A SYNTHESIS OF TRANS- AND CIS-CARONALDEHYDES

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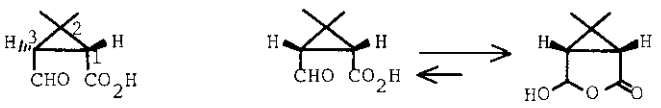
Abstract——A preparation of trans- and cis-caronaldehyde derivatives is described by employing iodolactonization reaction as a key step. Investigation is also carried out to establish an asymmetric synthesis by employing the same methodology which allows diastereoselective formation of optically active intermediates in both enantiomeric forms from a single precursor though the degree of asymmetric induction is found to be less satisfactory.

Both trans- and cis-caronaldehydes (1) and (2) are important starting materials in the synthesis of a number of potent pyrethroid insecticides which are safe to manmals and biodegradable.[1] Of these the cis-isomer (2) has become of interest in recent years since it can be used not only as the precursor for exceptionally potent insecticides such as NRDC 182[2] but also as an effective resolving agent for secondary alcohols.[3-5] We report here a synthesis of trans- and cis-caronaldehyde derivatives from prenyl alcohol (3) employing halolactonization reaction[6] as a key step.

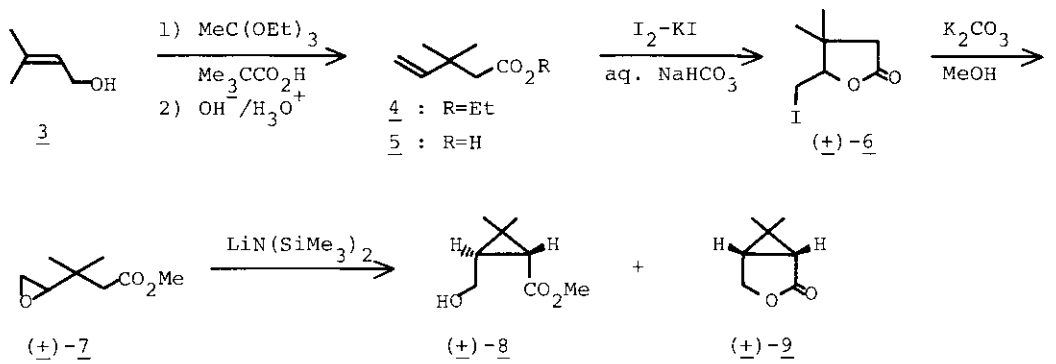


1 2a 2b

Scheme 1

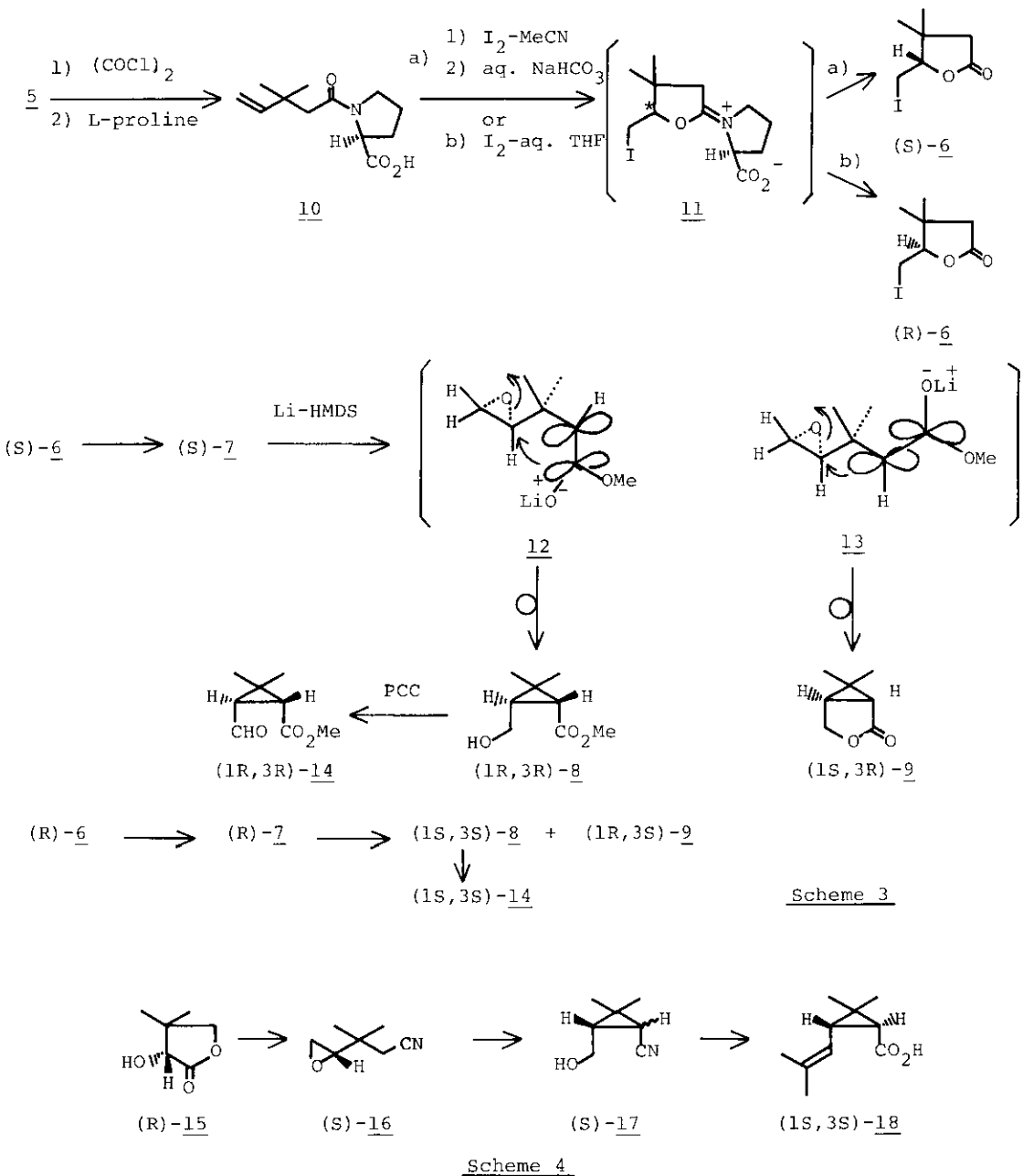
Prenyl alcohol (3) was converted into 3,3-dimethyl-4-pentenoic acid (5) in 64% overall yield in two steps via the ester (4) by employing the Johnson version of the Claisen rearrangement.[7] The same rearrangement reaction has been already carried out in 0.1 mol scale using five fold excess of triethyl orthoacetate to give the ester (4) in 34% yield after careful distillation,[8] however, the reaction could be carried out in 1 mol scale using one equivalent amount of the orthoacetate[9] and the product could be easily isolated as the acid (5) after saponification. Treatment of (5) with a mixture of iodine and

