Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 2, pp. 595-602, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00043-7

Enantioselective Esterification of 5-Hydroxy-2-methyl-6-(diethoxymethyl)-1-cyclohexenecarbaldehyde. Synthesis of Both Enantiomers of 6-Methylbicyclo[4.1.0]hept-2-ene-1,2-dicarbaldehyde

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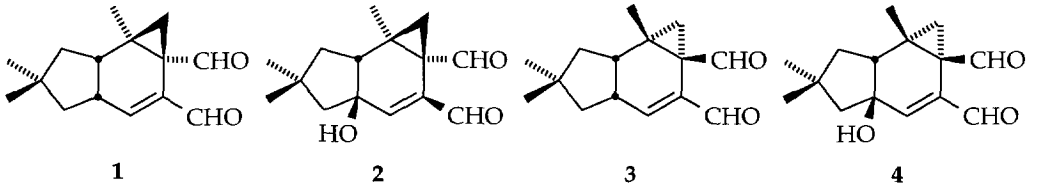
Abstract: Racemic 5-hydroxy-2-methyl-6-(diethoxymethyl)-1-cyclohexenecarbaldehyde [(±)-**5**] was resolved by enantioselective transesterification with vinyl acetate in cyclohexane catalysed by lipase from *Candida antarctica*. The absolute stereochemistry of the acetate obtained was determined by CD technique. The products were used to synthesise both enantiomers of 6-methylbicyclo[4.1.0]hept-2-ene-1,2-dicarbaldehyde (**7**), an analogue of the bioactive sesquiterpene isovelleral (**1**). The mutagenic activity of the three dialdehydes in the Ames' Salmonella/microsome assay is compared.

Isovelleral (**1**) is an example of a fungal sesquiterpene possessing potent antimicrobial, cytotoxic and antifeedant activities.[1,2] In addition, isovelleral (**1**) is mutagenic in both bacteria and mammalian cells,[3,4] a feature not shared by similar and in other respects equally bioactive unsaturated dialdehydes which lack the cyclopropane ring.[3] A QSAR study of bicyclo[4.1.0]hept-2-ene-1,2-dicarbaldehydes suggested that the absolute configuration of the cyclopropane ring is important for the mutagenic activity.[5] For example, isovelleral (**1**) and 9-hydroxyisovelleral (**2**) are approximately 10 times more mutagenic than their diastereomers **3** and **4**[3] (see Figure 1). Also, a recent comparison of the mutagenic activity of (+)-isovelleral (**1**) (the natural enantiomer) with that of racemic isovelleral (**1**) prepared by synthesis indicated that the (-)-enantiomer possesses either no or only very weak mutagenic activity.[6] It would therefore be interesting to compare the biological activities of the enantiomers of unsaturated dialdehydes. In this paper we wish to report the preparation and mutagenicity in the Ames' Salmonella/microsome assay of both enantiomers of the isovelleral analogue 6-methylbicyclo[4.1.0]hept-2-ene-1,2-dicarbaldehyde, (+)-**7** and (-)-**7** (see Figure 2).



1 **2** **3** **4**

Figure 1.

Recently, a synthesis of racemic 6-methylbicyclo[4.1.0]hept-2-ene-1,2-dicarbaldehyde [(±)-**7**] by stereoselective cyclopropanation, acetal hydrolysis and elimination of the racemic acetate (±)-**5b** was described.[7] The racemic alcohol (±)-**5a** was prepared as described previously,[8] and the (5*R*)-enantiomer (the determination of the absolute configuration is discussed below) was selectively transesterified with vinyl acetate in cyclohexane, using lipases from *Candida antarctica* as catalyst.[9] After 17 hours the conversion had come to a standstill, and the acetate (5*R*, 6*R*)-**5b** and the alcohol (5*S*, 6*S*)-**5a** were separated by chromatography on silica gel. In order to determine the enantiomeric excess, the alcohols (5*R*, 6*R*)-**5a** (obtained by the hydrolysis of (5*R*, 6*R*)-**5b** with K_2CO_3 in methanol) and (5*S*, 6*S*)-**5a** were converted to their (*R*)-Mosher esters. Inspection of the ^1H NMR spectra[10] of these showed that the enantioselective transesterification had yielded an enantiomeric excess of more than 99 % (there were no traces of the diastereomer) for the acetate (5*R*, 6*R*)-**5b** and of 84 % for the remaining alcohol (5*S*, 6*S*)-**5a**.

