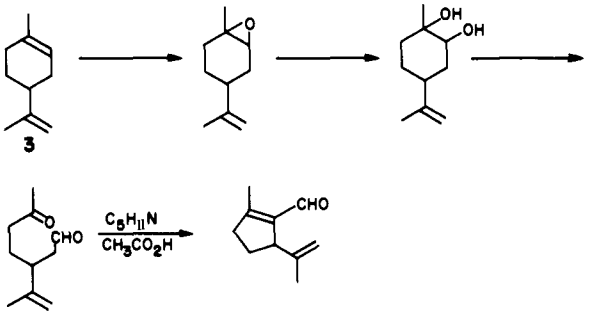
detailed study are extremely small. We have now carried out syntheses of **1** and **2** which confirm the structure and stereochemistry of these natural products, and which allow the preparation of samples for more extensive biological studies.

An attractive strategy for the synthesis of cyclopentanoid monoterpenes, based on the cleavage and recyclization of limonene (**3**) as outlined in Scheme I, has been described by Wolinsky et al.[6]

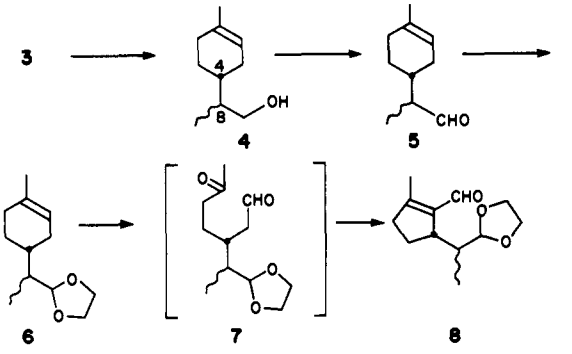
For our purposes (see Scheme II), it was expedient to modify this approach by functionalizing the terminal double bond of **3** prior to oxidative opening of the cyclohexene ring. Treatment of (+)-(4*R*)-**3** with disiamylborane resulted in the formation of (+)-(4*R*)-*p*-menth-1-en-9-ol (**4**, as a 3:2 mixture of 4*R*,8*R* and 4*R*,8*S* epimers), as described by Pawson et al.[7] Oxidation of **4** with pyridinium chlorochromate[8] gave (4*R*)-*p*-menth-1-en-9-al (**5**),[9] which was protected as the corresponding dioxolane (**6**) by treatment with ethylene glycol. We anticipated that ozonolysis of **6** would provide the desired keto aldehyde (**7**) in a single step. Disappointingly, ozonolysis of an ethereal solution of **6** at −78 °C gave only polymeric product. Nevertheless, in tetrahydrofuran solution, ozonolysis at −78 °C, followed immediately by catalytic hydrogenation (Pd/C), gave **7** as an unstable intermediate which could be cyclized directly to the cyclopentene-aldehyde **8** under Knoevenagel condensation conditions.[6,10] Refluxing 50% aqueous acetic acid[11] removed the protecting group from **8**, and yielded the dialdehyde **1** in 41% overall yield from **6**. As anticipated, **1** produced in this way proved to be a mixture of two diastereomers (in 3:1 ratio), as could be readily seen from its ^{1}H NMR spectrum.[21] This mixture of epimers could not be separated into its individual components by TLC or GLC. However, the mass spectrum and ^{1}H NMR spectrum of synthetic **1** gave clear confirmation of the chrysomelidial structure.[3,4]

Because of the difficulty encountered in separating the two stereoisomers present in synthetic **1**, we returned to an examination of its precursor (**8**), which was found to be readily separable into two pure epimers by preparative GLC. Hydrolysis of each of these acetals as described above gave ep-

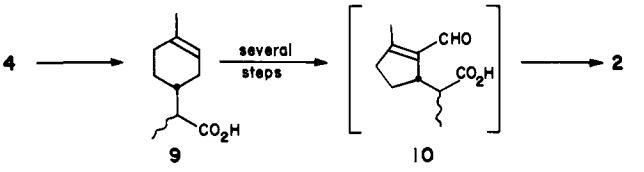
Scheme I



Scheme II



Scheme III



imerically pure samples of dialdehyde **1**. The minor isomer produced in this sequence (whose stereochemistry is discussed later in this paper) corresponded exactly to natural chrysomelidial (^{1}H NMR, MS, GLC).[3,4]

The synthesis of plagiolactone also started with alcohol **4**, and followed a similar pattern (see Scheme III). Jones oxidation of **4** gave acid **9**,[9] which was subjected to ozonolysis, hydrogenation, Knoevenagel condensation to **10** (in benzene, without added acetic acid), and finally cyclization[12] to give **2**, without the isolation of any of the intermediates. Once again, the product obtained in this way was a pair of diastereomers which could not be separated by TLC or GLC. Nevertheless, spectral comparisons confirmed that one of the two synthetic stereoisomers was identical to natural plagiolactone.

