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A NEW SYNTHESIS OF SERRICORNIN [(4*S*,6*S*,7*S*)-7-HYDROXY-4,6-DIMETHYL-3-NONANONE], THE SEX PHEROMONE OF THE CIGARETTE BEETLE†

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Abstract—Serricornin, the sex pheromone of *Lasioderma serricorne* F, was synthesised in 7 6% overall yield starting from methyl (*R*)-3-hydroxypentanoate of microbial origin Its (4*R*,6*S*,7*S*)-isomer was also synthesised

Serricornin is the sex pheromone produced by the female cigarette beetle (*Lasioderma serricorne* F), which is a serious pest of cured tobacco leaves [1] The structure of serricornin was assigned to be (4*S*,6*S*,7*S*) - 7 - hydroxy - 4,6 - dimethyl - 3 - nonanone **1a** [2] Two syntheses of the natural and optically active serricornin were reported later, one starting from an amino acid[3] and the other starting from a sugar [4] These syntheses, however, were lengthy and not so effective in preparing the quantity of serricornin required for biological study We report here a new and more effective synthesis of serricornin **1a**

The basic synthetic strategy for serricornin as shown in Fig. 1 is the same as that employed previously [3] In our previous synthesis,[3] the coupling of the two building blocks **A** and **B** was executed by Enders and Eichenauer's method of asymmetric alkylation of ketones [5] Although the method was quite satisfactory with regard to the optical yield, it was not so effective with regard to the chemical yield [3] We therefore sought a simpler and more efficient method Incidentally we had a chance to prepare a stereoisomeric mixture of (±)-7 - hydroxy - 4,6 - dimethyl - 3 - nonanone **1a** according to the method of Ono *et al* [6] TLC analysis of the mixture as shown in Fig 2 revealed an interesting fact the mixture was readily separable into three fractions, which were acetylated and analysed by GLC [1–4] The least polar fraction was (4*S**,6*R**,7*S**)-**1a**, and the most polar fraction was (4*R**,6*S**,7*S**)-**1a** The broad spot between the least and the most polar fractions contained (4*S**,6*S**,7*S**)-**1a** and (4*R**,6*R**,7*S**)-**1a** ‡ It is therefore possible to separate serricornin (4*S*,6*S*,7*S*)-**1a** from its (4*R*,6*S*,7*S*)-isomer A mixture of these two

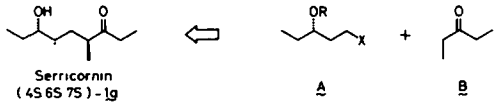

Fig. 1 Retrosynthetic analysis of serricornin

isomers will be the product of the alkylation of diethyl ketone **B** with the optically pure alkylating agent **A** This means that we can avoid the Enders and Eichenauer's process[5] to improve the chemical yield and that we can prepare optically pure (4*R*,6*S*,7*S*)-**1a**, which has not been synthesised or bioassayed We were also fortunate in that when we planned the synthesis methyl (*R*)-3-hydroxypentanoate **3a** became accessible by microbial β-oxidation of pentanoic acid **2** by *Candida rugosa* IFO 0750 followed by methylation [7] By employing **3a** as our starting material we could shorten considerably the synthetic route and actually obtained (4*S*,6*S*,7*S*)-**1a** in 7 6% yield from **3a**, in contrast with the overall yield of < 1% by the previous method [3]

Our synthetic route is shown in Fig 3 The optical purity of **3a** kindly given to us by Dr J Hasegawa (Kanegafuchi Chemical Industries Co Ltd) was 93%, which could be enhanced to 100% by recrystallising the corresponding 3,5-dinitrobenzoate **3b** Hydrolysis of the purified **3b** with KOH gave **3a**, whose optical purity was confirmed to be 100% by the HPLC analysis of its α-methoxy-α-trifluoromethylphenylacetate (MTPA ester)[8] **3c** It was later found, however, that an advanced intermediate **6a** was crystalline and could be readily purified We therefore employed **3a** (93% e e) as

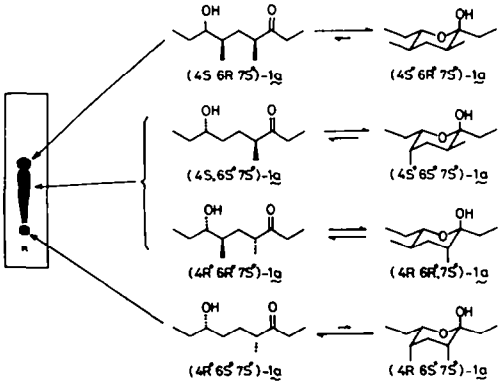

Fig. 2 TLC separation of the stereoisomers of serricornin

† Pheromone Synthesis, Part 66 Part 65, K Mori and M Ikunaka, *Tetrahedron* **40**, 3471 (1984) This work was presented as a part of K M 's lecture at the Institut für Organische Chemie und Biochemie, Universität Hamburg (October 25, 1983) The experimental part of this work was taken from the forthcoming M Sc Thesis of H W (March 1985)

‡ As shown in Fig. 2, the open-chain forms **1a** are in equilibrium with the hemiacetal forms **1a'**, the latter being less polar than the former The stereoisomer with a large R_f value is the one with the tendency to easily cyclise to **1a'** This explanation was supported by the NMR study of **1a** as described later in this paper Chromatographic separation of the stereoisomers of serricornin was also observed by Dr T Chuman and Mr M Mori of the Japan Tobacco and Salt Public Corporation A detailed account of the separation experiment will be reported by them in due course

