SYNTHESIS OF OPTICALLY ACTIVE 1-(2-FURYL)-3-PENTANOL. A SIMPLE ROUTE TO (2*S*, 5*R*/*S*)-CHALCOGRAN

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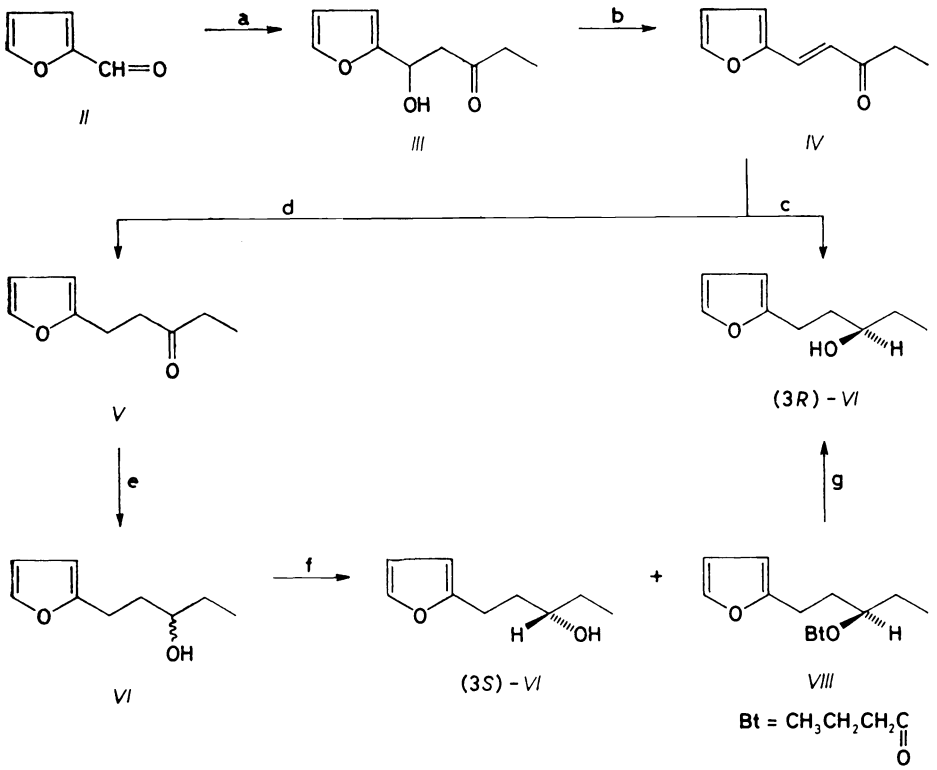
Received July 14, 1989
Accepted September 12, 1989

Enantioselective synthesis of the title alcohol *VI* is reported, which utilizes either pig pancreatic lipase mediated transesterification or a reduction with baker's yeast as the key steps. The transesterification of *VI* gives (*S*)-(+)-*VI* (e.e. 80%) or (*R*)-(−)-*V*)(e.e. 50%), while the reduction of the corresponding α,β-unsaturated ketone *IV* affords (*R*)-(−)-*VI*(e.e. 30%). These intermediates allowed to prepare a mixture of chalcogran *I* diastereoisomers containing 54% of the biologically active (2*S*, 5*R*) isomer.

In the chemistry of natural products there is still a continuing interest in simple and effective synthetic procedures leading to optically active secondary alcohols, which may serve as chiral synthons for the preparation of various substances, as insect pheromones etc. Many of these chiral alcohols are now commercially available. However, furyl substituted pentanols constituting key intermediates for the synthesis of chalcogran (2-ethyl-1,6-dioxaspiro[4.4]nonane (*I*) – the component of the aggregation pheromone of the bark beetle *Pityogenes chalcographus* (L.))[1,2], have yet to be synthesized in the optically active form. Although several syntheses have been reported of optically active chalcogran *I* (refs[3–10]), they are either tedious or involve steps that do not allow larger scale preparations.