In its ^{1}H NMR spectrum, natural plagiolactone shows a doublet at δ 1.29 (J = 6.8 Hz) arising from its saturated (C_4)

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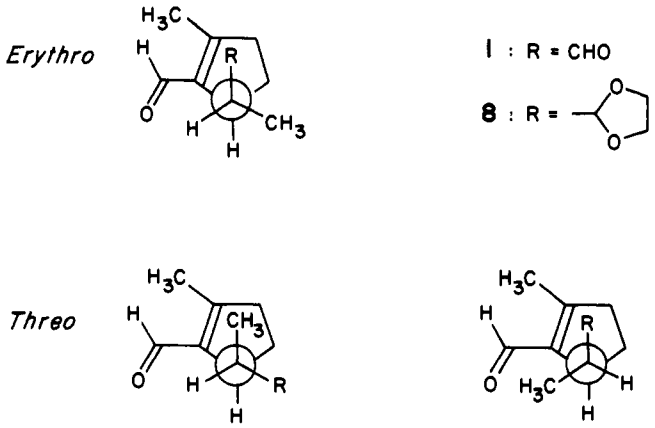
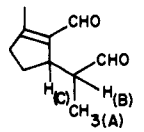
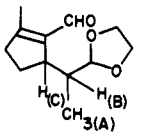
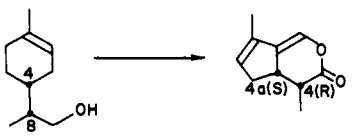


Figure 1. Preferred conformations of 1 and 8.

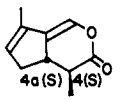
Table I. Selected 90-MHz ^{1}H NMR Data for Individual Stereoisomers of 1 and 8

Structure	Isomer identification and assigned configuration	δ, ppm from Me_4Si A	B	C
	Major—erythro	1.01	2.83	3.43
	Minor—threo	0.88	3.13	3.70
	Major—erythro	0.92	2.25	3.18
	Minor—threo	0.72	2.46	3.43

methyl group. Synthetic **2** shows this doublet along with another doublet (δ 1.08, J = 6.8 Hz) attributable to the corresponding methyl group in the C_4 epimer. The stereochemistry of this C_4 epimer ("epiplagiolactone") was rigorously established by subjecting pure (4*R*,8*R*)-**4**[13] to the synthetic sequence outlined in Scheme III. This gave (4a*S*,4*R*)-epiplagiolactone (showing the δ 1.08 doublet) as a single, stereochemically pure product (see eq 1). This erythro product, with


(1)

an *S* chiral center attached directly to the diene chromophore, shows a negative Cotton effect, as does natural plagiolactone itself.[3] These observations support our earlier assignment of the *S* configuration to C_{4a} in plagiolactone, which was originally based on an empirical correlation put forward by Charney et al.[14] The configuration of plagiolactone at C_4 must also be *S*, making it a (4a*S*,4*S*) threo isomer, since natural plag-



plagiolactone

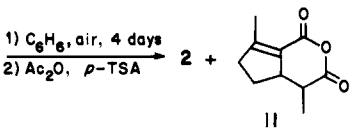
iolactone and epiplagiolactone are epimeric at C_4.

Three independent arguments can be made to assign the stereochemistry of natural chrysomelidial. Hydroboration of (*R*)-limonene (**3**) is known to produce (4*R*,8*R*)-**4** as the major product, and (4*R*,8*S*)-**4** as the minor product.[7,15] Assuming that the ratio of stereoisomers remained substantially unchanged throughout the synthesis of **1**, the product should contain more (1*S*,α*R*)-**1** than (1*S*,α*S*)-**1**. On this basis, the natural product is the (1*S*,α*S*) threo isomer (or its enantiomer).