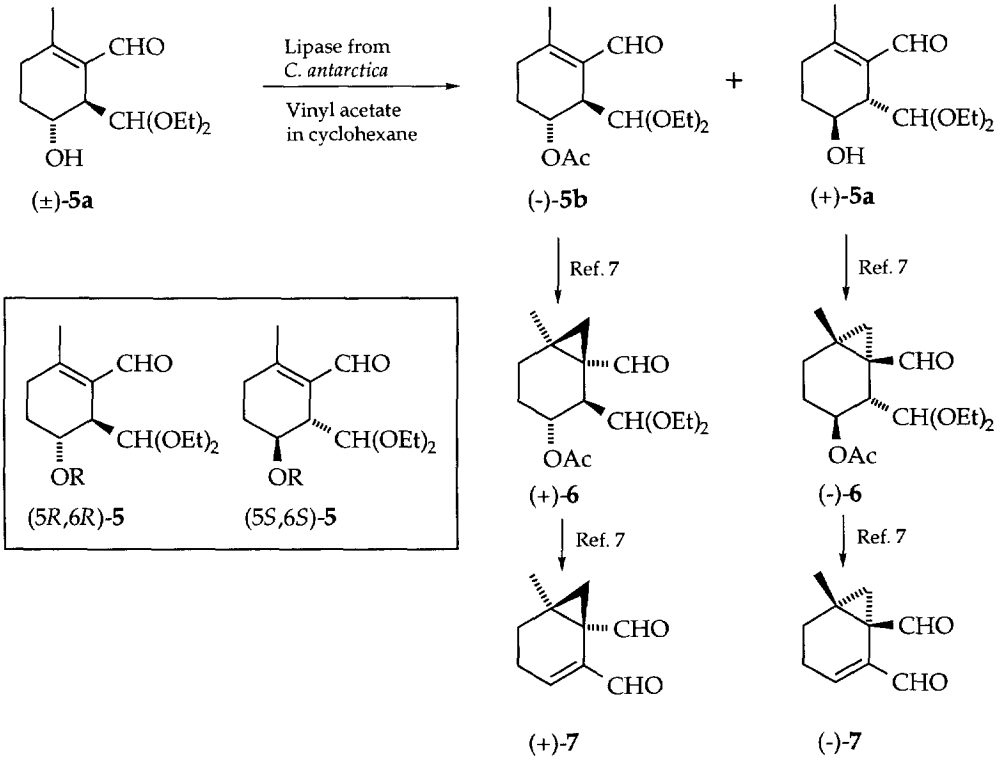


Figure 2. a: R = H; b: R = Ac; c: R = C_6H_5CO; d: R = (*R*)-MTPA; e: R = (*S*)-MTPA.

The enantioselectivity of the esterification of secondary alcohols catalysed by lipases has been shown to depend on the relative sizes of the two neighbouring groups. If the groups are similar, poor resolution is obtained. However, as in the case of the alcohol **5a**, if the two groups differ substantially in size, one can expect good resolution.[11a-c] On the basis of the results reported in the literature, one could expect that the lipase-catalysed transesterification of racemic **5a** should yield the (5*R*)-acetate **5b** and the (5*S*)-alcohol **5a**. In

order to establish this we decided to determine the absolute configuration of the products by independent methods.