The aim of this paper is to report the synthesis of optically active 1-(2-furyl)-3-pentanol (*VI*) and to investigate stereoselectivity of the cyclization leading to chalcogran diastereoisomers. The key requirements imposed on the synthetic approach in question are its relative simplicity and rather low cost of the product, which is to be prepared in quantities enabling field trials. For the given purpose, there are no strict requirements of the high optical purity of chalcogran, because sufficiently enriched optically active material can provide adequate biological response[10]. Moreover, chalcogran itself epimerizes easily at C-5 (refs[3,10]). In this respect, it appears more reasonable to focus the attention to the chirality at C-2. We examined two syntheses of the optically active 1-(2-furyl)-3-pentanol (*VI*), both utilizing enzymatic reactions. In the first case, the α,β-unsaturated ketone *IV* was

reduced enantioselectively with baker's yeast. We assumed that both the double bond and the carbonyl group could be reduced in a single step as observed by Gramatica and coworkers for α,β-unsaturated aldehydes[12]. In the second method, the resolution of the racemic alcohol *VI* was attempted by enantioselective transesterification of 2,2,2-trichloroethyl butyrate in the presence of pig pancreatic lipase (PPL, EC 3.1.1.3). The latter approach was reported to give quite high yields of chiral secondary alcohols exhibiting enantiomeric excess in the range 60–100% (ref.[13]).



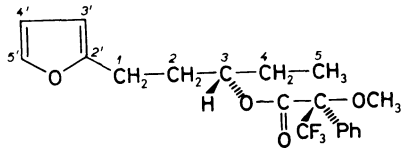
SCHEME 1

a 2-Butanone, lithium diisopropylamide; b NaOH; c baker's yeast, D-glucose; d sodium amalgam; e sodium borohydride; f lipase, 2,2,2-trichloroethyl butyrate; g KOH, ethanol

Preparation of the substrates for these reactions (Scheme 1) follows the procedure described by Francke and Reith[14] with several modifications: The original aldol condensation leading to a 2 : 1 mixture of the desired 1-(2-furyl)-1-pentene-3-one (*IV*) with 4-(2-furyl)-3-methyl-3-buten-2-one was replaced by a more selective two-step procedure. In the first step, the β-hydroxyketone *III* was prepared by a low

temperature aldol reaction in the presence of lithium diisopropylamide, as described by Smith and Levenberg[15] for other β-hydroxyketones. In the second step, the treatment of *III* with 1% aqueous NaOH afforded the α,β-unsaturated ketone *IV* containing only 3% of the undesired 4-(2-furyl)-3-methyl-3-buten-2-one (as determined by GLC). The racemic alcohol *VI* was prepared by a two-step reduction of the enone *IV* with sodium amalgam and, afterwards, with sodium borohydride.

For the analysis of enantiomeric excess exhibited by the above reactions we used ^{1}H NMR and HPLC of diastereoisomeric esters *VII* of the alcohol *VI* with (*R*)-(+)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoic acid (MTPA). (We could not utilize optical rotations because optically pure *VI* is not known). ^{1}H NMR data of these diastereoisomers enabled also determination of absolute configuration at C-3 of *VI*. According to the method described by Rinaldi[16] the chemical shifts of protons H-1, H-3′, H-4′, H-5′ resp. H-4, H-5 are sensitive to the orientation of these protons with respect to various substituents at the asymmetric centre of MTPA (of known absolute configuration). Consequently, the chemical shift differences found for the compounds (*R*)-*VII* and (*S*)-*VII* (see Tables I and II) when interpreted on the basis of the different shielding by either the bulky phenyl group or by the methoxyl group of the MTPA residue provide the unambiguous assignment of the absolute configuration at C-3.



(3S)-*VII*

RESULTS AND DISCUSSION

Asymmetric reduction of *IV* with baker's yeast under usual conditions (aqueous medium containing D-glucose at room temperatur) afforded 47% of *VI* in six days. Both the double bond and the carbonyl group of *IV* were reduced in one step. The product was enriched by the (*R*)-(−) enantiomer, but the enantiomeric excess was low (~30%).