chrysomelidial

Since the assumptions made in the above argument may not be justified, we also undertook ^{1}H NMR studies of the individual epimers of **1** and their precursors to establish the configurations of the individual diastereomers of **1** more definitively. In several instances described in the literature, it has been possible to distinguish between threo and erythro isomers with adjacent chiral centers, on the basis of the coupling constants observed between the vicinal protons on these chiral centers.[16,17] This technique proved to be inapplicable to our dialdehydes, however, since irradiation of the saturated methyl group at C_α in each isomer showed the proton at C_α to be split by its neighboring proton with the same coupling constant (4.5 Hz). Consideration of chemical shift values provides a more reliable criterion for assigning configurations to erythro and threo isomers, at least in some cases.[18,19] The first step in this analysis requires the selection of the most important conformation(s) of the compound in question; predictions about relative chemical shifts are then based on these conformations. In our case, conformations in which the vicinal protons under consideration are *antiperiplanar* to each other seem to be unimportant, as judged from the small value of their mutual coupling constant referred to above. We have selected the conformations shown in Figure 1 as the most likely to predominate. The ^{1}H NMR spectra of the major and minor isomers of both **1** and **8** show particularly clear differences for each of three signals, leading to the assignment of erythro and threo configurations, respectively, as summarized in Table I. Based on the conformations given in Figure 1, the C_α methyl protons (A in Table I) would be expected to appear at higher field in the threo isomers, because of their preferential positioning over the plane of the *enal* chromophore. Similarly, the C_α protons (B in Table I) should resonate at higher fields in the erythro isomers. Finally, the C_1 protons would be expected to be deshielded, by either the dioxolane ring in **8** or the aldehyde function in **1**, in the threo isomers. These three sets of chemical shift differences make a consistent pattern for both **1** and **8** and support the tentative configurational assignment of the erythro configuration to the major synthetic isomer and threo configuration to the minor one, made on the basis of isomer ratios persisting throughout the synthesis.

The conclusion that natural chrysomelidial has the threo configuration is in no way surprising since we have already established the (4a*S*,4*S*)-threo configuration for its congenor, plagiolactone.[22] In fact, the obviously close relationship between these two terpenoids[3] led us to investigate the autoxidation of **1**, which might be expected to give **2** and/or an isomeric enol lactone, as well as the corresponding cyclic anhydride. Our experimental results are summarized in eq 2. While


(2)

it is not unexpected that the major volatile product (80%) proved to be a mixture of stereoisomeric acid anhydrides (**11**), the second most important product was shown to be **2** (undoubtedly a mixture of plagiolactone and epiplagiolactone) on the basis of GC/MS analysis.[23] While this exploratory

autoxidation experiment does not suggest that plagiolactone could be made efficiently from chrysomelidial in the laboratory, it does serve to relate these two naturally occurring cyclopentanoid terpenoids to each other.

Experimental Section

Ultraviolet spectra were obtained using a Cary 14 spectrophotometer. Infrared spectra were obtained from neat liquid films with a Perkin-Elmer 257 grating infrared spectrophotometer. Nuclear magnetic resonance spectra were obtained at 60 MHz with a Varian A-60A instrument, at 90 MHz with a Varian EM-390 instrument, and at 100 MHz with a Jeolco XL-100 instrument. Mass spectra were obtained using a Finnigan Model 3300 GC/MS coupled to a System Industries Model 150 computer. High-resolution mass spectra were obtained using an AEI MS-902 instrument coupled to a VG Data System 2020 computer. Optical rotatory dispersion curves were obtained using a Cary Model 60 ORD/CD spectrophotometer.

***p*-Menth-1-en-9-al (5).**[9] A solution containing 2.0 g (13 mmol) of *p*-menth-1-en-9-ol[7] in 15 mL of CH_2Cl_2 was added all at once to a rapidly stirred suspension of 4.2 g of pyridinium chlorochromate[8] in 40 mL of CH_2Cl_2. After 2 h, the mixture was diluted with three volumes of ether and stirred for an additional 1 h. The mixture was filtered through Florisil and distilled to give 1.3 g of pure aldehyde (68% yield), bp 82–85 °C (8 mmHg): IR 2700, 1725 cm^{-1}; NMR (60 MHz) δ 1.05 (3 H, d, J = 7 Hz), 1.5–2.3 (11 H, complex multiplet), 5.34 (1 H, br s), 9.63 (1 H, d, J = 2 Hz); MS *m/e* (rel intensity) (0.4), 95 (16), 94 (100), 93 (13), 79 (73), 77 (11), 68 (10), 67 (22), 55 (10), 53 (8); calcd *m/e* for $C_{10}H_{16}O$, 152.1201 (found, 152.1209).