Initially an attempt was made to determine the absolute configuration of the alcohol (+)-**5a**, which was not esterified by the lipase, by the Mosher method.[12] (+)-**5a** was converted to its (*R*)- and (*S*)-MTPA esters (+)-**5d** and (+)-**5e**. The significant ^{1}H NMR data of the two esters are given in Table 1. Comparison of the chemical shift differences between the two β-substituents (i.e. 4-H_2 and 6-H) according to the original method suggested by Mosher,[12] indicates an (*R*)-configuration of the C-5 of the alcohol (+)-**5a**, in contrast to what was expected (*vide supra*). Recently a modified high field FT NMR variant of the Mosher method was developed[13] in which the shift differences Δδ (δS–δR) between all assignable protons of the (*R*)- and (*S*)-MTPA esters are calculated and compared (see Table 1). Although this method is considered to be more reliable, it also suggested the (*R*)-configuration of C-5 of the alcohol (+)-**5a**. However, MM2 calculations indicate that the MTPA esters prefer a transdiaxial conformation, which is also the case for the TBDMS derivative of compound **5**.[8] The axial orientation of the MTPA group could result in irregular Δδ-values due to steric compression of the ester.[13]

Table 1. ^{1}H NMR Data (500 MHz) of the (*R*)- and (*S*)-MTPA Esters of (+)-**5a** in $CDCl_3$.

Proton(s)	(*S*)-MTPA ester of (+)-**5a** δ (ppm)	(*R*)-MTPA ester of (+)-**5a** δ (ppm)	Δδ (Hz)
3-Ha[a]	2.21	2.22	-5
3-Hb[a]	2.24	2.14	+50
4-Ha[a]	1.90	1.87	+15
4-Hb[a]	2.30	2.23	+35
5-H[a]	5.73	5.74	-5
6-H[a]	3.21	3.22	-5
C<u>H</u>O	10.02	10.07	-25
C<u>H</u>$(OEt)_2$	4.53	4.53	0
2-CH_3	2.09	2.11	-10

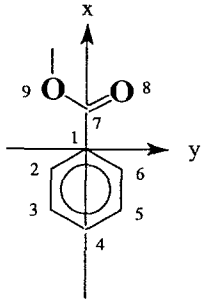
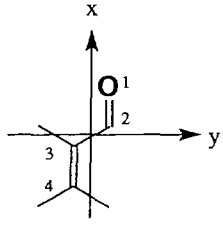
[a]The signal was not resolved, and the shift was determined by COSY and NOESY experiments.

We then turned to measurements of circular dichroism, since the benzoate (-)-**5c** (prepared from the acetate (-)-**5b** via hydrolysis and bensoylation) seems well suited for determination of its absolute configuration by the CD technique, employing the "exciton coupling" method of Harada and Nakanishi.[14,15] Initially, this method was mainly used to determine the absolute configuration of diols *via* their bensoates, but it has also proven valuable to study bensoates of hydroxyenones,[16] and it has gradually developed into a very powerful tool in organic stereochemistry.[17] The first $\pi \longrightarrow \pi^*$ transition in the enal chromophore and the ^1L_a transition[18] in the bensoate chromophore are close to each other in energy and should show appreciable coupling. The CD spectrum of the benzoate (-)-**5c** (Figure 3) shows a medium-strong negative couplet centered at 234 nm (217 nm, $\Delta\varepsilon = 4.0$, 234 nm, $\Delta\varepsilon = 0.0$, 242 nm, $\Delta\varepsilon = -3.0$) and a broad negative band (335

nm, $\Delta\varepsilon$ = -1.65). The couplet is assigned to the above-mentioned $\pi \longrightarrow \pi^*$ and ^1L_a transitions and the band at 335 nm to the enal $n \longrightarrow \pi^*$ transition.

Inspection of the MM2 energy-minimized structure of the (5*R*, 6*R*) enantiomer of the benzoate (-)-**5c** reveals that the dihedral angle between the long axes of the bensoate and enal chromophores is c:a -73°, in concordance with the observed negative couplet. However, in order to obtain a more detailed picture of the interaction between the two chromophores, we have performed a calculation of the CD spectrum using the matrix method of Schellman and coworkers.[19] The input for the $\pi \longrightarrow \pi^*$ transitions consists of the transition energies, the electric transition moments (μ), and the transition charge densities for the benzoate ^1L_a and enal transitions. For the enal $n \longrightarrow \pi^*$ transition the transition charge density is replaced by the transition quadrupole and the electric transition moments by the magnetic transition moment (**m**). The transition energies and moments are obtained from experimental spectra. The transition charges and the polarization directions (α) are obtained by CNDO/S calculations, the charges being scaled so as to agree with the experimental transition moments. The quadrupolar charges and their location are obtained from Slater type orbitals. The input data are shown in Table 2.