potassium iodide in 0.5 N aqueous sodium hydrogen carbonate brought about facile halolactonization to give the iodolactone (6) which on successive methanolysis in the presence of potassium carbonate afforded the γ,δ-epoxy ester (7), in 76% overall yield from (5). Cyclopropane ring formation via intramolecular concurrent ring opening-ring closing[10-12] of (7) could best be accomplished by using 1.5 equivalent of lithium hexamethyldisilazide in tetrahydrofuran at -30 °C. Under these conditions, (7) gave methyl trans-3-hydroxymethyl-2,2-dimethylcyclopropanecarboxylate (8) in 62% yield and cis-3-hydroxymethyl-2,2-dimethylcyclopropane-1-carboxylic acid lactone (9)[13-15] in 20% yield after separation by column chromatography. When lithium diisopropylamide was used in place of lithium hexamethyldisilazide yields of the products were decreased to 42.1 and 7.4%, respectively.



Scheme 2

On the other hand, we also investigated asymmetric synthesis of these cyclopropane derivatives applying the asymmetric iodolactonization developed by us.[16,17] The acid (5) was converted into the amide (10) in 85% overall yield via the acid chloride by treatment with oxalyl chloride followed by (S)-proline. Upon treatment with iodine in acetonitrile at 0 °C followed by 0.5 N aqueous sodium hydrogen carbonate at room temperature, the amide (10) furnished the optically active iodolactone ((S)-6), $[\alpha]_D$ + 10.1° ($CHCl_3$), in 71% yield, which gave the optically active epoxide ((S)-7), $[\alpha]_D$ + 2.22° ($CHCl_3$), in 74% yield, by methanolysis in the presence of potassium carbonate. Employing the same procedure for the racemic (7), the optically active ((S)-7) was treated with the base to give the cyclopropane ester ((1R,3R)-8), $[\alpha]_D$ - 7.0° ($CHCl_3$), in 63% yield and the cyclopropane lactone ((1S,3R)-9), $[\alpha]_D$ + 12.2° ($CHCl_3$), in 17% yield. Since the lactone (9) with (1R,3S)-configuration has been already known[18] ($[\alpha]_D$ - 72.8° (c 1.4, $CHCl_3$), 81% ee), the our lactone (9) should have (1S,3R)-configuration with about 10% ee of optical purity. In order to determine absolute configuration and optical purity, the ester ((1R,3R)-8) was oxidized with pyridinium chlorochromate to give the known trans-caronaldehyde ester[19] ((1R,3R)-14), $[\alpha]_D$ + 1.65° ($CHCl_3$), in 74% yield. The reported data[19] for the optically pure material (14) with (1R,3R)-configuration

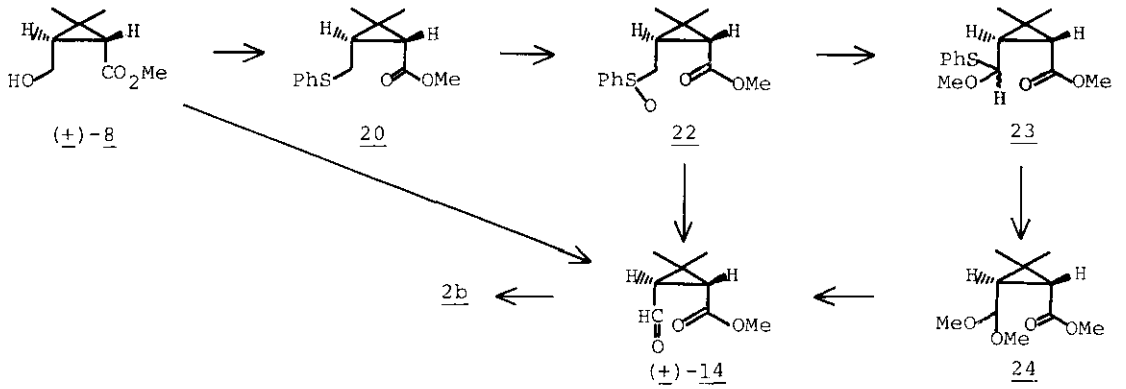


Scheme 3

Scheme 4

$[\alpha]_D$ + 16.0° (c 12, $CHCl_3$)) indicated that the our compound (14) should have (1R,3R)-configuration with about 10% ee of optical purity. Very interestingly, when the halolactonization was carried out in aqueous tetrahydrofuran an enantiomeric iodolactone ((R)-6), $[\alpha]_D$ - 4.43° ($CHCl_3$), was obtained in 93% yield. Employing the same procedure above, (R)-6 was converted into the epoxide ((R)-7), in 79% yield, which

then was converted into the trans-(1S,3S)-cyclopropane ester ((1S,3S)-8), $[\alpha]_D$ + 1.69° ($CHCl_3$), and the cis-(1R,3S)-cyclopropane lactone ((1R,3S)-9), $[\alpha]_D$ - 1.64° ($CHCl_3$), in 42% and 7.4% yields. The ester ((1S,3S)-8) was further oxidized to trans-caronaldehyde ester ((1S,3S)-14), $[\alpha]_D$ - 0.45° ($CHCl_3$), in 47% yield. In these conversions, though asymmetric induction ratio was disappointingly low, it is concluded that the two products obtained after the intramolecular cyclopropanation possessed the opposite configuration at 1 position each other as expected. This diastereoselectivity may be explained by simple intramolecular S_N2 pathway in the formation of both the trans-ester (8) and cis-lactone (9) with inversion of the configuration of C-4 position of (7) via the enolates (12) and (13) respectively as shown in Scheme 3. Absolute configuration of the optically active iodolactone (6) and the epoxide (7) was simply deduced by correlating the established data by Matsui et al.[11] who reported the synthesis of unnatural (1S,3S)-trans-chrysanthemic acid (18) from (2R)-pantolactone (15) by intramolecular cyclopropanation of the (3R)-epoxynitrile (16). This result allowed us to deduce the stereochemistry of our products as shown since stereochemical correlation between optically active chrysanthemic acid and caronaldehyde derivatives has been already reported.[20,21]