***p*-Menth-1-en-9-al Ethylene Acetal (6).** A solution containing 1.2 g of aldehyde (**5**), 0.5 g of ethylene glycol, and a few crystals of *p*-toluenesulfonic acid in 20 mL of benzene was refluxed using a Dean-Stark trap for 5 h. The mixture was cooled, washed with saturated $NaHCO_3$, and dried over anhydrous K_2CO_3. Distillation gave 1.3 g of pure acetal (**6**) (86% yield), bp 116–120 °C (7.5 mmHg): NMR (60 MHz) δ 0.90 (3 H, br d, J = 7 Hz), 1.4–2.1 (11 H, complex multiplet), 3.88 (4 H, br d, J = 2 Hz), 4.8 (1 H, multiplet), 5.35 (1 H, br s); MS *m/e* (rel intensity) 196 (11), 139 (31), 95 (13), 94 (94), 93 (12), 79 (31), 74 (4), 73 (100), 72 (9), 67 (13), 45 (14); calcd *m/e* for $C_{12}H_{20}O_2$, 196.1463 (found, 196.1468).

5-[3-(1,3-Dioxolan-2-yl)ethyl]-2-methyl-1-cyclopentene-1-carboxaldehyde (8). Ozone was passed through a solution containing 1.0 g (5.1 mmol) of acetal (**6**) in 30 mL of THF at −78 °C for 15 min. A slurry of 100 mg of 10% Pd/C in 10 mL of THF was added to this mixture, which was then hydrogenated at atmospheric pressure (0 °C) until the uptake of hydrogen (130 mL) ceased. After filtration, the solvent was removed, and the residue was taken up in 15 mL of benzene. Piperidine (0.06 mL) and acetic acid (0.06 mL) were added, and the mixture was refluxed under a Dean-Stark trap for 2 h. Upon cooling, the mixture was washed with 2% HCl and saturated $NaHCO_3$, and dried over anhydrous $MgSO_4$. Gas chromatographic analysis indicated that two major components were obtained. IR 2740, 1660, 1625, and 1090 cm^{-1}; MS *m/e* (rel intensity) 210 (3), 149 (3), 148 (3), 109 (5), 108 (4), 107 (6), 101 (8), 100 (11), 91 (8), 81 (22), 79 (15), 77 (11), 74 (4), 73 (100), 67 (5), 65 (5), 53 (7), 51 (4), 45 (9); calcd *m/e* for $C_{12}H_{18}O_3$, 210.1256 (found, 210.1274). The individual stereoisomers of **8** were isolated by preparative GLC (2 m × 10 mm column packed with 6% SE-30 on Gas Chrom Q). The major isomer, with shorter retention time, showed the following ^1H NMR spectrum (90 MHz): δ 10.02 (1, s, CHO), 4.72 (1, d, J = 4.5, $CH(OCH_2)_2$), 3.84 (4, m, $-OCH_2CH_2O-$), 3.18 (1, m, $C{=}C(CH)CHO$), 2.45 (2, br t, $CH_2C{=}C$), 2.25 (1, m, $CHCH_3$), 2.13 (3, br s, $CH_3C{=}C$), 1.94 (2, m, $CH_2CH_2C{=}C$), 0.92 (3, d, J = 7.5 Hz, CH_3CH). The minor stereoisomer showed the following ^1H NMR spectrum (90 MHz): δ 10.02 (1, s, CHO), 4.75 (1, d, J = 6 Hz, $CH(OCH_2)_2$), 3.91 (4, m, $-OCH_2CH_2O-$), 3.43 (1, m, $C{=}C(CH)CHO$), 2.46 (3, m, $CH_2C{=}C$ and $CHCH_3$), 2.14 (3, br s, $CH_3C{=}C$), 1.89 (2, br t, $CH_2CH_2C{=}C$), 0.72 (3, d, J = 7.5 Hz, CH_3CH).