Table 2. Input for the Calculation of the Theoretical CD Spectrum of (5R, 6R)-**5c**. Dielectric constant = 2.00.

Chromophore	Energy/ $cm^{-1} \cdot 10^{-3}$	μ/D m/B[b]	α/°[a]	Transition charges Atom	q_i
	43.57[c]	4.43[c]	+13.2	1	-0.4552
				2	+0.4572
				3	-0.4255
				4	+0.4759
				5	-0.4168
				6	+0.4639
				7	+0.0500
				8	-0.1297
				9	-0.0126
	41.67[d]	3.13[d]	+8.9	1	+0.0578
				2	-0.0341
				3	+0.1608
				4	-0.1845
	29.85[d]	1.0[b]	--	1	±0.2000[e]

[a]Angle of μ to positive x axis in positive xy plane. [b]Bohr magneton. [c]From Ref. 15, p.34. [d]From Ref. 20. [e]Quadrupolar charges, placed at y, z = ±0.44 Å with x-axis along the C=O bond and with the O atom in the origin.

As can be seen in Figure 3, the calculated CD curve reproduces the experimental one quite well with respect to the $\pi \longrightarrow \pi^*$ transitions, which indicates the C-5 of the benzoate (-)-**5c** to have the absolute configuration *R*. The sign of the calculated $n \longrightarrow \pi^*$ band is correct but the intensity is far too low. This may be due to the fact that only the magnetic-electric coupling mechanism[19,21] has been used in the calculation, and it is clear that other contributions to the rotational strength of the $n \longrightarrow \pi^*$ transition ($R_{n \longrightarrow \pi^*}$) need to be considered. Part of $R_{n \longrightarrow \pi^*}$ probably arises through interaction with the enal $\pi \longrightarrow \pi^*$ transition. This should create an equivalent positive $R_{\pi \longrightarrow \pi^*}$, in agreement with the relatively low intensity of the negative lobe of the $\pi \longrightarrow \pi^*$ couplet. Coupling may occur under the influence of the chiral framework or through deviation of the enal chromophore from planarity, but a quantitative treatment is not feasible at present.

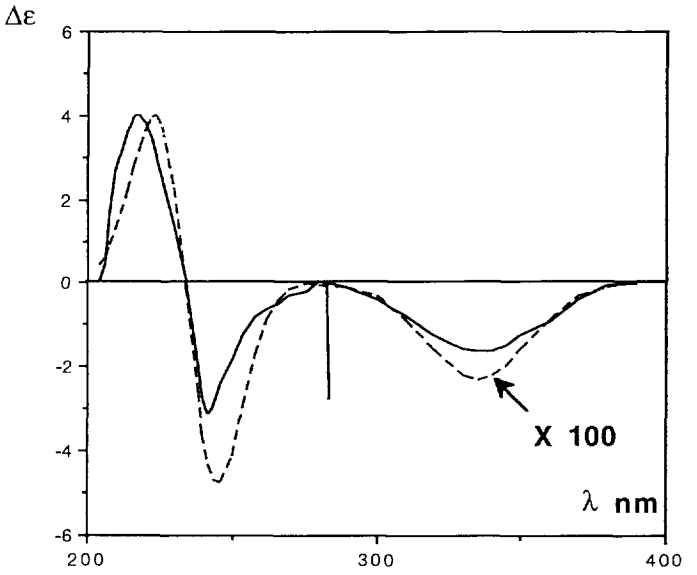


Figure 3. Experimental CD spectrum of the benzoate (-)-**5c** (————) in ethanol, and theoretical CD spectrum of (5*R*, 6*R*)-**5c** (- - - - - -).