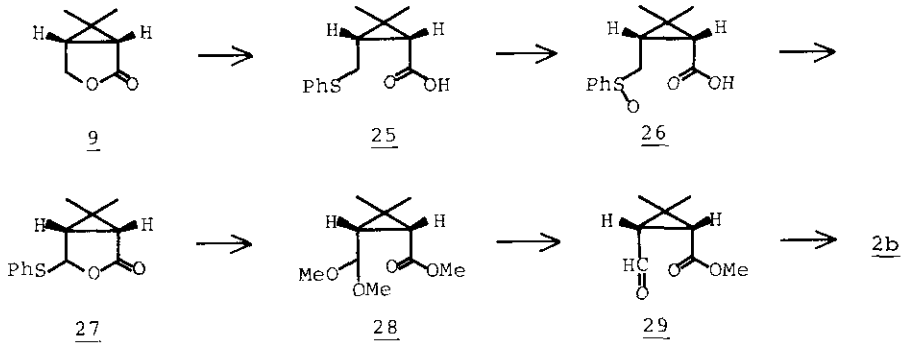


Scheme 5

Having failed to establish satisfactory chiral synthesis, the racemic substrates were used in the following investigation. Oxidation of the trans-ester (8) was first investigated. As for optically active case, the racemic (8) was oxidized with pyridinium chlorochromate to give trans-caronaldehyde ester (14) in 89% yield. In order to avoid using a chromium oxidant, two Moffatt type oxidations and other method were also explored. Thus, treatment of (8) with oxalyl chloride in dimethyl sulfoxide in the presence of

triethylamine[22] gave 14 in 90% yield, while (8) with pyridine-sulfur trioxide complex in dimethyl sulfoxide in the presence of triethylamine[23] also gave 14 in 88% yield but a small amount of an unseparable by-product presumably the sulfide (19) was contaminated in the latter conditions. The ester (8), on the other hand, was converted into the sulfide (20) in 87% yield employing Hata's method.[24,25] Although the dimeric by-product (21) was also obtained in 6.9% yield in this conversion, it could be easily separated by column chromatography. The major sulfide 20 was transformed into the sulfoxide (22) in 84% yield by treating with aqueous hydrogen peroxide, which, upon treatment with trifluoroacetic anhydride and 2,6-lutidine[26] followed by aqueous potassium carbonate, afforded the trans-caronaldehyde ester (14) in 39% overall yield. When methanolic potassium carbonate was applied to the Pummerer product, two separable thioacetals (23) was obtained in 52 and 24% yields, the both of which were converted into the same ester acetal (24) excellently with iodine in methanol, respectively. Upon hydrolysis with aqueous acid 24 gave trans-caronaldehyde methyl ester (14) in 63% yield. Conversion of (14) into cis-caronaldehyde (2b) has been first appeared in a patent claimed by Roussel-Uclaf[27] and later in the report by Montellano and Dinizo[28] by epimerization with sodium methoxide in refluxing methanol.

We next investigated the conversion of the cis-lactone (9) into cis-caronaldehyde (2b). Treatment of 9 with sodium phenylmercaptide gave the sulfide acid (25), in 81% yield, which gave the sulfoxide (26) quantitatively on treatment with aqueous hydrogen peroxide. Under the Pummerer reaction conditions using trifluoroacetic anhydride[26] 26 gave the lactone hemithioacetal (27), in 60% yield, which on stirring with iodine in methanol gave cis-caronaldehyde methyl ester dimethyl acetal (28), in 91% yield. As trans-acetal (24), upon brief exposure to aqueous acid 28 afforded cis-caronaldehyde methyl ester (29) which gave cis-caronaldehyde (2b) on prolonged treatment under the same hydrolytic conditions.



Scheme 6

EXPERIMENTAL

All reactions were carried under argon. Melting points are not corrected. IR spectra were measured with JASCO A-102 spectrophotometer, NMR spectra with JEOL PMX-60 and JEOL-FX 100 spectrometers (in deuteriochloroform solution using tetramethylsilane as internal references), MS spectra with a JEOL JMS-OISG 2 spectrometer, and optical rotations with a JASCO-DIP-4 automatic polarimeter.

3,3-Dimethyl-4-pentenoic Acid (5) A mixture of prenyl alcohol 3 (76.72 g, 0.89 mol) and triethyl orthoacetate (144.51 g, 0.89 mol) was refluxed in the presence of pivalic acid (9.1 g, 89 mmol) with removal of generating ethanol using a Dean-Stark apparatus for 37 h. The mixture was then refluxed with potassium hydroxide (75 g, 1.34 mol) in 95% ethanol (2 l) for 1 h. After removal of ethanol in vacuo, the residue was dissolved in water and the solution was washed with methylene chloride. The aqueous layer, after making acidic by addition of conc. hydrochloric acid, was extracted with methylene chloride and the extract was washed, dried with magnesium sulfate, evaporated in vacuo, and distilled under vacuum to give 5 as a colorless oil; yield: 58.01 g (63.9%); bp 100-102 $^{\circ}$C/14 torr; IR ν_{max}^{neat} cm^{-1}: 2950, 1702, 1638; NMR δ: 1.13 (s, 6H), 2.32 (s, 2H), 4.77-5.20 (m, 2H), 5.92 (dd, 1H, J=18 and 10 Hz), 11.5 (br.s, 1H, exchangeable); MS m/e: 128 (M^+), 70 (100%); Anal. Calcd. for $C_7H_{12}O_2$: m/e 128.0835. Found: 128.0835.