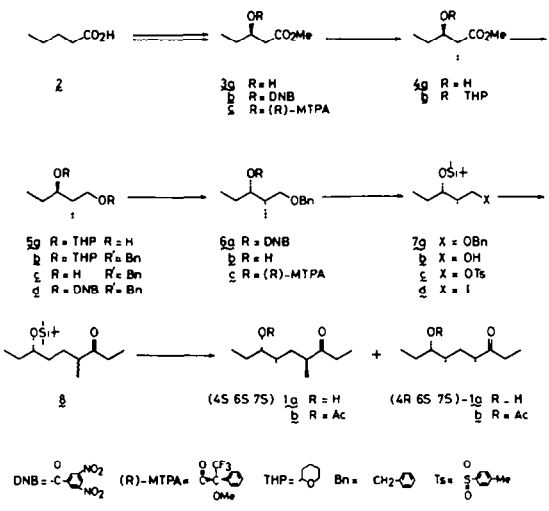

Fig 3 Synthesis of serricornin

received from Dr Hasegawa. Alkylation of a dianion derived from **3a** according to Frater[9] afforded **4a** (OR and Me in anti-orientation) as the major product contaminated with a small amount of **3a** and the *syn*-isomer of **4a** (**3a** **4a** the *syn*-isomer = 8 83 9) This mixture was treated with dihydropyran in the presence of PPTS to give a mixture of THP ethers Chromatographic purification of the mixture removed the THP ether of **3a** giving **4b** contaminated with a small amount of its *syn*-isomer in 61% yield from **3a** Reduction of **4b** with LAH yielded **5a**, whose benzylation gave **5b** in satisfactory yield Treatment of **5b** with 0 2% TsOH in MeOH afforded **5c** in 92 4% yield from **4b** The (3*R*)-alcohol **5c** was submitted to Walden inversion under the Mitsunobu condition[10] Thus **5c** was treated with Ph_3P, 3,5-dinitrobenzoic acid and $EtO_2CN{=}NCO_2Et$ in THF to give **6a**, m p 65 9–66 2°, in 42% yield after repeated recrystallisation The use of 3,5-dinitrobenzoic acid instead of benzoic acid in the original procedure[10] is very effective, because 3,5-dinitrobenzoates of alcohols are usually crystalline and can be purified by recrystallisation Another merit of using 3,5-dinitrobenzoic acid is that the course of the reaction can be followed by observing the colour of the reaction mixture, which turns from yellow to yellowish green, blue, blue-violet, red and finally to yellow when the reaction is complete No colour change could be observed when benzoic acid was employed By recrystallising **6a**, both the chemical and the optical purities of **6a** were improved The ^{13}C-NMR spectrum of the purified **6a** indicated no contamination of the *anti*-isomer **5d** (m p 84–85°), which was prepared by treating **5c** with 3,5-dinitrobenzoic acid and DCC Saponification of **6a** with KOH aq gave **6b**, whose GLC analysis showed its chemical purity to be 100% The optical purity of **6b** was confirmed to be 100% by the HPLC analysis of the corresponding MTPA ester **6c** Silylation of **6b** with *t*-butyldimethylsilyl chloride gave **7a**,[11 13] which was hydrogenolised over Pd–C to give **7b**, $[\alpha]_D^{22\ 5}$ −3 5° ($CHCl_3$) [lit [11] $[\alpha]_D^{20}$ −2 6° ($CHCl_3$)] The corresponding tosylate **7c** was treated with NaI in the presence of $NaHCO_3$ to give **7d**, $[\alpha]_D^{23}$ +15 6° ($CHCl_3$) In their syntheses of (4*RS*,6*S*,7*S*)-serricornin, Hoffmann *et al* [11] and Baker and Devlin[13] reported the specific rotation of **7d** to be +11 7° ($CHCl_3$) and +11 8° ($CHCl_3$), respectively Evidently their samples of **7d** were not optically pure

Now that the required alkylating agent **7d** was secured, we proceeded to the next step Alkylation of diethyl ketone with **7d** in the presence of LDA gave **8** in 80% yield GLC analysis of **8** revealed it to be a 3 4 mixture of (4*R*,6*S*,7*S*)-**8** and (4*S*,6*S*,7*S*)-**8** Deprotection of **8** by treatment with AcOH aq–THF gave a mixture of (4*S*,6*S*,7*S*)-**1a** and its (4*R*,6*S*,7*S*)-isomer without any formation of anhydroserricornin The mixture was chromatographed over SiO_2 and elution with n-pentane–ether (15 1) gave pure serricornin (4*S*,6*S*,7*S*)-**1a** in 7 6% overall yield from **3a** Pure (4*R*,6*S*,7*S*)-**1a** was also obtained by elution with n-pentane–ether (2 1) in 6 5% overall yield from **3a** Serricornin and its (4*R*,6*S*,7*S*)-isomer were acetylated and purified by chromatography and distillation to give pure serricornin acetate (4*S*,6*S*,7*S*)-**1b**, $[\alpha]_D^{21\ 5}$ −18 2° (n-hexane), and its (4*R*,6*S*,7*S*)-isomer, $[\alpha]_D^{19\ 5}$ −6 2° (n-hexane) † The spectral (IR, ^{1}H-NMR, ^{13}C-NMR) as well as GLC data of our synthetic serricornin acetate (4*S*,6*S*,7*S*)-**1b** were identical with those of the acetate derived from the natural pheromone [1 3 4] The overall yield of (4*S*,6*S*,7*S*)-**1b** from **3a** attained by the present synthesis was 5 9% in 14 steps, accompanied with 5 5% overall yield of (4*R*,6*S*,7*S*)-**1b** as a by-product

There now follows a brief discussion on the equilibrium among the acyclic and cyclic forms of serricornin and its (4*R*,6*S*,7*S*)-isomer Figure 4 shows the free energy differences among various forms of (4*S*,6*S*,7*S*)-**1a** and (4*R*,6*S*,7*S*)-**1a** In our argument the most stable hemiacetal form **1a'** of (4*S*,6*R*,7*S*) - 7 - hydroxy - 4,6 - dimethyl - 3 - nonanone with all of the four alkyl substituents in eq orientation was taken as standard and was given an arbitrary free energy value of 0 kcal/mol Conformational energies ($-\Delta G°$, kcal/mol at room temp (*ca* 23°)) used for the calculation were as follows Anomeric effect 1 4 kcal mol,[14–16] OH 0 7 kcal/mol,[17] Me 1 7 kcal/mol,[17] Et 1 8 kcal/mol,[17] 1,3-diaxial interaction of two Me's 5 5 kcal/mol [17] The