The mutagenicity[22] of the two enantiomers (+)-**7** and (-)-**7** towards the Ames' Salmonella tester strains TA98 (sensitive to frameshift mutations) and TA100 (sensitive to base pair substitutions) in the absence of metabolic activation (S9 mix) was compared with that of isovelleral (**1**). The results are presented in Table 3. It is evident that the two enantiomers prepared in this investigation are about equally active, and less active than isovelleral (**1**). This was rather unexpected in view of the results reported previously and discussed above, and suggests that the cyclopentane ring of isovelleral (**1**) is of greater importance for its bioactivities than has previously been recognized. This will be further investigated.

Table 3. The Mutagenic Activity in the Salmonella/Microsome Assay of Compounds (+)-**1**, (+)-**7**, and (-)-**7** in the Absence of Metabolic Activation.

Compound (No.)	µg/plate[a]	Mutagenic response[b]		Mutagenic activity[c]	
		TA98	TA100	TA98	TA100
(+)-**1**	0.5	$48^{0.98}$	$164^{0.90}$	25	76
(+)-**7**	5	$83^{0.98}$	$207^{0.95}$	2.6	7.4
(-)-**7**	5	$62^{0.96}$	$223^{0.97}$	2.3	7.9

[a]The highest non-toxic dose. Each plate contains 20 ml of medium. [b]The mutagenic response is recorded as the number of revertant colonies in excess of the solvent control at the given concentration. Superscripts are correlation coefficients. [c]The mutagenic activity is given by the slope of the dose-response curve in number of excess revertants per nmole.

EXPERIMENTAL

^{1}H NMR (300 and 500 MHz) and ^{13}C NMR (75 MHz) were recorded at room temperature in $CDCl_3$ solutions using a Varian XL300 (300 and 75 MHz) or a Bruker ARX500 (500 MHz) spectrometer. The coupling constants *J* are given in Hz and the chemical shifts (δ) in ppm, the solvent peaks (7.26 and 77.0 ppm) serving as reference. Air and/or moisture sensitive reactions were carried out in oven-dried glassware under argon atmosphere using dry solvents. EI and CI (NH_3) mass spectra were recorded by a JEOL SX102 spectrometer at 70 eV. Optical rotations were measured by a Perkin Elmer 141 polarimeter at 25 ° C, as $CDCl_3$ solutions. UV spectra were recorded by a Varian Cary 2290 spectrophotometer. CD measurements were made on a Jasco Model J-500A spectropolarimeter. All reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel coated glass plates (Merck 60 F_{254}) using UV and/or p-anisaldehyde and heat as developing agents. Flash column chromatography was performed with Merck 60 silica gel (0.040-0.063 mm) using mixtures of heptane and ethyl acetate as the mobile phase. GC analyses were performed with a Varian 3700 gas chromatograph equipped with a J &W Scientific DB-5. 30m x 0.25 mm i.d. capillary column. The carrier gas was He (12 Psi), the injector temperature 250° C, and the detector temperature 270° C. Melting points, which are uncorrected, were determined using a Reichert microscope. The lipases obtained from *Candida antarctica* (SP435A) was a kind gift from Novo-Nordisk A/S, Denmark. The enzyme was immobilised on a macroporous acrylic resin, and had an approximate activity of 7000 PLU/g (Propyl Laureate Units). (*R*)-(+)- MTPA-Cl and (*S*)-(+)- MTPA-Cl (enantiomeric purity >99.5 %) were purchased from Fluka, and vinyl acetate was obtained from Merck. Racemic **5a** was prepared according to Ref. 8. The Salmonella/microsome assay was made according to the standard procedure,[22] using plates containing a total of 20 ml of substrate. All plates were triplicated, and at least 5 concentration levels (differentiated by a factor of 2) of each compound were tested. The solvent used throughout was acetone.

The lipase catalysed transesterification of (±)-5a.