5-Iodo-4-hydroxy-3,3-dimethylpentanoic Acid Lactone (6) To a stirred solution of 5 (14.72 g, 115 mmol) in 0.5 N aqueous sodium hydrogen carbonate (500 ml) was added dropwise a solution of iodine (58.6 g, 230 mmol) and potassium iodide (114.6 g, 690 mmol) in water (200 ml) at room temperature. After 1 h the mixture was extracted with ether and the extract was washed with 5% aqueous sodium thiosulfate, brine, dried with magnesium sulfate, and evaporated in vacuo to give practically pure 6 as a pale yellow oil; yield: 28.05 g (96.1%); IR ν_{max}^{neat} cm^{-1}: 1778; NMR δ: 1.08 (s, 3H), 1.26 (s, 3H), 2.45 (s, 2H), 3.17-3.48 (m, 2H), 4.36 (dd, 1H, J=6 and 8 Hz); MS m/e: 254 (M^+), 127 (100%); Anal. Calcd. for $C_7H_{11}IO_2$: m/e 253.9803. Found: 253.9844.

Methyl 4,5-Epoxy-3,3-dimethylpentanoate (7) A suspension of 6 (4.00 g, 15.7 mmol) and potassium carbonate (6.53 g, 47.2 mmol) in methanol (40 ml) was stirred at room temperature for 1.5 h. The mixture was poured into brine and was extracted with ether. The extract was washed with brine, dried with magnesium sulfate, evaporated in vacuo, and distilled under vacuum to give 7 as a colorless oil; yield: 1.97 g (79.1%); bp 60-70 $^{\circ}$C/14 torr (kugelrohr); IR ν_{max}^{neat} cm^{-1}: 1734, 1235; NMR δ: 1.01 (s, 6H), 2.28 (s, 2H), 2.61 (d, 2H, J=3.5 Hz), 2.87 (t, 1H, J=3.5 Hz), 3.63 (s, 3H); MS m/e 158 (M^+), 145 (100%); Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.31; H, 8.75.

Methyl trans-3-Hydroxymethyl-2,2-dimethylcyclopropane-1-carboxylate (8) and cis-3-Hydroxymethyl-2,2-dimethylcyclopropane-1-carboxylic Acid Lactone (9) To a stirred solution of hexamethyldisilazane (14.23 ml, 20.0 mmol) in tetrahydrofuran (250 ml) was added dropwise n-butyllithium

in hexane (15% w/w) (12.9 ml, 20.0 mmol) at 0 °C and the stirring was continued for 30 min at the same temperature. The solution was cooled to -30 °C and to this solution was added 7 (2.12 g, 13.4 mmol) in tetrahydrofuran (50 ml) dropwise. After stirring for 4 h at the same temperature, brine was added to the mixture and the mixture was extracted with ether. The extract was washed with brine, dried with magnesium sulfate, and evaporated in vacuo. The residue was purified by a silica gel column (95 g) using a mixture of n-hexane and ether (4:1 v/v) as eluant to give 8 (1.30 g, 61.5%) and 9 (344 mg, 20.4%) both as faint yellow oil.

8: bp 85-100 °C/0.3 torr (Kugelrohr); IR ν_{max}^{neat} cm^{-1}: 3432, 1728; NMR δ: 1.21 (s, 3H), 1.25 (s, 3H), 1.41 (d, 1H, J=5 Hz), 1.57 (s, 1H, exchangeable), 1.71 (dt, 1H, J=5 and 6.5 Hz), 3.65 (s, 3H), 3.68 (t, 2H, J=6.5 Hz); MS m/e: 159 (M^+-1), 128 (100%); Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.67; H, 8.88.

9: bp 65-110 °C/14 torr (Kugelrohr); IR ν_{max}^{neat} cm^{-1}: 1766; NMR δ: 1.17 (s, 6H), 1.98 (m, 2H), 4.22 (m, 2H); MS m/e: 126 (M^+), 67 (100%); Anal. Calcd. for $C_7H_{10}O_2$: 126.0680. Found: 126.0674.

(S)-1-(3,3-Dimethyl-4-pentenoyl)proline (10) A mixture of 5 (10.24 g, 80 mmol) and oxalyl chloride (10.5 ml, 120 mmol) in methylene chloride (300 ml) was refluxed for 2.5 h. After evaporation of the solvent in vacuo, the crude acid chloride remained in methylene chloride (200 ml) was added dropwise to a stirred solution of (S)-proline (11.05 g, 96 mmol) and triethylamine (16.7 ml, 120 mmol) in methylene chloride (400 ml) at the room temperature and the stirring was continued for 18 h at the same temperature. The mixture was washed successively with 5% hydrochloric acid, water, brine, and dried with magnesium sulfate. Evaporation of the solvent left a crystalline residue which recrystallized from a mixture of n-hexane and ether to give 10 as colorless prisms; yield: 15.34 g (85.2%); mp 88-90 °C; $[\alpha]_D$ - 141.3° (c 2.75, $CHCl_3$); IR ν_{max}^{Nujol} cm^{-1}: 3300-2500, 1738, 1638, 915; NMR δ: 1.18 (s, 6H), 1.73-2.32 (m, 4H), 2.05 (s, 2H), 3.58 (m, 2H), 4.60 (m, 1H), 4.78-5.23 (m, 2H), 5.96 (dd, 1H, J=18 and 12 Hz), 8.95 (br s, 1H, exchangeable); MS m/e: 225 (M^+), 71 (100%); Anal. Calcd. for $C_{12}H_{19}NO_3$: C, 63.97; H, 8.50; N, 6.22. Found: C, 63.85; H, 8.27; N, 5.92.

(S)-5-Iodo-4-hydroxy-3,3-dimethylpentanoic Acid Lactone ((S)-6) To a stirred solution of iodine (7.62 g, 30 mmol) in acetonitrile (30 ml) was added dropwise 10 (2.25 g, 10 mmol) in acetonitrile (20 ml) at 0 °C and the stirring was continued for 1.5 h. To a mixture was 0.5 N aqueous sodium hydrogen carbonate (100 ml) and the stirring was continued for 24 h at 0 °C. The mixture was extracted with ether and the extract was washed successively with 5% aqueous sodium thiosulfate, brine, and dried with magnesium sulfate. After evaporation of the solvent in vacuo, the residue was purified by a silica gel column (73 g) using a mixture of n-hexane and ether as eluant to give (S)-6 as a pale yellow oil; yield: 1.82 g (71.4%); $[\alpha]_D$ + 10.1° (c 2.67, $CHCl_3$); chromatographical behavior and spectral data were identical in all respects with those of racemic 6.