2-Formyl-α,3-dimethyl-2-cyclopentene-1-acetaldehyde (Chrysomelidial, 1). A solution containing all of the crude product (**8**) from ozonolysis and cyclization of 2.0 g of acetal (**6**) in 20 mL of 50% aqueous acetic acid was heated to reflux for 45 min. The mixture was cooled, poured into brine, and extracted with ether. The combined ether extracts were washed with dilute aqueous sodium bicarbonate and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was chromatographed on a 25 × 2 cm Florisil column. Elution with ether/hexane (1:3) gave 0.7 g (41% yield from acetal **6**) of chrysomelidial: UV λ_{max} (EtOH) 252 nm (ϵ 6900); IR 2710, 1720, 1660, 1625 cm^{-1}; NMR (100 MHz) δ 10.01 (1 H, s, $C{=}CCHO$), 9.70, 9.67 (1 H, s, s, $CHCHO$), 3.68, 3.45 (1 H, a pair of broad multiplets, $C{=}C(CHO)CH$), 3.10, 2.85 (1 H, a pair of complex multiplets, $CHCHO$), 2.55 (2 H, br t, $CH_2C{=}C$), 2.17 (3 H, br s, $CH_3C{=}C$), 2.1–1.5 (2 H, complex multiplet), 1.02, 0.89 (3 H, a pair of doublets, J = 7.0 Hz, CH_3CH); MS *m/e* (rel intensity) 166 (3), 148 (15), 138 (13), 136 (2), 120 (5), 109 (40), 108 (27), 107 (11), 105 (20), 96 (2), 95 (13), 93 (10), 91 (23), 82 (8), 81 (100), 80 (16), 79 (51), 78 (8), 77 (27), 67 (15), 65 (12), 55 (8), 53 (15), 51 (9); calcd *m/e* for $C_{10}H_{14}O_2$, 166.0994 (found, 166.0990).

Hydrolysis of Individual Acetal Aldehyde (8) Diastereomers. A small sample of each diastereomer of **8** (ca. 10 mg) was obtained by preparative GLC (2 m × 10 mm column packed with 6% SE-30 on Gas Chrom Q). Each compound was dissolved in 1.5 mL of 50% acetic acid and heated to reflux for 15 min. The cooled solutions were treated carefully with excess $NaHCO_3$ and extracted with chloroform. The chloroform extracts were dried over anhydrous $MgSO_4$ and filtered through a 1-cm plug of Florisil, and the solvent was removed with a gentle stream of argon.

The major acetal aldehyde diastereomer gave only one (erythro) diastereomer of chrysomelidial: NMR (90 MHz) δ 10.08 (1, s, $C{=}CCHO$), 9.72 (1, d, J < 1 Hz, $CHCHO$), 3.43 (1, m, $C{=}C(CH)CHO$), 2.83 (1, d of d of q, J = < 1, 4.5, and 6.8 Hz, $CHCH_3$), 2.54 (2, br t, $CH_2C{=}C$), 2.17 (3, br s, $CH_3C{=}C$), 1.65 (2, m, $CH_2CH_2C{=}C$), 1.01 (3, d, J = 6.8 Hz, CH_3CH); ORD (*c* 2.06 mg/mL) Φ_{270nm} −3900, Φ_{225nm} + 5400.

The minor acetal aldehyde diastereomer gave another (threo) diastereomer of chrysomelidial: NMR (90 MHz) δ 10.02 (1, s, $C{=}CCHO$), 9.72 (1, d, J = <1 Hz, $CHCHO$), 3.70 (1, m, $C{=}C(CH)CHO$), 3.13 (1, d of d of q, J = <1, 4.5, and 6.8 Hz, $CHCH_3$), 2.54 (2, br t, $CH_2C{=}C$), 2.18 (3, br s, $CH_3C{=}C$), 1.84 (2, m, $CH_2CH_2C{=}C$), 0.88 (3, d, J = 6.8 Hz, CH_3CH).

In *erythro*-chrysomelidial, irradiation of the doublet at 1.01 ppm collapsed the doublet of doublet of quartets at 2.83 ppm to a doublet of doublets, J = <1 and 4.5 Hz.

In *threo*-chrysomelidial, irradiation of the doublet at 0.88 ppm also collapsed the doublet of doublet of quartets at 3.13 ppm to a doublet of doublets, J = <1 and 4.5 Hz.