Vinyl acetate (2.5 ml, 26.7 mmol), NaH_2PO_4 (100 mg), NaH_2PO_4-2 H_2O (100 mg) and lipase (200 mg) were added to a solution of racemic alcohol **5a** (598 mg, 2.47 mmol) in 25 ml cyclohexane. The suspension was

stirred at rt. for 17 h until GC showed approximately 45 % conversion. The reaction mixture was then filtered through cotton wool and the solvent was evaporated under reduced pressure. Chromatography on silica gel gave the acetate (-)-**5b** and the alcohol (+)-**5a** as oils.

(5*R*,6*R*)-5-Acetoxy-2-methyl-6-(diethoxymethyl)-1-cyclohexenecarbaldehyde [(-)-5b].

Colourless oil, yield 216 mg (28 %), $[\alpha]_D^{23}$ = - 114 (c = 1.0, $CDCl_3$). The spectral data were identical to those reported for the racemic material.[8] The (*R*)-(-)-MTPA ester (prepared via hydrolysis of (-)-**5b** with K_2CO_3 in MeOH, see also below) contained only one diastereomer according to ^1H NMR.

(5*S*,6*S*)-5-Hydroxy-2-methyl-6-(diethoxymethyl)-1-cyclohexenecarbaldehyde [(+)-5a].

Colourless oil, yield 283 mg (44 %), $[\alpha]_D^{23}$ = + 1.7 (c = 0.6, $CDCl_3$). The spectral data were identical to those reported for the racemic material.[8] The e.e. of its (*R*)-(-)-MTPA-derivative (prepared as described below) was found to be 84 % according to ^1H NMR.

(5*S*,6*S*)-5-Acetoxy-2-methyl-6-(diethoxymethyl)-1-cyclohexenecarbaldehyde [(+)-5b].

The alcohol (+)-**5a**, acylated by acetic anhydride (ca 100 equiv) in pyridine containing catalytic amounts of DMAP, was obtained in quantitative yield as a colourless oil, $[\alpha]_D^{23}$ = + 90 (c = 0.7, $CDCl_3$). The spectral data were identical with those reported for the racemic material.[8]

General procedure for the preparation of (*R*)- and (*S*)-MTPA esters.

(*R*)-(-) or (*S*)-(+)-MTPA-Cl (2-3 equiv) was added to a stirred solution of the secondary alcohol in CH_2Cl_2, Et_3N (10 equiv.) and DMAP (catalytic amounts), via a syringe. After stirring at rt for 3h, quenching with saturated $NaHCO_3$, extraction with diethyl ether, and evaporation of the solvent, the esters were obtained in quantitative yields as yellowish oils. These were immediately analysed by ^1H NMR to determine the e.e. of the alcohol. Chromatography on silica gel gave the pure products as colourless oils.

(*R*)-MTPA ester of (-)-5a (compound (-)-5d).

$[\alpha]_D^{23}$ = - 90 (c = 0.4, $CDCl_3$), ^1H-NMR 1.10 (t, 3H, *J* = 7.0), 1.24 (t, 3H, *J* = 7.0), 1.90 (m, 1H), 2.09 (s, 3H), 2.21 (m, 1H), 2.24 (m, 1H), 2.30 (m, 1H), 3.21 (m, 1H), 3.47 (s, 3H), 3.54-3.75 (m, 3H), 4.53 (d, 1H, *J* = 4.4), 5.73 (m, 1H), 7.31-7.46 (m, 5H), 10.02 (s, 1H); EIMS (*m/z*): 458.1917 (M^+, 14%, $C_{23}H_{29}O_6F_3$ requires 458.1916), 189 (100 %), 179 (51 %), 103 (77 %) and 75 (42 %).

(*R*)-MTPA ester of (+)-5a (compound (+)-5d).