(R)-5-Iodo-4-hydroxy-3,3-dimethylpentanoic Acid Lactone ((R)-6) A mixture of 10 (4.50 g, 20 mmol) and iodine (15.23 g, 60 mmol) in 50% aqueous tetrahydrofuran (50% v/v) (200 ml) was stirred at room temperature for 3 h. The mixture was extracted with ether and the extract was successively washed with 5% aqueous sodium thiosulfate, brine, and dried with magnesium sulfate. After evaporation of the solvent in vacuo, a part of the residue 1.02 g of 5.02 g was purified by a silica gel column (30 g) using a mixture of n-hexane and ether as eluant to give (R)-6 as a pale yellow oil; yield; 960 mg (93.0%); $[\alpha]_D$ - 4.43° (c 2.08, $CHCl_3$); chromatographical behavior and spectral data were identical in all respects with those of racemic 6.

(S)-Methyl 4,5-Epoxy-3,3-dimethylpentanoate ((S)-7) A suspension of (S)-6 (1.82 g, 7.17 mmol) and potassium carbonate (2.97 g, 21.5 mmol) in methanol (20 ml) was treated as for racemic 6 to give (S)-7; yield: 832 mg (73.5%); $[\alpha]_D$ + 2.22° (c 2.43, $CHCl_3$); chromatographical behavior and spectral data were identical in all respects with those of racemic 7.

(R)-Methyl 4,5-Epoxy-3,3-dimethylpentanoate ((R)-7) A suspension of (R)-6 (4.00 g, 15.7 mmol) and potassium carbonate (6.53 g, 47.2 mmol) in methanol (40 ml) was treated as for racemic 6 to give (R)-7; yield: 1.97 g (79.1%); $[\alpha]_D$ 0° (c 2.27, $CHCl_3$); chromatographical behavior and spectral data were identical in all respects with those of racemic 7.

(1R,3R)-Methyl trans-3-Hydroxymethyl-2,2-dimethylcyclopropane-1-carboxylate ((1R,3R)-8) and (1S,3R)-cis-3-Hydroxymethyl-2,2-dimethylcyclopropane-1-carboxylic Acid Lactone ((1S,3R)-9) (S)-7 (832 mg, 5.27 mmol) was treated with lithium hexamethyldisilazide prepared from hexamethyldisilazane (1.67 ml, 7.92 mmol) and n-butyllithium in n-hexane (15% w/w) (5.08 ml, 7.92 mmol) as for racemic 7 to give (1R,3R)-8, $[\alpha]_D$ - 7.0° (c 2.03, $CHCl_3$), and (1S,3R)-9, $[\alpha]_D$ + 12.2° (c 1.67, $CHCl_3$) (lit.[17]: $[\alpha]_D$ - 72.8° (c 1.4, $CHCl_3$), 81% ee), in 62.9% (524 mg) and 16.6% (110 mg) yield, respectively.

(1S,3S)-Methyl trans-3-Hydroxymethyl-2,2-dimethylcyclopropane-1-carboxylate ((1S,3S)-8) and (1R,3S)-cis-3-Hydroxymethyl-2,2-dimethylcyclopropane-1-carboxylic Acid Lactone ((1R,3S)-9) To a stirred solution of diisopropylamine (3.52 ml, 25 mmol) in tetrahydrofuran (50 ml) was added dropwise n-butyllithium in hexane (15% w/w) (16.1 ml, 25 mmol) at -15 °C. After stirring for 30 min, the mixture was cooled to -65 °C and a solution of (R)-6 (1.59 g, 10 mmol) in tetrahydrofuran (20 ml) was added to this stirred solution. After 3 h, saturated aqueous ammonium chloride was added to the mixture and was extracted with ether. The extract was washed with brine, dried with magnesium sulfate, evaporated in vacuo, and purified by a silica gel column (47.6 g) using a mixture of n-hexane and ether (3:1 v/v) as eluant to give (1S,3S)-8, $[\alpha]_D$ + 1.69° (c 2.25, $CHCl_3$), and (1R,3S)-9, $[\alpha]_D$ - 1.64° (c 0.98, $CHCl_3$), in 42.1% (668 mg) and 7.4% (93 mg) yield, respectively. Chromatographical behavior and spectral data of both compounds were identical in all respects with those of racemic materials, respectively.

(1R,3R)-trans-Caronaldehyde Methyl Ester ((1R,3R)-14) To a stirred suspension of pyridinium

chlorochromate (1.19 g, 5.52 mmol) in methylene chloride was added dropwise (1R,3R)-8 (435 mg, 2.75 mmol) in methylene chloride (10 ml) at room temperature. After stirring for 13.5 h, the insoluble material was removed by filtration using a Celite. The organic layer was evaporated in vacuo and the residue was purified by a silica gel column (12.5 g) using a mixture of n-hexane and ether (4:1 v/v) to give (1R,3R)-14 as colorless oil; yield: 317 mg (74.3%); $[\alpha]_D$ + 1.65° (c 3.51, $CHCl_3$) (lit.[18]: $[\alpha]_D$ + 16.0° (c 12, $CHCl_3$)); spectral data were identical with those reported.[18]

(1S,3S)-trans-Caronaldehyde Methyl Ester ((1S,3S)-14) (1S,3S)-8 (486 mg, 3.08 mmol) was oxidized with pyridinium chlorochromate (1.33 g, 6.16 mmol) as for (1R,3R)-8 to give (1S,3S)-14; yield: 227 mg (47.3%); $[\alpha]_D$ - 0.45° (c 2.93, $CHCl_3$); chromatographical behavior and spectral data were identical in all respects with those of (1R,3R)-14.

(rac)-trans-Caronaldehyde Methyl Ester (14): (a) by pyridinium chlorochromate Racemic 8 (87 mg, 0.55 mmol) was oxidized with pyridinium chlorochromate (237 mg, 1.10 mmol) as for optically active 8 to give racemic 14; yield: 76 mg (88.5%); chromatographical behavior and spectral data were identical in all respects with those of the optically active material.