The second approach included the transesterification of 2,2,2-trichloroethyl butyrate with the racemic alcohol *VI* in the presence of excess of the PPL. The reaction was carried out in the non-aqueous medium (diethylether–suspended enzyme) at room temperature. We obtained a mixture containing the (*S*)-(+) alcohol *VI* and the (*R*)-butyrate *VIII*. The butyrate, after the hydrolysis gave the (*R*)-(−) alcohol *VI*. The chemical yields and the enantiomeric excess of both products isolated from

the enzymatic reaction depended on the reaction time. In general, longer reaction time (about five days) caused an increase of the (*S*)-(+) isomer content in the free

TABLE I

^{1}H NMR parameters of compounds *III*, *IV*, *VI*, (3*R*)-*VII*, (3*S*)-*VII* in deuterochloroform

Proton	Compound				
	III[a]	*IV*	*VI*[b]	(3*R*)-*VII*[c]	(3*S*)-*VII*[d]
H-1	5·17 ddd	6·65 dt	2·70 m 2·81 m	2·65 ddt	2·52 m
H-2	1·88 ddd 2·06 ddd	7·32 d	1·79 m	1·87—2·07 m	1·87—2·07 m
H-3	—	—	3·55 m	5·98 dq	5·92 dq
H-4	2·50 q	2·64 q	1·49 m	1·65 dq	1·71 dq
H-5	1·08 t	1·16 t	0·95 t	0·83 t	0·93 t
H-3′	6·26 dt	6·65 dq	6·00 dq	5·98 dq	5·92 dq
H-4′	6·33 dd	6·48 dd	6·27 dd	6·27 dd	6·25 dd
H-5′	7·36 dd	7·49 dq	7·29 dd	7·30 dd	7·28 dd

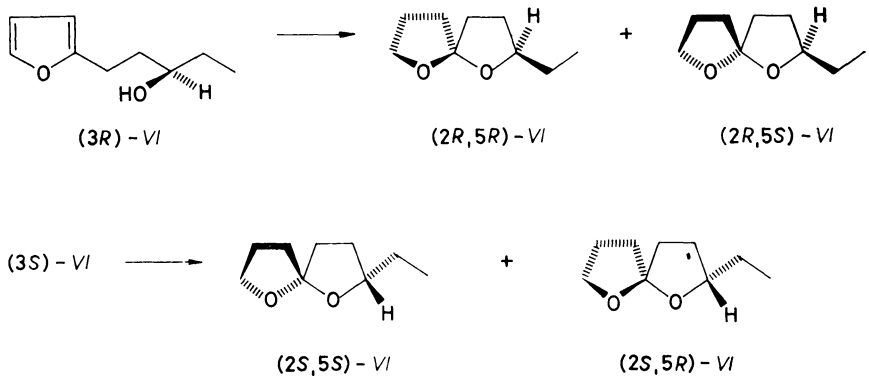
Coupling constants: [a] $J(1,2) = 3{\cdot}8$, $J(1,2') = 8{\cdot}6$, $J(2,2') = 17{\cdot}5$, $J(4,5) = 7{\cdot}4$; *IV* — $J(1,2) = 16{\cdot}0$, $J(4,5) = 7{\cdot}4$; [b] $J(1,2) = 7{\cdot}4$, $J(1,2') = 8{\cdot}2$, $J(1',2) = 6{\cdot}4$, $J(1',2') = 8{\cdot}6$, $J(1,1') = 15{\cdot}2$, $J(2,3) = 4{\cdot}0$, $J(2',3) = 7{\cdot}0$, $J(3,4') = 8{\cdot}2$; [c] $J(1,2) = J(1,2') = 7{\cdot}2$, $J(2,3) = 6{\cdot}1$, $J(3,4) = 6{\cdot}1$, $J(4,5) = 7{\cdot}5$; [d] $J(3,4) = 6{\cdot}1$, $J(4,5) = 7{\cdot}5$.

TABLE II

^{13}C NMR data of compounds *III*, *IV*, *VI* in deuterochloroform

Carbon	Compound		
	III	*IV*	*VI*
C-1	63·77 d	128·20 d	35·05 t
C-2	46·76 t	123·01 d	30·15 t
C-3	211·10 s	200·24 s	72·41 d
C-4	36·71 t	34·32 t	24·23 t
C-5	7·44 q	8·08 q	9·81 q
C-2′	154·99 s	150·95 s	155·88 s
C-3′	106·13 d	112·33 d	104·78 d
C-4′	110·18 d	115·30 d	110·05 d
C-5′	141·99 d	144·63 d	140·80 d