$[\alpha]_D^{23}$ = + 16 (c = 0.55, $CDCl_3$), ^1H-NMR 1.10 (t, 3H, *J* = 7), 1.23 (t, 3H, *J* = 7), 1.87 (m, 1H), 2.11 (s, 3H), 2.14 (m, 1H), 2.22 (m, 1H), 2.23 (m, 1H), 3.22 (m, 1H), 3.32 (m, 1H), 3.49 (s, 3H), 3.57-3.75 (m, 3H), 4.53 (d, 1H, *J* = 4.5), 5.74 (m 1H), 7.32-7.40 (m, 2H), 7.43 (app d, 3H), 10.07 (s, 1H). EIMS (*m/z*): 458.1922 (M^+, 4 %, $C_{23}H_{29}O_6F_3$ requires 458.1916), 189 (100 %), 179 (11 %), 103 (89 %) and 75 (71 %).

(*S*)-MTPA ester of (+)-5a (compound (+)-5e).

$[\alpha]_D^{23}$ = +77 (c = 0.57, $CDCl_3$). The spectral data were identical to those of compound (-)-**5d** (*vide supra*), except for the fact that the e.e. of (+)-**5e** is only 84 %.

(5*R*,6*R*)-5-Bensoyloxy-2-methyl-6-(diethoxymethyl)-1-cyclohexenecarbaldehyde [(-)-5c].

Et_3N (0.1 ml), DMAP (5 mg) and bensoyl chloride (10µl, 0.086 mmol) were added to a stirred solution of alcohol (-)-**5a** (4.4 mg, 0.018 mmol) in dry CH_2Cl_2 (1.0 ml) at 0 °C. The resulting solution was stirred at rt. for 14 h and was quenched with 5 drops of a saturated aqueous solution of $NaHCO_3$. Extractive work-up and chromatography on silica gel yielded the bensoate as a colourless oil (6 mg, 95 %). $[\alpha]_D^{23}$ = -92 (c = 0.16, $CDCl_3$). UV: λ_{max}^{EtOH} 232 (ε 17,500) and 248 nm (shoulder, ε 10,500). ^1H-NMR: 1.12 (t, 3H, *J* = 7.1), 1.22 (t, 3H, *J* = 7.1), 1.50-2.05 (m, 1 H), 2.17-2.34 (m, 2H), 2.35-2.52 (m, 1H), 2.25 (s, 3H), 3.23-3.28 (m, 1 H),

3.30-3.3.41 (m, 1H), 3.58-3.79 (m, 3H), 4.58 (d, 1H, J = 4.3), 5.72-5.76 (m, 1H), 7.36-7.44 (m, 2 H), 7.49-7.56 (m, 1H), 7.90-7.96 (m, 2H), 10.13 (s, 1H); ^{13}C 15.2, 15.3, 18.9, 23.6, 30.0, 40.6, 63.5, 63.6, 68.2, 102.6, 128.3, 128.3, 129.5, 129.5, 130.1, 130.8, 132.8, 157.4, 165.64, 191.2. CIMS (*m/z*): 378 (M + NH_4^+, 13 %), 315 (35 %), 193 (100 %) and 164 (36 %); EIMS (*m/z*): 193 (12 %), 192 (11 %), 179 (12 %), 164 (10 %), 149 (9 %), 105 (91 %), 103 (100 %), 75 (88 %) and 47 (56 %).

(1*S*,2*R*,3*R*,6*S*)-3-Acetoxy-6-methyl-2-(diethoxymethyl)-bicyclo[4.1.0]heptane-1-carbaldehyde [(+)-6].

Colourless oil. $[\alpha]_D^{23}$ = + 266 (c = 2.3, $CDCl_3$). (+)-**6** was prepared by cyclopropanation of the acetate (-)-**5b** according to Ref. 7. The spectroscopic data were identical to those of the racemic compound.

(1*R*,2*S*,3*S*,6*R*)-3-Acetoxy-6-methyl-2-(diethoxymethyl)-bicyclo[4.1.0]heptane-1-carbaldehyde [(-)-6].

Colourless oil. $[\alpha]_D^{23}$ = -174 (c = 2.3, $CDCl_3$). (-)-**6** was prepared by cyclopropanation of the acetate (+)-**5b** according to Ref. 7. The spectroscopic data were identical to those of the racemic compound.