† The specific rotation of serricornin acetate (4*S*,6*S*,7*S*)-**1b** was reported to be −17 7° (a sample derived from natural serricornin),[3] −16 7° (a synthetic material)[3] and −19 67° (a synthetic material) [4] As we rigorously checked the purity of the present material by both GLC and NMR analyses, the value reported here (−18 2°) should be taken as the correct one As to the specific rotation of (4*R*,6*S*,7*S*)-**1b**, the difference between the value ($[\alpha]_D^{23}$ +36 75° (*c* = 0 33, n-hexane)) previously reported for (4*S*,6*R*,7*R*)-**1b**[2] and our value of ($[\alpha]_D^{21\ 5}$ −6 2° (*c* = 0 88 n-hexane)) was so large that we carried out the following experiment to confirm that our value was correct Equilibration at C-4 of serricornin acetate derived from the natural pheromone was reported to give a stereoisomeric mixture at C-4, (4*RS*,6*S*,7*S*)-**1b**, $[\alpha]_D^{23}$ −13 8° (*c* = 0 08, MeOH), whose GLC analysis showed it to be a 47 6 52 4 mixture of (4*S*,6*S*,7*S*)-**1b** and (4*R*,6*S*,7*S*)-**1b** ^{13}C-NMR spectral analysis of the mixture suggested the ratio of about 43 5 56 5 By measuring the specific rotation of MeOH solns of the present samples of (4*S*,6*S*,7*S*)-**1b** and (4*R*,6*S*,7*S*)-**1b**, we could calculate the $[\alpha]_D$ value of the equilibration mixture of these two isomers The $[\alpha]_D$ values of (4*S*,6*S*,7*S*)-**1b** and (4*R*,6*S*,7*S*)-**1b** were −23 5° (*c* = 0 09, MeOH) and −7 0° (*c* = 0 17, MeOH), respectively The calculated value for the specific rotation of the equilibration mixture was −14 2 to −14 9°, which was in agreement with the observed value of −13 8° We therefore became confident of our value, $[\alpha]_D^{21\ 5}$ −6 2° (n-hexane), for the specific rotation of (4*R*,6*S*,7*S*)-**1b**

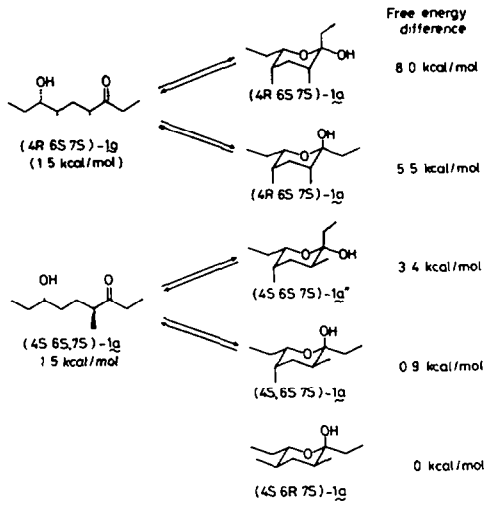

Fig 4 Free energy differences among various acylic and cyclic isomers of (4S,6S,7S)-serricornin and its (4R,6S,7S)-isomer

calculated free energy differences among the cyclic hemiacetal forms indicate that only the hemiacetal form **1a'** of the natural (4S,6S,7S)-serricornin may exist favourably under equilibrium conditions on the basis of the well-known relationship between ΔG° and the equilibrium constant K $\Delta G^\circ = -RT \ln K$ Actually our observation by the NMR measurement of (4S,6S,7S)-serricornin indicated that the ratio of the acyclic (4S,6S,7S)-**1a** to the cyclic **1a'** is 1 2 8 at 23°, since the signal due to C_7-H appeared at δ 3 17 (0 26H) and δ 3 82 (0 74H), the former being due to (4S,6S,7S)-**1a**, the latter being due to its hemiacetal form **1a'** This ratio enabled us to calculate the free energy difference between (4S,6S,7S)-**1a** and its cyclic form **1a'** with an ax OH at anomeric C to be 0 6 kcal/mol, and we concluded that (4S,6S,7S)-**1a** is 1 5 kcal/mol less stable than the most stable cyclic form (4S,6R,7S)-**1a'** We then assumed the acyclic form (4R,6S,7S)-**1a** to be of the same free energy level as that of (4S,6S,7S)-**1a** (1 5 kcal/mol) This demands that (4R,6S,7S)-isomer of serricornin exists solely in the acyclic form Its NMR measurement supported the prediction and only those signals due to the open-chain form (4R,6S,7S)-**1a** were observed As mentioned earlier, this difference between their ease of hemiacetal formation was the reason why the separation of (4S,6S,7S)-**1a** from its (4R,6S,7S)-isomer was possible by chromatography

In conclusion we completed a new and more efficient synthesis of (4S,6S,7S)-serricornin, the cigarette beetle pheromone, starting from methyl (*R*)-3-hydroxypentanoate of microbial origin

EXPERIMENTAL

All m ps and b ps were uncorrected IR spectra were measured as film or as Nujol mull on a Jasco A-102 spectrometer NMR spectra were recorded at 60 MHz with TMS as an internal standard on a Hitachi R-24A spectrometer unless otherwise stated Optical rotations were measured on a Jasco DIP-140 automatic polarimeter HPLC analyses were performed on a Shimadzu LC-2 chromatograph

Methyl (R)-3-(3',5'-*dinitrobenzoyloxy*)*pentanoate* **3b**

3,5-Dinitrobenzoic acid (60 6 g, 286 mmol) was added to a stirred and ice-cooled soln of **3a** (93% e e , 25 0 g, 189 mmol), N,N-dicyclohexylcarbodiimide (DCC, 47 3 g, 230 mmol) and 4-(N,N-dimethylamino)pyridine (DMAP, 1 89 g, 15 5 mmol) in CH_2Cl_2 (380 ml) The ice-bath was removed and the mixture was stirred for 3 hr at room temp To the stirred mixture was added n-pentane (100 ml) and the stirring was continued for 5 min at room temp The mixture was filtered and the residue was washed with CH_2Cl_2 The combined filtrate and washings were concentrated *in vacuo* to give a crude product (100 g) This was purified by chromatography over Merck Kieselgel 60 to give 64 g of the product Recrystallisation of it from n-hexane–ether (7 3, 1500 ml) gave 53 4 g (86 5%) of **3b** This was further recrystallised several times to give 38 6 g (72% recovery) of **3b** as pale yellow needles, m p 64 0–65 0°, $[\alpha]_D^{22} - 9\ 6°$ (c = 2 64, $CHCl_3$), ν_{max} 3180 (w), 1740 (sh), 1738 (s), 1625 (m), 1555 (s), 1340 (s), 1295 (s), 1180 (s), 720 (s) cm^{-1}, δ (CCl_4) 1 03 (3H, t, J = 8 Hz), 1 86 (2H, dq, J = 7 and 8 Hz), 2 71 (2H, d, J = 7 Hz), 3 64 (3H, s), 5 41 (1H, dd, J = 7 and 7 Hz), 9 00–9 30 (3H, m) (Calc for $C_{13}H_{14}O_8N_2$ C, 47 85, H, 4 33, N, 8 59 Found C, 47 78, H, 4 37, N, 8 54%)