(b) by Moffatt oxidation using pyridine-sulfur trioxide complex To a mixture of racemic 8 (157 mg, 1.0 mmol) and triethylamine (0.42 ml, 3.0 mmol) in dimethyl sulfoxide (1.5 ml) is added dropwise pyridine-sulfur trioxide complex (318 mg, 2.0 mmol) in dimethyl sulfoxide (1.5 ml) at room temperature and the mixture was stirred at the same temperature for 4 h. To a mixture was added ice-water and then extracted with ether. The extract was successively washed with 5% hydrochloric acid, saturated aqueous sodium hydrogen carbonate, brine, and dried with magnesium sulfate. After evaporation of the solvent in vacuo, the residue was purified by a silica gel column to give racemic 14 (137 mg, 88%) which accompanied by unseparable by-product (19) (14:19=8:1).

(c) by Moffatt oxidation using oxalyl chloride (Swern modification) To a stirred solution of oxalyl chloride (0.191 ml, 2.19 mmol) in methylene chloride (1 ml) was added dropwise dimethyl sulfoxide (0.311 ml, 4.38 mmol) at -70 °C and, after 30 min, 8 (315 mg, 1.99 mmol) in methylene chloride (3 ml) was added dropwise, then after 30 min, triethylamine (1.39 ml, 9.53 mmol) was added. After stirring at -70 °C for 50 min, the temperature was gradually warmed to room temperature and the mixture was extracted with ether. The extract was washed successively with 5% hydrochloric acid, saturated aqueous sodium hydrogen carbonate, brine, dried with magnesium sulfate, and evaporated in vacuo to give 14 as practically pure state; yield: 280 mg (90.0%); chromatographical behavior and spectral data were identical in all respects with those of 14 obtained by (a).

(rac)-trans-2,2-Dimethyl-3-carbomethoxycyclopropylmethyl Phenyl Sulfide (20) and the Dimeric by-product (21) A mixture of 8 (510 mg, 3.23 mmol), diphenyl disulfide (846 mg, 3.88 mmol), and tri-n-butylphosphine (1.04 ml, 3.88 mmol) in pyridine (5 ml) was stirred at room temperature for 10 h.

After volatile components were evaporated under vacuum at room temperature, the residue was taken up to ether. The ether layer was washed successively with 10% hydrochloric acid, 15% aqueous sodium hydroxide, brine, and dried with magnesium sulfate. After evaporated in vacuo, the residue was purified by a silica gel column (30 g) using a mixture of n-hexane and ether (6:1 v/v) as eluant to give 21 as a colorless oil, 31 mg (6.9%) and 20 as crystalline solid which was recrystallized from n-hexane as needles, 704 mg (87.2%).

20: mp 53-54 °C; IR ν_{max}^{Nujol} cm^{-1}: 1720; NMR δ: 1.11 (s, 3H), 1.19 (s, 3H), 1.31 (d, 1H, J=5.4 Hz), 1.67 (dt, 1H, J=7.1 and 5.4 Hz), 2.95 (m, 2H), 3.61 (s, 3H), 7.04-7.45 (m, 5H); MS m/e: 250 (M^+), 74 (100%); Anal. Calcd. for $C_{14}H_{18}O_2S$: C, 67.16; H, 7.25; S, 12.81. Found: C, 67.17; H, 7.07; S, 12.98.

21: IR ν_{max}^{neat} cm^{-1}: 1722; NMR δ: 1.13 (s, 3H), 1.17 (s, 6H), 1.25 (s, 3H), 1.18-1.91 (m, 4H), 2.95 (dd, 2H, J=3 and 7 Hz), 3.63 (s, 3H), 4.06 (dd, 2H, J=7 and 3 Hz), 7.07-7.53 (m, 5H); MS m/e: 376 (M^+), 74 (100%); Anal. Calcd. for $C_{21}H_{28}O_4S$: m/e 376.1707. Found: m/e 376.1692.

(rac)-trans-2,2-Dimethyl-3-carbomethoxycyclopropylmethyl Phenyl Sulfoxide (22) A mixture of 20 (501 mg, 2.0 mmol) and 30% hydrogen peroxide (1.6 ml, 8.0 mmol) in methanol (10 ml) was stirred at room temperature for 9 days. After brine was added to the reaction mixture, the mixture was extracted with ether and the extract was washed successively with aqueous potassium iodide, 5% aqueous sodium hydrogen carbonate, 5% aqueous sodium thiosulfate, brine, and dried with magnesium sulfate. Evaporation of the solvent left a colorless solid which was recrystallized from a mixture of n-hexane and ether to give racemic 22 as colorless needles; yield: 448 mg (84.0%); mp 66-68 °C; IR ν_{max}^{Nujol} cm^{-1}: 1720, 1043; NMR δ: 0.99-1.17 (2 x s, 6H), 1.21-1.41 (m, 1H), 1.41-1.83 (m, 1H), 2.97 (d, 2H, J=7 Hz), 6.25 (s, 3H), 7.35-7.80 (m, 5H); MS m/e: 266 (M^+), 141 (100%); Anal. Calcd. for $C_{14}H_{18}O_3S$: C, 63.13; H, 6.81; S, 12.04. Found: C, 63.08; H, 6.87; S, 11.94.

(rac)-trans-Caronaldehyde Methyl Ester (14) from 22 To a stirred solution of 22 (134 mg, 0.5 mmol) and 2,6-lutidine (0.30 ml, 2.58 mmol) in acetonitrile (3 ml) was added dropwise trifluoroacetic anhydride (0.285 ml, 2.00 mmol) at -30 °C and the mixture was stirred for 4 h at the same temperature, then for 30 min at room temperature. Aqueous potassium carbonate (345 mg in 3 ml) was added to the mixture and after 1 h the mixture was extracted with ether. The extract was washed successively with brine, 5% hydrochloric acid, brine, dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by a silica gel column using a mixture of n-hexane and ether (10:1 v/v) as eluant to give 14 as a pale yellow oil; yield: 31 mg (39.4%); chromatographical behavior and spectral data were identical in all respects with those of 14 obtained from 8 by direct oxidation.