alcohol *VI* (up to e.e. 80%), while the interruption of the reaction after a shorter period (about two days) resulted in the increase of e.e. for the butyrate. In the latter case, the corresponding (*R*)-(−) enriched enantiomer exhibited higher optical purity (e.e. 50%). Although the chemical yield was always lower for the product exhibiting higher e.e., it was still in the range 60−70%. Thus, the PPL-assisted transesterification provides the advantage of the control over the enantiomeric excess of the particular isomer. Moreover, the product isolation is easier. The yield and enantiomeric excess were comparable to those reported by Kirchner and coworkers[13] for the series of secondary alcohols. However, there is one notable difference: we found that the alcohol *VI* possessed higher optical purity than the butyrate. Steric requirements of the groups at C-3 of *VI* (ethyl and 2-(2-furyl)ethyl, which are decisive for chiral discrimination) are rather similar as follows from the HPLC analysis of the corresponding MTPA esters. (The maximal R_s between (*R*)-*VII* and (*S*)-*VII* was 0·70). Considering this fact, the best enantiomeric excess achieved with this substrate (80%) was quite high.



SCHEME 2

The above mentioned synthesis of optically active alcohol *VI* exhibiting quite high enrichment by the (*S*)-(+) enantiomer enabled cyclization attempts leading to diastereoisomers of *I*. Hydrogenation of partially optically active (*S*)-(+)-*VI* on Pd/C resulted in a mixture of chalcogran diastereoisomers of the following composition: 40% (2*R*, 5*R*) and (2*S*, 5*S*), 60% (2*R*, 5*S*) and (2*S*, 5*R*) (determined by GLC). Hence, stereoselectivity of the cyclization was the same as for the alternative synthesis[9]. This finding implied that the diastereoisomeric composition of *I* prepared from (*S*)-(+)-*VI* (e.e. 80%) should be as follows: 36% (2*S*, 5*S*), 54% (2*S*, 5*R*), 4% (2*R*, 5*R*), 6% (2*R*, 5*S*). Optical rotation estimated for this mixture on the basis of known $[\alpha]_D^{25}$ values (ref.[9]) of pure chalcogran diastereoisomers (−21·2°) is in

a reasonable agreement with the experimental finding (−18·5°). As recently reported[10] the biologically active isomer of *I* is of (2S, 5R) configuration. Consequently, our modification of chalcogran synthesis, which involved PPL, resulted in the product at least twice enriched by the desired isomer.

The important aspect of the implementation of such a product in field testing concerns its configurational stability. As mentioned above, chalcogran isomers epimerize easily at the spirocarbon C-5, while no configuration changes have been observed at C-2. The equilibrium mixture contains about 46% of (2S, 5R/S) isomers and 54% of the other pair[10]. Considering the analogous equilibration of our mixture of diastereoisomers the content of (2S, 5R)-*I* can decrease to about 41%, which still represents almost twofold enrichment over the racemic compound.

Availability of the partially optically active *I* allowed to record preliminary CD data of this interesting spirocyclic system involving acetal chromophore (for the data see Experimental). For the above diastereoisomeric mixture there is a positive circular dichroism at 183 – 195 nm. The data indicate that the observed band features the maximum at 186 nm, however, it is to be noted that reliability of this finding is limited as the measurement is taken very close to the instrument cut-off. For more accurate data it would be necessary to perform the experiment on a vacuum UV CD instrument and to use a sample having higher enantiomeric enrichment at the spirocarbon C-5, since it is the configuration at C-5 which largely determines the observed optical activity (cf. optical rotations of (2S, 5R)-*I* and (2S, 5S)-*I* in ref.[9]). But even for the present sample the observed CD is of considerable magnitude. Assignment of the above band to the particular electronic transition is based on the vacuum UV CD studies of oxirane chromophore by Gedanken[17] and Rodger[18]. The lowest absorption band of a single ether chromophore (at about 174 nm) is assigned therein to the electric dipole allowed Rydberg *n*(O)–3*s* transition (polarized perpendicularly to the C–O–C plane). Within the acetal group of *I* a pair of these transitions should exhibit distinct exciton splitting giving rise to a couplet of oppositely signed CD bands centered around 174 nm. Consequently, we can assign the observed positive CD band at 186 nm to the long wavelength branch of such a couplet. In principle, this situation is amenable to theoretical calculations of optical rotatory strengths, once the complete CD data are known. Thus, the chromophoric system of *I* seems to be a useful model which might contribute to understanding of the ether chromophore in general.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on FT-NMR spectrometer Varian XL-200 (at 200·01 and 50·31 MHz) in deuterochloroform using tetramethylsilane as an internal reference. The chemical shifts (δ, ppm) and coupling constants (J, Hz) were obtained by the analysis of the first order spectra. The IR spectra (ν, cm^{-1}) were measured on UR-20 spectrophotometer