Methyl (R)-3-*hydroxypentanoate* **3a**

To a stirred and ice-cooled soln of **3b** (35 0 g, 107 mmol) in THF–MeOH (1 1, 440 ml) was added dropwise N KOH aq (113 ml, 113 mmol) for a period of 20 min After the addition, the dark violet mixture was stirred for 30 min at 0° The mixture was diluted with satd $NaHCO_3$ soln (330 ml) and extracted with CH_2Cl_2 The extract was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* The residue was distilled to give 12 8 g (90%) of **3a**, b p 78–82°/25 mm, n_D^{22} 1 4204, $[\alpha]_D^{22} - 36\ 9°$ (c = 1 31, $CHCl_3$) The IR and NMR spectra of the purified **3a** were identical with those of the starting **3a** with 93% e e Both the purified and the starting **3a** were converted to the corresponding (*R*)-MTPA ester[8] and analysed by HPLC (column, Partisil 5, 25 cm × 4 6 mm, solvent, n-hexane–THF–MeOH (6000 100 1), press, 30 kg/cm², detector, SPD-1, 217 nm) R_t (before purification) 48 5 min (96 5%), 55 2 min (3 5%), R_t (after purification) 49 6 min (single peak) The optical purities of these materials are therefore 93% and 100% e e , respectively

Methyl (2R,3R)-3-*hydroxy*-2-*methylpentanoate* **4a**

A soln of LDA was prepared by the dropwise addition of n-BuLi soln (1 54 N in n-hexane, 147 ml, 226 mmol) to a stirred and cooled soln of Pr^i_2NH (22 9 g = 31 7 ml, 227 mmol) in dry THF (70 ml) at −10 to −5° under Ar The mixture was stirred for 30 min at −10 to −5° To the stirred and cooled (−60°) soln of LDA was added dropwise a soln of **3a** (93% e e , 15 0 g, 113 mmol) in dry THF (40 ml) at −60 to −30° The mixture was stirred for 45 min at −10 to −5° To the stirred and cooled (−40°) mixture was added dropwise a soln of MeI (16 1 g, 113 mmol) in HMPA (34 ml) at −40 to −30° The stirring was continued for 45 min after the addition with a gradual rise of the reaction temp to room temp The mixture was quenched with satd NH_4Cl at 0°, and extracted with ether The ether soln was washed with brine and filtered through a column of SiO_2 (Merck Kieselgel 60, 100 g) The filtrate was concentrated *in vacuo* to give a residue (40 g) This was chromatographed over SiO_2 (Merck Kieselgel 60) The crude **4a** was distilled to give 12 5 g (75%) of **4a**, b p 86–89°/20 mm, n_D^{21} 1 4259, $[\alpha]_D^{21} - 13\ 5°$ (c = 1 02, $CHCl_3$), ν_{max} 3450 (m), 1720 (s), 1195 (m), 1170 (m), 975 (m) cm^{-1}, GLC (column, OV-101, 40 m × 0 25 mm at 90° + 1°/min, carrier gas, N_2, 0 5 ml/min) R_t 24 8 min (**3a**, 8%), 30 9 min (**4a**, 83%), 32 3 min (*syn*-isomer of **4a**, 9%), MS (GC-MS, CI) m/z 147 ($M^+ + 1$, 100%), 129 ($M^+ + 1 - 18$, 66%) 115 ($M^+ - 31$, 40%), 88 ($M^+ + 1 - 18 - 31$, 13%) This was employed in the next step without further purification

Methyl (2R,3R)-2-*methyl*-3-*tetrahydropyranyloxypentanoate* **4b**

To a stirred soln of **4a** (12 3 g, 84 mmol) and dihydropyran (12 7 g, 151 mmol) in dry CH_2Cl_2 (120 ml) was added PPTS (2.3 g) The stirring was continued for 2 hr at room temp The mixture was poured into satd $NaHCO_3$ soln and extracted with ether The ether soln was washed with water and brine,

dried ($MgSO_4$) and concentrated *in vacuo* The residue (26 g) was chromatographed over SiO_2 (Merck Kieselgel 60) to remove the THP ether of **3a** The crude **4b** was distilled to give 15 7 g (61% from **3a**) of **4b**, b p 98–102°/5 mm, n_D^{22} 1 4430, $[\alpha]_D^{22}$ −23 9° (*c* = 1 15, $CHCl_3$), ν_{max} 1725 (s), 1260 (m), 1200 (s), 1170 (s), 1120 (s), 1080 (s), 1030 (sh), 1025 (s), 995 (s) cm^{-1}, δ (CCl_4) 0 96 and 1 02 (total 3H, each t, J = 7 Hz), 1 08 (3H, d, J = 7 Hz), 1 20–2 00 (8H, br), 2 63 (1H, dq, J = 7 and 7 Hz), 3 60 (3H, s), 3 20–4 00 (3H, m), 4 58 (1H, br) (Calc for $C_{12}H_{22}O_4$ C, 62 58, H, 9 63 Found C, 62 59, H, 9 67%)

(2S,3R) - 2 - *Methyl* - 3 - *tetrahydropyranyloxy* - 1 - *pentanol* **5a**

A soln of **4b** (15 6 g, 67 7 mmol) in dry ether (50 ml) was added dropwise to a stirred suspension of LAH (3 0 g, 79 mmol) in dry ether (200 ml) under ice-cooling. The mixture was stirred for 2 hr at room temp It was then ice-cooled and the excess LAH was destroyed by the successive addition of water (3 ml), 4 N NaOH aq (3 ml) and water (9 ml) After stirring for 1 hr at room temp, the mixture was filtered and the filter cake was washed with THF The combined filtrate and washings were concentrated *in vacuo* The residue was distilled to give 13 5 g (98 5%) of **5a**, b p 91–95°/0 3 mm, n_D^{20} 1 4555, $[\alpha]_D^{20}$ −9 4° (*c* = 1 36, $CHCl_3$), ν_{max} 3470 (m), 1200 (m), 1170 (m), 1130 (s), 1120 (s), 1075 (s), 1025 (s), 995 (s) cm^{-1}, δ (CCl_4) 0 70–1 10 (6H, m), 1 20–2 10 (9H, br), 2 90 (1H, br), 3 10–4 20 (5H, m), 4 60 (1H, br) (Calc for $C_{11}H_{22}O_3$ C, 65 31, H, 10 96 Found C, 65 53, H, 10 95%)