(rac)-trans-Methyl 3-(α-methoxy-α-phenylthio)methyl-2,2-dimethylcyclopropanecarboxylate (23) To a stirred solution of 22 (105 mg, 0.39 mmol) and 2,6-lutidine (0.23 ml, 1.2 mmol) in acetonitrile (3 ml) was added dropwise trifluoroacetic anhydride (0.23 ml, 1.6 mmol) at -30 °C and the stirring was continued for

2 h. After warming to room temperature, potassium carbonate (164 mg, 1.2 mmol) and methanol (3 ml) was added to the mixture and the stirring was continued for 1 h at the same temperature. The mixture was taken in ether and the ether was washed successively with brine, 5% hydrochloric acid, brine, and dried with magnesium sulfate. After evaporation of the solvent in vacuo, the residue was purified by a silica gel plate using a mixture of n-hexane and ether (4:1 v/v) to give the one of the isomer (a) of 23 (28 mg, 23.5%) as a viscous oil and the other isomer (b) of 23 (57 mg, 51.6%) as colorless needles after recrystallization from n-hexane.

23a: IR ν_{max}^{neat} cm^{-1}: 1724; NMR δ: 1.15 (s, 3H), 1.19 (s, 3H), 1.52 (d, 1H, J=3.9 Hz), 1.74 (dd, 1H, J=9.3 and 3.9 Hz), 3.46 (s, 3H), 3.64 (d, 1H, J=9.3 Hz), 7.14-7.54 (m, 5H); MS m/e: 281 (M^++1, 100%). Anal. Calcd. for $C_{15}H_{20}O_3S$: C, 64.26; H, 7.19; S, 11.44. Found: C, 64.45; H, 7.28; S, 11.68.

23b: mp 63-64 °C; IR ν_{max}^{Nujol} cm^{-1}: 1719; NMR δ: 1.13 (s, 3H), 1.21 (s, 3H), 1.56 (d, 1H, J=5.5 Hz), 1.69 (dd, 1H, J=8.5 and 5.5 Hz), 3.45 (s, 3H), 3.59 (s, 3H), 4.39 (d, 1H, J=8.5 Hz), 7.17-7.55 (m, 5H); MS m/e: 281 (M^++1, 100%); Anal. Calcd. for $C_{15}H_{20}O_3S$: C, 64.26; H, 7.19; S, 11.44. Found: C, 64.10; H, 7.14; S, 11.42.

(rac)-trans-Caronaldehyde Methyl Ester Dimethyl Acetal (24) A solution 23 (diastereomeric mixture: 328 mg, 1.17 mmol) in methanol (6 ml) was added iodine (150 mg, 0.60 mmol) at room temperature with stirring. After stirring for 24 h, the mixture was taken in ether and the organic layer was washed successively with saturated aqueous sodium hydrogen carbonate, 5% aqueous sodium thiosulfate, brine, and dried with magnesium sulfate. The solvent was evaporated in vacuo and the residue was purified by a silica gel column (14 g) using a mixture of n-hexane and ether (10:1 v/v) as eluant to give 24 as a pale yellow oil; yield: 178 mg (76.7%); IR ν_{max}^{neat} cm^{-1}: 1724; NMR δ: 1.18 (s, 6H), 1.50-1.89 (m, 2H), 3.25 (s, 6H), 3.64 (s, 3H), 4.18 (d, 1H, J=6 Hz); MS m/e 171 (M^+-31), 76 (100%); Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97. Found: C, 58.84; H, 9.18.

(rac)-trans-Caronaldehyde Methyl Ester (14) from 24 A mixture of 24 (113 mg, 0.6 mmol) in tetrahydrofuran (2 ml) and 10% hydrochloric acid (2 ml) was stirred at room temperature for 9 h. The mixture was extracted with ether and the extract was washed with aqueous sodium hydrogen carbonate, brine, dried with magnesium sulfate, and evaporated in vacuo to leave an oily residue. The residue was purified by a silica gel column (1.4 g) using a n-hexane and ether (2:1 v/v) as eluant to give pure 14 as a faint yellow oil; yield: 55 mg (63.0%); chromatographic behavior and spectral data were identical in all respects with those of 14 obtained from 8.

(rac)-cis-2,2-Dimethyl-3-carboxycyclopropylmethyl Phenyl Sulfide (25) Sodium hydride (60% in oil) (1.49 g, 37.1 mmol) was washed with n-hexane (3 times) and was suspended in tetrahydrofuran (40 ml). To this stirred suspension was added thiophenol (4.13 ml, 40.2 mmol) at 0 °C and after 20 min at room temperature, 9 (3.90 g, 31 mmol) in tetrahydrofuran was added dropwise and the mixture was refluxed for

5 h. After evaporation of the solvent in vacuo, the residue was dissolved in 10% aqueous sodium hydroxide and the aqueous layer was washed with ether. The aqueous layer was then made acidic by addition of conc. hydrochioric acid and was extracted with ether. The extract was washed with brine, dried with magnesium sulfate, and evaporated in vacuo to leave a crystalline solid which was recrystallized from n-hexane to give 26 as colorless leaflets; yield: 5.88 g (80.5%); mp 101-103 °C; IR ν_{max}^{Nujol} cm^{-1}: 3400-2500, 1682; NMR δ: 1.15 (s, 3H), 1.18 (s, 3H), 1.57 (m, 2H), 3.15-3.40 (m, 2H), 7.10-7.60 (m, 5H), 11.5-12.2 (br.s, 1H, exchangeable); MS m/e: 236 (M^+), 110 (100%); Anal. Calcd. for $C_{13}H_{16}SO_2$: C, 66.07; H, 6.82; S, 13.57. Found: C, 66.15; H, 6.94; S, 13.41.

(rac)-cis-2,2-Dimethyl-3-carboxycyclopropylmethyl Phenyl Sulfoxide (26) A mixture of 25 (2.36 g, 10.0 mmol) and 30% aqueous hydrogen peroxide (2.6 ml, 25.5 mmol) in methanol (30 ml) was stirred at room temperature for 5 days. The reaction mixture, after acidification by addition of 5% hydrochloric acid, was extracted with methylene chloride and the extract was washed with brine, dried with magnesium sulfate, and evaporated in vacuo to give 26 as a visous oil which was used without further purification; yield: quantitative; IR ν_{max}^{neat} cm^{-1}: 3600-2400, 1702; NMR δ: 0.93-1.25 (2 x s, 6H), 1.48 (s, 1H), 1.68 (s, 1H), 3.07-3.48 (m, 2H), 7.32-7.76 (m, 5H), 8.78-9.33 (br.s, 1H, exchangeable); MS m/e: 236 (M^+-16), 126 (100%); Anal. Calcd. for $C_{13}H_{16}O_3S$: m/e 252.0819. Found: 252.0787.