(Zeiss, Jena) in tetrachloromethane. GLC analyses were performed on HP 5880A instrument equipped with a flame-ionization detector and a 25 m capillary column (internal diameter 0·3 mm, Hewlett–Packard HP5). HPLC analyses were carried out on HP 1090 instrument equipped with a diode array UV detector. The analyses were performed on two serially connected glass columns (3·3 × 150 mm, Tessek Prague) packed with Separon SGX straight phase (particle size 5 μm). Hexane with ether (1·25%) was used as mobile phawe; flow rate 0·5 ml/min. The resolution of peaks was as follows: $R_s = (1/4)(\alpha - 1)(N)^{1/2}(k/(1 + k))$, where α denotes selectivity, N is the number of theoretical plates and k is the average of capacity factors of the two peaks. Optical rotations were measured on Perkin–Elmer 141 polarimeter. CD Spectra were recorded on a Jobin Yvon Autodichrographe Mark V. The spectra were measured in cyclohexane (concentrations 10^{-3}—10^{-4} mol l^{-1}). The MTPA esters (3*R*)-*VII* and (3*S*)-*VII* were prepared according to Svatoš and coworkers[19].

1-(2-Furyl)-1-hydroxy-3-pentanone (*III*)

Under nitrogen at −78°C, 1·6M butyllithium in hexane (116 ml, 0·186 mol) was added to a solution of diisopropylamine (20·2 g, 0·2 mol) in tetrahydrofurane (THF, 900 ml). Within 5 min ethylmethylketone (12·3 g, 0·170 mol) in THF (90 ml) was added dropwise. After 50 min stirring 2-furaldehyde (*II*) (19·2 g, 0·2 mol) in THF (90 ml) was added. The mixture was stirred for 5 min at −78°C, then decomposed with 90 ml of saturated NH_4Cl solution and poured into 2 000 ml of ether. The ethereal layer was washed with 500 ml of saturated NaCl solution, dried with $MgSO_4$ and evaporated yielding 33·1 g of the crude product, which was purified by flash -chromatography on a silica gel (chloroform–3% ethanol). Yield 23·7 g (70%) of the pure compound. For $C_9H_{12}O_3$ (168·2) calculated: 64·29% C, 7·19% H; found: 64·31% C, 7·22% H. IR spectrum: 3 610, 3 480 (OH); 1 714 (C=O).

1-(2-Furyl)-1-penten-3-one (*IV*)

The aldol *III* (23·7 g, 0·141 mol) was added dropwise to 1% aqueous NaOH (320 ml) at 10°C. The mixture was stirred for 4 h, neutralized with diluted H_2SO_4, and extracted with ethyl acetate. The extract was washed with saturated NaCl solution, dried with $MgSO_4$ and evaporated yielding 20·0 g of the crude product. Purification by flash-chromatography (silica gel, light petroleum–10% ethyl acetate) afforded 14·8 g (70%) of *V*, purity 97% (GLC). For $C_9H_{10}O_2$ (150·2) calculated: 71·98% C, 6·71% H; found: 72·30% C, 6·72% H. IR spectrum: 1 693, 1 670, 1 617, 1 554.

1-(2-Furyl)-3-pentanone (*V*)

The ketone *IV* (41·5 g, 0·276 mol) was dissolved in ethanol (136 ml) and pH of the solution was adjusted to about 5 with acetic acid. Under vigorous shaking 2% sodium amalgam (8·07 g, 0·7 mol) was gradually added. After separation of mercury the mixture was partitioned between water and ether. The ethereal layer was dried with $MgSO_4$ and evaporated yielding 35·3 g of the crude product. Purification by flash chromatography afforded 23·0 g (55%) of pure *V*. For $C_9H_{12}O_2$ (152·2) calculated: 71·02% C, 7·94% H; found: 71·52% C, 7·63% H.