(2S,3R) - 2 - *Methylpentane* - 1,3 - *diol* 1 - *benzyl*, 3 - *THP* - *ether* **5b**

To a stirred suspension of 50% NaH (5 1 g, 106 mmol) in dry THF (93 ml) was added dropwise a soln of **5a** (13 5 g, 66 7 mmol) in dry THF (68 ml) The mixture was stirred and heated under reflux for 1 5 hr Subsequently a soln of $PhCH_2Cl$ (11 8 g, 93 1 mmol) in dry THF (31 ml) was added dropwise and the mixture was stirred and heated under reflux overnight After cooling, the mixture was poured into ice-water and concentrated *in vacuo* to remove THF The residue was extracted with ether The ether soln was washed with water, satd $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* The residue (25 9 g) was chromatographed over SiO_2 (Merck Kieselgel 60) The crude product was distilled to give 18 3 g (93 8%) of **5b**, b p 130–139°/0 23 mm, $n_D^{22\,5}$ 1 4923, $[\alpha]_D^{22\,5}$ −7 2° (*c* = 1 05, $CHCl_3$), ν_{max} 1500 (w), 1205 (m), 1115 (s), 1080 (s), 1030 (s), 1000 (s), 735 (m), 700 (m) cm^{-1}, δ 0 70–1 10 (6H, m), 1 20–1 80 (8H, br), 2.00 (1H, m), 3 10–4 00 (5H, m), 4 43 (2H, s), 4 51 (1H, br), 7 28 (5H, s) (Calc for $C_{18}H_{28}O_3$ C, 73 93, H, 9 65 Found C, 73 75, H, 9 65%)

(2S,3R) - 2 - *Methylpentane* - 1,3 - *diol* 1 - *benzyl ether* **5c**

TsOH (0 5 g) was added to a soln of **5b** (18 3 g, 62 6 mmol) in MeOH (250 ml) The soln was stirred for 30 min at room temp and neutralised by the addition of satd $NaHCO_3$ aq (20 ml) It was then concentrated *in vacuo* to remove MeOH The residue was extracted with ether The ether soln was washed with water and brine dried ($MgSO_4$) and concentrated *in vacuo* to give 14 2 g of crude **5c** This was distilled to give 13 1 g (quantitative) of pure **5c**, b p 99–104°/0 28 mm, $n_D^{22\,5}$ 1 4960, $[\alpha]_D^{22\,5}$ +15 4° (*c* = 1 10, C_6H_6), ν_{max} 3450 (m), 1495 (w), 1450 (m), 1085 (s), 970 (s), 730 (s), 695 (s) cm^{-1}, δ (CCl_4) 0 85 (3H, d, J = 7 Hz), 0 91 (3H, t, J = 7 Hz), 1 10–2 00 (3H, m), 2 70 (1H, d, J = 6 Hz), 3 10–3 60 (3H, m), 4 42 (2H s), 7 25 (5H, s) (Calc for $C_{13}H_{20}O_2$ C, 74 96, H, 9 68 Found C, 74 62, H, 9 69%)

(2S,3R) - 3 - (3',5' - *Dinitrobenzoyloxy*) - 2 - *methylpentan* - 1 - *ol benzyl ether* **5d**

To a stirred and ice-cooled soln of **5c** (4 0 g, 19 2 mmol), DCC (4 8 g, 23 3 mmol) and DMAP (190 mg, 1 56 mmol) in dry CH_2Cl_2 (40 ml) was added 3,5-dinitrobenzoic acid (6 2 g, 29 2 mmol) The mixture was stirred for 12 hr at room temp, diluted with n-pentane (10 ml) and filtered The residue on the filter was washed with CH_2Cl_2 (20 ml × 2) The combined filtrate and washings were concentrated *in vacuo* The residue was chromatographed over SiO_2 (Merck Kieselgel 60) to give 7 8 g (quantitative) of **5d** This was repeatedly recrystallised from n-hexane–ether (5 1) to give 5 2 g (67% recovery) of pure **5d** as pale yellow rods, m p 84–85°, $[\alpha]_D^{19\,5}$ −16 3° (*c* = 1 15, ether), ν_{max} 3180 (w), 1737 (s), 1645 (m), 1550 (s), 1465 (s), 1355 (s), 1290 (s), 1180 (m), 1110 (m), 1080 (m), 915 (m), 720 (m), 700 (m) cm^{-1}, δ ($CDCl_3$) 0 98 (3H, t, J = 7 Hz), 1 05 (3H, d, J = 7 Hz), 1 55–2 50 (3H, m), 3 48 (2H, d, J = 6 Hz), 4 39 (2H, s), 5 25 (1H, dt, J = 7 and 7 Hz), 7 18 (5H, s), 9 00–9 20 (3H, m), ^{13}C-NMR (25 MHz) δ ($CDCl_3$) 9 62, 13 78, 24 37, 36 97, 72 89, 73 25, 80 53, 121 98, 127 39, 127 59, 128 09, 129 26, 134 50, 138 10, 148 54, 162 37 (Calc for $C_{20}H_{22}O_7N_2$ C, 59 69, H, 5 51, N, 6 96 Found C, 59 97, H, 5 54, N, 7 11%)

(2S,3S) - 3 - (3',5' - *Dinitrobenzoyloxy*) - 2 - *methylpentan* - 1 - *ol benzyl ether* **6a**