4a,5-Dihydro-4,7-dimethylcyclopenta[*c*]pyran-3(4*H*)-one (Plagiolactone, 2). Jones reagent[20] (16 mL) was added dropwise to a well-stirred solution containing 2.0 g (13 mmol) of *p*-menth-1-en-9-ol in 160 mL of acetone at 0 °C. Stirring was continued 45 min after the addition was complete. After filtration, the solvent was removed under reduced pressure and the residue was taken up in ether, washed with water, and dried over anhydrous $MgSO_4$. Removal of the solvent gave 2.1 g of crude acid (**9**) (IR 3300–2500 and 1710 cm^{-1}). This acid was taken up in 25 mL of tetrahydrofuran, cooled to −78 °C, and treated with an excess of ozone. A slurry of 0.5 g of 10% Pd/C in 5 mL of tetrahydrofuran was added, and the mixture was hydrogenated at 0 °C and atmospheric pressure until hydrogen uptake (350 mL) ceased.

The hydrogenation mixture was filtered and the solvent removed under reduced pressure. The residue was taken up in 30 mL of benzene, treated with 0.12 mL of piperidine, and refluxed under a Dean-Stark trap for 1 h. The cooled solution was washed with 2% HCl and dried over anhydrous $MgSO_4$.

After filtration, the benzene solution was treated with 8.4 mL of acetic anhydride and 0.2 g of *p*-toluenesulfonic acid and stirred overnight at room temperature under nitrogen. Following the addition of 1.0 g of sodium acetate, the solvents were removed in vacuo, and the residue was taken up in ether, filtered, and concentrated. Chromatography on a 25 × 2 cm Florisil column (hexane) gave 461 mg (22% yield from the Jones oxidation product) of **2**: UV λ_{max} (EtOH) 254 nm ϵ 7600); IR 3080, 3030, 1760, 1665, 1610, 1305, 1215, 1180, 1145, 1118, 1095, 1075, 1042, 1028, 1000, 920, and 800 cm^{-1}; NMR (90 MHz) δ 6.53 (1 H, s, $C{=}CHO$), 5.73 (1 H, s, $HC{=}C$), 3.35 (1 H, complex multiplet), 2.55–3.10 (1 H, complex multiplet), 2.40 (2 H, br multiplet, $CH_2C{=}C$), 1.78 (3 H, br s, $CH_3C{=}C$), 1.28, 1.08 (3 H, a pair of doublets, J = 6.8 Hz, CH_3CH); MS *m/e* (rel intensity) 164 (66), 136 (22), 121 (35), 108 (12), 107 (55), 106 (15), 105 (12), 93 (39), 91 (47), 80 (76), 79 (100), 78 (14), 77 (47), 65 (16), 51 (13); calcd *m/e* for $C_{10}H_{12}O_2$, 164.0837 (found, 164.0832).

(4a*S*,4*R*)-Plagiolactone (Epiplagiolactone, 2). A sample of approximately 2 g of (4*R*,8*R*)-*p*-menth-1-en-9-ol (**4**) was carried

through the above reaction sequence. Preparative gas chromatography (2 m × 10 mm column packed with 6% SE-30 on Gas Chrom Q) gave a sample of pure (4a*S*,4*R*)-plagiolactone: NMR (90 MHz) δ 6.53 (1 H, d, J = 3 Hz), 5.73 (1 H, s), 3.35 (1 H, complex multiplet), 2.91 (1 H, d of q, J = 5.3, 6.8 Hz, C*H*CH_3), 2.40 (2 H, multiplet, $CH_2C{=}C$), 1.76 (3 H, br s, $CH_3C{=}C$), 1.08 (3 H, d, J = 6.8 Hz, CH_3CH); ORD (c 3.2 mg/10 mL) (ethanol) Φ_{278nm} − 9200, Φ_{243nm} + 40 300.

Autoxidation of Chrysomelidial. A solution containing 100 mg of chrysomelidial (isomeric mixture from (*R*)-limonene) in 0.5 mL of benzene was stirred vigorously in an open vessel for 4 days. The reaction was followed by TLC until starting material could not be detected. The solution was then diluted with 5 mL of benzene, and treated with 1.0 mL of acetic anhydride and a few crystals of *p*-toluenesulfonic acid. After stirring overnight, 1.0 g of sodium acetate was added and the solvents were removed in vacuo. The residue was taken up in ether, filtered, and examined by GC/MS.