(rac)-cis-Caronaldehyde Lactone Monothiophenyl Acetal (27) To a stirred solution of 26 (1.98 g, 7.86 mmol) and 2,6-lutidine (5.24 ml, 45 mmol) in acetonitrile (30 ml) was added dropwise trifluoroacetic anhydride 3.81 ml, 27.0 mmol) at -25 °C and the mixture was stirred for 4 h at the same temperature and then saturated aqueous sodium hydrogen carbonate (60 ml) was added. After stirring was continued for 1 h at room temperature, the mixture was extracted with ether and the extract was washed with 5% hydrochloric acid, saturated aqueous sodium hydrogen carbonate, brine, and dried with magnesium sulfate. After evaporation of the solvent in vacuo, the residue was purified by a silica gel column (45 g) using a mixture of n-hexane and ether (7:1-4:1 v/v) as eluant to give β-thio-epimer 27a (790 mg, 44.5%) as a pale yellow oil and α-thio-epimer 27b (260 mg, 15.0%) as colorless needles after recrystallization from n-hexane.

27a: bp 110-130 °C/0.1 torr (Kugelrohr); IR ν_{max}^{neat} cm^{-1}: 1775; NMR δ: 1.03 (s, 3H), 1.20 (s, 3H), 1.88 (d, 1H, J=9 Hz), 2.17 (d, 1H, J=9 Hz), 5.42 (s, 1H), 7.13-7.75 (m, 5H); MS m/e: 234 (M^+), 125 (100%); Anal. Calcd. for $C_{13}H_{14}O_2S$: C, 66.64; H, 6.02; S, 13.68. Found: C, 66.27; H, 6.06; S, 13.45.

27b: mp 72.5-73.5 °C; IR ν_{max}^{Nujol} cm^{-1}: 1756; NMR δ: 1.18 (s, 3H), 1.45 (s, 3H), 2.07 (d, 1H, J=6 Hz), 2.30 (dd, 1H, J=5 and 6 Hz), 5.90 (d, 1H, J=5 Hz), 7.17-7.60 (m, 5H); MS m/e: 234 (M^+), 125 (100%); Anal. Calcd. for $C_{13}H_{14}O_2S$: C, 66.64; H, 6.02; S, 13.68. Found: C, 66.93; H, 5.81; S, 13.64.

(rac)-cis-Caronaldehyde Methyl Ester Dimethyl Acetal (28) A solution of 27a (615 mg, 2.63 mmol) in methanol (15 ml) was added iodine (2.00 g, 7.88 mmol) portionwise at room temperature with stirring. After 15 h, the mixture was taken in ether and the organic layer was washed successively with 5%

aqueous sodium hydrogen carbonate, 5% aqueous sodium thiosulfate, brine, dried with magnesium sulfate, and evaporated in vacuo. The residue was purified by a silica gel column (24 g) using a mixture of n-hexane and ether (5:1 v/v) as eluant to give 28 as a pale yellow oil; yield: 483 mg (91.0%); bp 75-90°/14 torr (Kugelrohr); IR ν_{max}^{neat} cm^{-1}: 1724; NMR δ: 1.18 (s, 3H), 1.30 (s, 3H), 1.50-1.78 (m, 2H), 3.32 (s, 3H), 3.35 (s, 3H), 3.63 (s, 3H), 4.83 (d, 1H, J=7 Hz); MS m/e; 171 (M^+-31), 76 (100%); Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97. Found: C, 58.96; H, 8.92.

(rac)-cis-Caronaldehyde Methyl Ester (29) A mixture of 28 (53 mg, 0.26 mmol) in tetrahydrofuran (1.0 ml) and 10% hydrochloric acid (1.0 ml) was stirred at room temperature for 3 h. The mixture was basified with saturated aqueous sodium hydrogen carbonate and then saturated with sodium chloride. The mixture was extracted with methylene chloride, dried with magnesium sulfate, evaporated in vacuo, and purified by a silica gel column (2.0 g) using a mixture of n-hexane and ether (8:1 v/v) as eluant to give pure 29 as a faint yellow oil; yield: 24 mg (59%); IR ν_{max}^{neat} cm^{-1}: 1724, 1694; NMR δ: 1.28 (s, 3H), 1.56 (s, 3H), 1.84 (dd, 1H, J=6 and 8 Hz), 2.15 (d, 1H, J=8 Hz), 3.70 (s, 3H), 9.72 (d, 1H, J=6 Hz); MS m/e: 155 (M^+-1), 73 (100%). Anal. Calcd. for $C_8H_{12}O_3$: 156.0786. Found: 155.0738 (M^+-1).

(rac)-cis-Caronaldehyde (2b) from 28 A mixture of 28 (280 mg, 1.39 mmol) in tetrahydrofuran (3 ml) and 10% hydrochloric acid (3 ml) was stirred at room temperature for 55 h. The mixture was basified with saturated aqueous sodium hydrogen carbonate and extracted with ether. The extract was washed with brine, dried with magnesium sulfate, evaporated in vacuo, and purified by a silica gel column (5.2 g) using a mixture of n-hexane and ether (8:1 v/v) as eluant to give 29 (70 mg, 32.3 %) as a faint yellow oil. The mother liquor was acidified with conc. hydrochloric acid and extracted with methylene chloride after saturation with sodium chloride. The extract was dried with magnesium chloride, and evaporated in vacuo to leave a crystalline residue which was recrystallized from a mixture of n-pentane and ether to give pure 2b as colorless prisms; yield: 32 mg (16.3%; 23.9% based on recovered 29); mp 84-85.5 °C (lit.[28] 83.5-87 °C); IR ν_{max}^{Nujol} cm^{-1}: 3304, 1716; NMR δ: 1.21 (s, 6H), 2.11 (s, 2H), 5.49 (br.s, 1H), 5.67-6.30 (br.s, 1H, exchangeable); MS m/e; 142 (M^+), 97 (100%); Anal. Calcd. for $C_9H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 59.07; H, 7.16.

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