To a stirred and ice-cooled soln of **5c** (9 0 g, 43 2 mmol), Ph_3P (22 6 g, 86 3 mmol) and 3,5-dinitrobenzoic acid (18 3 g, 86 3 mmol) in dry THF (180 ml) was added dropwise a soln of $EtO_2CN{=}NCO_2Et$ (15 0 g, 86 2 mmol) in dry THF (65 ml) After the addition, the ice-bath was removed, and the mixture was stirred for 24 hr at room temp Then it was concentrated *in vacuo* to remove THF and the residue was filtered through SiO_2 (Merck Kieselgel 60, 300 g) using $CHCl_3$ as the solvent to remove Ph_3PO The filtrate was concentrated *in vacuo* and the residue was chromatographed over SiO_2 (Merck Kieselgel 60) to give 14 3 g (82%) of **6a** This was repeatedly recrystallised from n-hexane–ether (5 1) to give 7 5 g (52% recovery) of pure **6a** as pale yellow needles, m p 65 9–66 2°, $[\alpha]_D^{20\,5}$ +12 9° (*c* = 1 27, ether), ν_{max} 3140 (w), 1730 (s), 1635 (m), 1548 (s), 1460 (s), 1350 (s), 1290 (s), 1175 (m), 1078 (m), 750 (w), 715 (m), 700 (m) cm^{-1}, δ ($CDCl_3$) 0 97 (3H, t, J = 7 Hz), 1 13 (3H, d, J = 7 Hz), 1 50–2 50 (3H, m), 3 45 (2H, d, J = 6 Hz), 4 39 (2H, s), 5 40 (1H, dt, J = 4 and 7 Hz), 7 19 (5H, s), 9 00–9 20 (3H, m), ^{13}C-NMR (25 MHz) δ ($CDCl_3$) 10 18, 11 53, 24 86, 36 74, 72 78, 73 30, 79 53, 121 98, 127 42, 127 68, 128 15, 129 23, 134 53, 138 15, 148 57, 162 37 (Calc for $C_{20}H_{22}O_7N_2$ C, 59 69, H, 5 51, N, 6 96 Found C, 59 67, H, 5 50, N, 6 90%)

(2S,3S) - 2 - *Methylpentane* - 1,3 - *diol* 1 - *benzyl ether* **6b**

To a stirred soln of **6a** (5 0 g, 12 4 mmol) in THF–EtOH (1 1, 60 ml) was added dropwise N KOH aq (15 ml, 15 mmol) The red-violet-coloured reaction mixture was stirred for 1 hr at room temp, neutralised with satd $NaHCO_3$ aq (20 ml) and extracted with ether The ether soln was washed with water, satd $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 3 0 g of crude **6b** This was distilled to give 2 46 g (95 0%) of **6b**, b p 102–107°/1 0 mm, $n_D^{20\,5}$ 1 4977, $[\alpha]_D^{20\,5}$ +1 2° (*c* = 1 06, C_6H_6), ν_{max} 3500 (m), 3060 (w), 1500 (w), 1460 (m), 1090 (s), 1070 (sh), 970 (m), 730 (s), 695 (s) cm^{-1}, δ (CCl_4) 0 85 (3H, d, J = 7 Hz), 0 91 (3H, t, J = 7 Hz), 1 10–2 00 (3H, m), 2 46 (1H, br), 3 38 (2H, d, J = 6 Hz), 3 30–3 70 (1H, m), 4 40 (2H, s), 7 22 (5H, s), GLC (column, PEG 20M, 50 m × 0 25 mm at 170°, carrier gas, N_2, 0 5 ml/min) R_t 21 8 min (single peak) (Calc for $C_{13}H_{20}O_2$ C, 74 96, H, 9 68 Found C, 74 73, H, 9 62%) The corresponding (*R*)- and (*S*)-MTPA esters **6c** were prepared as usual and analysed by HPLC (column, Partisil 5, 25 cm × 4 6 mm, solvent, n-hexane–THF–MeOH (10,000 100 1), press, 20 kg/cm², detector, SPD-1, 217 nm) R_t 35 6 min ((*R*)-MTPA ester **6c**, single peak) or 37 7 min ((*S*)-MTPA ester **6c**, single peak) The optical purity of **6b** was therefore 100%

(2S,3S) - 3 - t - *Butyldimethylsilyloxy* - 2 - *methylpentan* - 1 - *ol benzyl ether* **7a**

To a stirred soln of TBDMS Cl (2 4 g, 15 9 mmol) and imidazole (2 16 g, 31 8 mmol) in dry DMF (40 ml) was added a soln of **6b** (100% e e, 100% diastereomeric purity, 2 2 g, 10 6 mmol) in dry DMF (20 ml) The mixture was stirred overnight at room temp, poured into ice-water (200 ml) and extracted with ether The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* The residue (4 3 g) was chromatographed over SiO_2 (Merck Kieselgel 60) and the resulting crude **7a** was distilled to give 3 4 g (quantitative) of **7a**, b p 102–107°/0 08 mm, n_D^{23} 1 4716, $[\alpha]_D^{23}$ +5 1° (*c* = 1 26,

$CHCl_3$), ν_{max} 1255 (m), 1105 (s), 1050 (s), 860 (m), 835 (s), 770 (s), 730 (m), 695 (m) cm^{-1}, δ (CCl_4)–0·00 (6H, s), 0·70–1·00 (15H, m), 1·38 (2H, q, J = 6 Hz), 1·50–2·00 (1H, m), 3·12 (1H, dd, J = 5 and 10 Hz), 3·35 (1H, dd, J = 7 and 10 Hz), 3·63 (1H, dt, J = 3·5 and 6 Hz), 4·34 (2H, s), 7·16 (5H, s) (Calc for $C_9H_{34}O_2Si$ C, 70·75, H, 10·62 Found C, 70·51, H, 10·55%)

(2S,3S)-3-t-*Butyldimethylsilyloxy*-2-*methylpentan*-1-*ol* **7b**

Ten percent Pd–C (670 mg) was added to a soln of **7a** (3·3 g, 15·8 mmol) in 99% EtOH (45 ml) and the suspension was stirred under H_2 at room temp until the H_2 uptake ceased The mixture was filtered through Celite and the filtrate was concentrated *in vacuo* The residue was distilled to give 2·3 g (96·7%) of **7b**, b p 72–77°/0·5 mm, $n_D^{22.5}$ 1·4381, $[\alpha]_D^{22.5}$ −3·5° (c = 1·98, $CHCl_3$), ν_{max} 3400 (m), 1255 (m), 1100 (m), 1050 (s), 1020 (s), 850 (m), 835 (s), 770 (s) cm^{-1}, δ (CCl_4) 0·07 (6H, s), 0·70–1·00 (15H, m), 1·47 (2H, dd, J = 7 and 7 Hz), 1·50–2·00 (1H, m), 2·13 (1H, br), 3·30–3·60 (2H, m), 3·66 (1H, dt, J = 3·5 and 7 Hz) This was employed in the next step without further purification