(1*S*,6*S*)-6-Methyl-bicyclo[4.1.0]hept-2-ene-1,2-dicarbaldehyde [(+)-7].

White crystals mp. 60-73° C. $[\alpha]_D^{23}$ = + 128 (c = 0.49, $CDCl_3$). (+)-**7** was prepared by acetal hydrolysis and elimination of the acetate (+)-**6** according to Ref. 7. The spectroscopic data were identical to those of the racemic compound.

(1*R*,6*R*)-6-Methyl-bicyclo[4.1.0]hept-2-ene-1,2-dicarbaldehyde [(-)-7].

Colourless oil. $[\alpha]_D^{23}$ = -104 (c = 0.56, $CDCl_3$). (-)-**7** was prepared by acetal hydrolysis and elimination of the acetate (-)-**6** according to Ref. 7. The spectroscopic data were identical to those of the racemic compound.

Acknowledgements
Financial support from the Swedish Science Research Council (NFR) is gratefully acknowledged.

REFERENCES AND NOTES

1. Anke, H.; Sterner, O. *Planta Med.* **1991**, *57*, 344-345.
2. Camazine, S.; Resch, J.; Eisner, T.; Meinwald, J. *J. Chem. Ecology* **1983**, *10*, 1439-1447.
3. Sterner, O.; Carter, R.E.; Nilsson, L.M. *Mut. Res.* **1987**, *188*, 169-174.
4. Morales, P.; Andersson, M.; Lewan, L.; Sterner, O. *Mut. Res.* **1992**, *268*, 315-321.
5. Nilsson, L.M.; Carter, R.E.; Sterner, O.; Liljefors, T. *Quant. Struct.-Act. Rel.* **1988**, *7*, 84-91.
6. Jonassohn, M.; Morales, P.; Sterner, O. Submitted for publication in *Acta Chem. Scand.* **1994**.
7. Gustafsson, J.; Sterner , O. submitted for publication in *Tetrahedron* **1994**.
8. Gustafsson and O. Sterner *J. Org. Chem.* **1994**, *59* , 3994-3997.
9. Arroyo, M.; Sinisterra, J.V. *J. Org. Chem.* **1994**, *59*, 4410-4417.
10. The ratio was obtained by comparing the integrals for the aldehyde protons.
11. a) Kaslauskas,R.J; Wiessfloch, A.N.E.; Rappaport, A.T.; Cuccia, L.A. *J. Org. Chem.* **1991**, *56*, 656-2665. b) Kim, M.J.; Choi, Y.K. *J. Org. Chem.* **1992**, *57*, 1605-1607. c) Georgens, U.; Schneider, M.P. *J. Chem. Soc. Chem. Commun.* **1991**, 1066-1068.
12. Dale, J.A.; Mosher, H.S. *J. Am. Chem. Soc.*, **1973**, *95*, 512-519.
13. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092-4096.
14. Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257-263.
15. Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy - Exciton Coupling in Organic Stereochemistry*. Oxford University Press: Oxford. 1983.
16. Koreedea, M.; Harada, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1974**, *96*, 266-268.
17. Nakanishi, K.; Berova, N. The Exciton Chirality Method. *In Circular Dichroism, Principles and Applications*; Nakanishi, K.; Berova, N.; Woody, R. W. Eds.; VCH Publishers: New York, 1994, pp. 361-398.
18. Platt, J. R. *J. Chem. Phys* **1949**, *17*, 484-495.
19 Bayley, P. M.; Nielsen, E. B.; Schellman, J. A. *J. Phys. Chem.* **1969**, *8*, 228-243.
20. Batty, J. W.; Heilbron, I. M.; Jones, W. E. *J. Chem. Soc.* **1939**, 1556-1560.
21. Tinoco Jr., I. *Adv. Chem. Phys.* **1962**, *4*, 113-160.
22. Ames, B.N.; McCann, J.; Yamasaki, E. *Mut. Res.* **1975**, *31*, 347-364.

(*Received in UK* 16 *December* 1994)