In the multicomponent product mixture, the next to the largest component (comprising ca. 5% of the mixture) was identified as plagiolactone by its characteristic mass spectrum. The largest component, 4,4a,5,6-tetrahydro-4,7-dimethylcyclopenta[*c*]pyran-1,3-dione (**11**) (ca. 80% of the mixture) was purified by preparative GLC (2 m × 10 mm column packed with 6% SE-30 on Gas Chrom Q) and had the following spectral data: IR 1790, 1745, 1640, 1428, 1372, 1340, 1260, 1232, 1215, 1170, 1140, 1118, 1104, 1070, and 980 cm^{-1}; NMR (90 MHz) δ 3.3 (1, m, C=C(CH)CO), 2.9 (1, m, C*H*CH_3), 2.62 (2, br t, $CH_2C{=}C$), 2.28 (3, br s, $CH_3C{=}C$), 1.30 and 1.14 (3, a pair of doublets, J = 7 Hz, CH_3CH); MS *m/e* (rel intensity) 180 (8), 152 (3), 136 (47), 121 (44), 108 (25), 107 (22), 94 (10), 93 (100), 91 (37), 80 (11), 79 (50), 78 (10), 77 (39), 65 (11), 51 (10); calcd *m/e* for $C_{10}H_{12}O_3$, 180.0786 (found, 180.0783).

References and Notes

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(2) This is Report No. 58 of the series "Defense Mechanisms of Arthropods". Report No. 57: T. Eisner, T. H. Jones, D. J. Aneshansley, W. R. Tschinkel, R. E. Silberglied, and J. Meinwald, *J. Insect Physiol.*, in press.
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(21) The natural chrysomelidial isolated by us from *Plagiodera versicolora* was also a mixture of these same diastereomers, but in the reverse (1:4) ratio. It is likely that our natural material was partially epimerized in the course of isolation,[3] since Blum et al.[4] isolated a *single* chrysomelidial isomer (from the larvae of *Gastrophysa cyanea*) whose ^1H NMR spectrum was identical to that of the major isomer from *P. versicolora*.
(22) Since **1** and **2** are almost certain to be closely related biosynthetically, it is likely that these two compounds also have the same absolute configurations. (This is our third argument for the configuration of **1**.)
(23) Interestingly enough, no other $C_{10}H_{12}O_2$ product, such as the enol lactone found in *Gastrophysa cyanea*,[4] was detected in this reaction mixture.

Synthesis of Mercury Mercaptide Azetidinones via 2- and 4-Methylthio-Substituted Cephalosporins

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Abstract: Treatment of 4β-methylthio-Δ^2-cephalosporins with methanol in the presence of mercuric acetate yields 4α-methoxy-Δ^2-cephalosporins and allylic rearrangement products including 2α- and 2β-methylthio-Δ^3-cephalosporins, 2α-acetoxy-Δ^3-cephalosporins, and bis[(4-oxo-2-azetidinyl)thio]mercury derivatives. The latter, which can also be obtained from 2α- and 2β-methylthio-Δ^3-cephalosporins, undergo ring closures to 2α- and 2β-methoxycephalosporins upon treatment with hydrogen sulfide.

We and other researchers have reported the conversion of 7α-methylthiocephalosporins to 7α-methoxycephalosporins by mercury(II)-mediated methanolysis.[2] We now report that mercuric acetate solvolysis of 2α- or 2β-methylthio-Δ^3- and 4β-methylthio-Δ^2-cephalosporins leads to various rearrangement products, including mercury mercaptide azetidinones that undergo facile ring closures to 2α- and 2β-alkoxy-Δ^3-cephalosporins when treated with H_2S.

Treatment of the 4β-methylthio-Δ^2-cephem **1a**[3,4] with 1.5 equiv of $Hg(OAc)_2$ in CH_3OH (30 min, 25 °C) afforded compounds **2a–6a** after isolation [TLC, silica gel, $CHCl_3$–EtOAc (9:1)]. The yields of most of these compounds were slightly lower with 1 equiv of $Hg(OAc)_2$. ^1H NMR spectral assignments of these and other compounds are indicated in Tables I and II.

The epimers **2a** [11%; amorphous; IR ($CHCl_3$) 1778 and 1740 cm^{-1}] and **3a** [7%; mp 97–99 °C; IR ($CHCl_3$) 1780 and 1745 cm^{-1}] both contained conjugated ester groups and were differentiated by the occurrence of a five-bonded coupling ($J_{2,7}$ = 0.5 Hz) in the 2α epimer.[5] The 2α-acetoxycephem **6a** [7%; amorphous; IR ($CHCl_3$) 1792 and ~1750 cm^{-1}] also exhibited in its ^1H NMR spectrum a five-bonded coupling ($J_{2,7}$ = 0.5

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