(2S,3S)-3-t-*Butyldimethylsilyloxy*-2-*methylpentyl tosylate* **7c**

To a stirred and ice-cooled soln of **7b** (1·4 g, 6·02 mmol) in dry C_5H_5N (5·8 ml) was added *p*-TsCl (1·8 g, 9 mmol) and the mixture was stirred overnight at 0° The mixture was poured into ice-water and extracted with ether The ether soln was washed with satd $CuSO_4$ aq, water, satd $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* to give 2·4 g of crude **7c**, ν_{max} 1610 (m), 1500 (w), 1370 (s), 1260 (m), 1190 (s), 1180 (s), 1100 (m), 1055 (m), 970 (s), 835 (s), 810 (m), 770 (s) cm^{-1}, δ (CCl_4) 0·02 (6H, s), 0·70–1·00 (15H, m), 1·10–2·00 (3H, m), 2.46 (3H, s), 3·30–4·40 (3H, m), 7·36 (2H, d, J = 8 Hz), 7·74 (2H, d, J = 8 Hz) This was employed directly in the next step without further purification

(2R,3S)-3-t-*Butyldimethylsilyloxy*-2-*methylpentyl iodide* **7d**

NaI (1·44 g, 5·7 mmol) and $NaHCO_3$ (3·8 g, 45 mmol) were added to a soln of **7c** (2·2 g, 6·7 mmol) in dry acetone (24 ml) The mixture was stirred and heated under reflux overnight under Ar The mixture was concentrated *in vacuo* The residue was diluted with water (20 ml) and extracted with ether The ether soln was washed with water, 10% $Na_2S_2O_3$ aq, water, satd $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* The residue was chromatographed over SiO_2 (Merck Kieselgel 60) to give 1·94 g (99·6% from **7b**) of **7d**, b p 73–76°/0·3 mm, n_D^{23} 1·4739, $[\alpha]_D^{23}$ +15·6° (c = 4·02, $CHCl_3$), ν_{max} 1255 (s), 1095 (s), 1060 (s), 1020 (s), 1005 (s), 860 (m), 830 (s), 770 (s) cm^{-1}, δ (CCl_4) 0·09 (6H, s), 0·89 (9H, s), 0·60–1·10 (6H, m), 1·43 (2H, q, J = 7 Hz), 1·82 (1H, dq, J = 5 and 7 Hz), 3·04 (1H, dd, J = 7 and 10 Hz), 3·11 (1H, dd, J = 7 and 10 Hz), 3·63 (1H, dt, J = 5 and 7 Hz) This was employed in the next step without further purification

(4RS,6S,7S)-7-t-*Butyldimethylsilyloxy*-4,6-*dimethyl*-3-*nonanone* **8**

A soln of LDA was prepared by the addition of a soln of n-BuLi (1·72 N in n-hexane, 17·7 ml, 30·4 mmol) to a stirred and cooled soln of Pr^i_2NH (4·41 ml, 31·5 mmol) in dry THF (20 ml) at −60° under Ar HMPA (9·2 ml) was added to the mixture at −60° The mixture was warmed to −20° to make it a homogeneous soln To the stirred and cooled LDA soln, a soln of Et_2CO (3·08 ml, 29·2 mmol) in dry THF (6 ml) was added dropwise at −55° The mixture was stirred for 30 min at −55° It was then cooled to −60° To the stirred and cooled soln was added dropwise a soln of **7d** (800 mg, 2·34 mmol) in dry THF (6 ml) at −60° After the addition, the reaction temp was gradually raised to −5° over 3 hr The stirring was continued overnight at −5 to 0° The mixture was poured into iced-brine and extracted with ether The ether soln was washed with N HCl, water, satd $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated *in vacuo* The residue (0·93 g) was chromatographed over SiO_2 (Merck Kieselgel 60) to give 560 mg (80%) of **8**, b p 100–102°/0·4 mm, n_D^{21} 1·4396, $[\alpha]_D^{21}$ −8·7° (c = 2·29, $CHCl_3$), ν_{max} 1730 (s), 1260 (s), 1110 (s), 1080 (s), 1060 (s), 1020 (s), 860 (sh), 840 (s), 775 (s) cm^{-1}, δ (CCl_4) 0·02 (6H, s), 0·89 (9H, s), 0·70–1·15 (12H, m), 1·15–2·00 (3H, m), 1·47 (2H, q, J = 7 Hz), 2.36 (2H, q, J = 8 Hz), 2·20–2·70 (1H, br), 3·20–3·60 (1H, m), GLC (Hitachi 163 gas chromatograph, column, 5% PEG 20M, 2 m × 3·5 mm at 100° + 5°/min, carrier gas, N_2, 1·0 kg/cm²) R_t 11·3 min ((4*R*,6*S*,7*S*)-**8**, 41%), 11·8 min ((4*S*,6*S*,7*S*)-**8**, 58%) (Calc for $C_{17}H_{36}O_2Si$ C, 67·44, H, 12·07 Found C, 67·61, H, 11·99%) This was employed in the next step without further purification

(4S,6S,7S)-7-*Hydroxy*-4,6-*dimethyl*-3-*nonanone* (*serricornin* **1a**) *and its* (4R,6S,7S)-*isomer*

A soln of **8** (440 mg, 1·46 mmol) in AcOH–H_2O–THF (3·1·1, 15 ml) was stirred and heated at 40° for 24 hr The mixture was then ice-cooled and neutralised by the addition of 3 N NaOH (40 ml, 0·8 equiv to AcOH used) It was poured into satd $NaHCO_3$ aq (50 ml) and extracted with ether The ether soln was washed with water, satd $NaHCO_3$ aq and brine, dried ($MgSO_4$) and concentrated to give 0·4 g of crude **1a** This was chromatographed over SiO_2 (Merck Kieselgel 60, 10 g, 20 cm × 1·3 cm) Elution with n-pentane–ether (15·1) gave *serricornin* (4S,6S,7S)-**1a** (116 mg, 43%), ν_{max} 3550 (m), 3020 (s), 2980 (s), 2930 (s), 1720 (s), 1470 (s), 1420 (w), 1385 (m), 1350 (w), 1260 (w), 1230 (w), 1150 (m), 1100 (s), 1040 (m), 1000 (s), 980 (s), 960 (s), 950 (sh), 915 (w), 900 (w), 870 (w), 830 (w), 800 (w), 770 (w) cm^{-1}, δ (400 MHz, C_6D_6) 3·17 (0·26H, m and br), 3·82 (0·74H, ddd, J = 2·6, 7·0 and 8·0 Hz) Other signals were difficult to analyse, because of the presence of two forms **1a** and **1a'** The ratio of **1a** to **1a'** = 0·26·0·74 = 1·2·8, ^{13}C-NMR (25 MHz) δ (C_6D_6) open-chain form **1a** 8·04, 10·82, 13·69, 16·44, 27·50, 33·87, 35·83, 36·83, 43·82, 76·35, 213·59 The assignments were done by comparing these signals with those of (4*R*,6*S*,7*S*)-**1a** Hemiacetal form **1a'** 7·37, 10·68, 11·70, 16·73, 26·18, 30·22, 31·27, 33·08, 36·18, 72·66, 98·58 Further elution with n-pentane–ether (2·1) gave (4*R*,6*S*,7*S*)-**1a** (101 mg, 37%), ν_{max} 3530 (m), 3020 (s), 2980 (s), 2930 (s), 1720 (s), 1470 (s), 1420 (w), 1385 (m) 1350 (w), 1250 (w), 1150 (m), 1110 (m), 1030 (m), 980 (s), 920 (w), 890 (w), 860 (w), 800 (w) cm^{-1}, δ (400 MHz, C_6D_6) 0·82 (3H d, J = 6·9 Hz), 0·88 (3H, d, J = 7·0 Hz), 0·91 (3H, t, J = 7·4 Hz), 0·96 (3H, t, J = 7·2 Hz), 1·01 (1H, ddd, J = 5·5, 8·3 and 13·9 Hz), 1·29 (1H, ddd, J = 4·3, 7·4 and 13·6 Hz), 1·30–1·40 (1H, m), 1·40 (1H, ddd, J = 7·4, 8·3 and 13·6 Hz), 1·90 (1H, br), 1·92 (1H, ddd, J = 6·1, 8·9 and 13·9 Hz), 2·05 (1H, dq, J = 18·0 and 7·2 Hz), 2·15 (1H, dq, J = 18·0 and 7·2 Hz), 2·40 (1H, ddq, J = 5·5, 8·9 and 7·0 Hz), 3·21 (1H, m, br), ^{13}C-NMR (25 MHz) δ (C_6D_6) 8·04, 10·91, 14·01, 17·78, 27·47, 34·11, 36·39, 37·21, 44·11, 75·50, 213·94 TLC of (4S,6S,7S)-**1a** and (4*R*,6*S*,7*S*)-**1a** (Merck Kieselgel 60 F-254, developed with n-hexane–ether = 3·1) R_f 0·17–0·48 [(4S,6S,7S)-**1a**], 0·13 [(4*R*,6*S*,7*S*)-**1a**] (*cf* R_f 0·78, anhydroserricornin) (4S,6S,7S)-Serricornin in $CHCl_3$ affords a mixture of anhydroserricornin, (4S,6S,7S)-serricornin and (4*R*,6*S*,7*S*)-serricornin after a while The NMR spectra of serricornin and its isomer were therefore measured in C_6D_6 to avoid the equilibration The NMR spectra indicated high diastereomeric purities of our products These were acetylated without further purification

(4S,6S,7S)-*Serricornin acetate* **1b**

Ac_2O (0·17 ml, 1·8 mmol) was added to a soln of (4S,6S,7S)-**1a** (38·8 mg, 0·208 mmol) in dry C_5H_5N (0·17 ml) and the mixture was stirred overnight at room temp The mixture was poured into ice-water and extracted with ether The ether soln was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo* The residue was chromatographed (Merck Kieselgel 60) and distilled to give 37·0 mg (77·8%) of (4S,6S,7S)-**1b**, b p 90–93° (bath temp)/2·5 mm, $n_D^{21.5}$ 1·4322, $[\alpha]_D^{21.5}$ −18·2° (c = 0·58, n-hexane), $[\alpha]_D^{21}$ −23·5° (c = 0·09, MeOH) The IR, ^{1}H-NMR and ^{13}C-NMR data were identical with those reported previously [3] Only the ^{13}C-NMR data will be described here δ (25 MHz, $CDCl_3$) 7·87, 10·15, 14·43, 16·61, 21·86, 24·20, 33·70, 34·25, 35·93, 43·53, 78·10, 170·92, 214·94, GLC (Shimadzu GC-7A gas chromatograph, column, OV-101, 50 m × 0·28 mm at 100° + 2°/min, carrier gas, N_2, 65

ml/min) 24 2 min (99 9%), 24 8 min (0 1%), GLC (column, Silar 10-C, 50 m × 0 27 mm at 140°, carrier gas, N_2, 50 ml/min) R_t 30 2 min (single peak) (Calc for $C_{13}H_{24}O_3$ C, 68 38, H, 10 59 Found C, 68 15, H, 10 51%)

(4R,6S,7S) - 7 - Acetoxy - 4,6 - dimethyl - 3 - nonanone **1b**

In the same manner as above (4*R*,6*S*,7*S*)-**1a** (42 0 mg, 0 225 mmol) was acetylated to give 44 0 mg (85%) of (4*R*,6*S*,7*S*)-**1b**, b p 105–110°/3 5 mm, $n_D^{21.5}$ 1 4316, $[\alpha]_D^{21.5}$ −6 2° (*c* = 0 88, n-hexane), $[\alpha]_D^{21}$ −7 0° (*c* = 0 17, MeOH) The IR, ^{1}H-NMR and ^{13}C-NMR data were identical with those reported for (4*S*,6*R*,7*R*)-**1b** [2] Only the ^{13}C-NMR data will be described here δ (25 MHz, $CDCl_3$) 7 78, 10 12, 14 63, 17 32, 21 03, 24 22, 33 61, 34 28, 36 39, 43 35, 77 81, 170 97, 214 88, GLC (Shimadzu GC-7A gas chromatograph, column, OV-101, 50 m × 0 28 mm at 100° + 2°/min, carrier gas, N_2, 65 ml/min) R_t 24 2 min (single peak), GLC (column, Silar 10-C, 50 m × 0 27 mm at 140°, carrier gas, N_2, 50 ml/min) R_t 30 7 min (single peak) (Calc for $C_{13}H_{24}O_3$ C, 68 38, H, 10 59 Found C, 68 38, H, 10 61%)

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