Racemic 1-(2-Furyl)-3-pentanol (*VI*)

The ketone *V* (4 g, 0·026 mol) was added to $NaBH_4$ (0·298 g, 0·008 mol) in aqueous tetrahydrofuran (9 : 1, 39 ml, alkalized by the addition of 1 ml of $Ba(OH)_2$) at 0°C. The mixture was stirred

overnight at room temperature, decomposed with diluted H_2SO_4, extracted with ether and dried with $MgSO_4$. Evaporation of the solvent afforded 3·6 g (90%) of the product having NMR and IR data identical to those of the optically active isomers of *VI* (see below).

Optically Active 1-(2-Furyl)-3-pentanol (*VI*)

Method A: Baker's yeast (400 g) was fermented in a solution of D-glucose (14 g) in water (500 ml) at 30°C. After 30 min 7·2 g of *IV* was added and the mixture was stirred for six days at room temperature. After first 24 h another 400 g of yeast fermented in the D-glucose–water system was added. The mixture was filtered through celite, the residue was washed several times with ethyl acetate and the filtrate was extracted with ethyl acetate. The combined extracts were washed with saturated NaCl solution, dried by $MgSO_4$ and evaporated yielding 8·6 g of the crude product. Purification by flash-chromatography (silica gel, light petroleum–30% ethyl acetate) yielded 3·4 g (47%) of (*R*)-(−)-*VI*, $[\alpha]_D^{25}$ −6·2° (*c* 0·2, hexane), e.e. 30%. For $C_9H_{14}O_2$ (154·2) calculated: 70·10% C, 9·15% H; found: 69·30% C, 8·91% H. IR spectrum: 3 630, 3 380 (OH); 1 598, 1 508 (C=C furan); 3 115 (=C—H furan).

Method B: Molecular sieves Nalsit 4A (1 g) were added to 2,2,2-trichloroethyl butyrate (21·6 g, 0·098 mol) in dry ether (150 ml). After 30 min stirring racemic alcohol *VI* (12·7 g, 0·082 mol) and PPL (15 g) was added. The mixture was stirred in dry atmosphere for 129 h at room temperature. The enzyme was filtered off and the filtrate partitioned between water and ether. The ethereal layer was washed with $NaHCO_3$, water and saturated NaCl solution. Evaporation yielded 31·0 g of the mixture of products, from which 4·2 g (34%) of (*S*)-(+)-*VI* ($[\alpha]_D^{25}$ +14·6° (*c* 1·4, hexane), e.e. 80%) was isolated by flash-chromatography (silica gel, pentane–10% ethyl acetate). CD spectrum: 215 nm ($\Delta\varepsilon$ +0·70). The less polar fraction (19 g) containing (*R*)-1-(2-furyl)-3-pentyl butyrate (*VIII*) and the excess trichloroethyl butyrate was added to a solution of KOH (13·0 g) in absolute ethanol (200 ml) and stirred for 12 h at room temperature. After evaporation the residue was partitioned between water and ether. The ethereal layer was dried with $MgSO_4$ and evaporated yielding 7·9 g (62%) of (*R*)-(−)-*VI*($[\alpha]_D^{25}$ −6·4° (*c* 1, hexane), e.e. 30%). The analogous hydrolysis of the butyrate isolated after 43 h of enzymatic reaction afforded (*R*)-*VI* ($[\alpha]_D^{25}$ −11·4° (*c* 1·3, hexane), e.e. 50%).

2-Ethyl-1,6-dioxaspiro[4.4]nonane (*I*)

(*S*)-(+)-*VI* e.e. 80%) (7·95 g, 0·052 mol) was dissolved in hexane (200 ml) and hydrogenated for 10 h at atmospheric pressure in the presence of 5% Pd/C (150 mg). After filtering off the catalyst the solvent was evaporated and the residue was purified by flash-chromatography (silica gel, light petroleum–10% ethyl acetate) yielding 6·06 g (75%) of *I*, chemical purity 99·6% (GLC), $[\alpha]_D^{25}$ −18·5° (*c* 1·2, hexane). Reference[9] reports $[\alpha]_D^{25}$ −100° (*c* 0·3, hexane) for (2*S*, 5*R*)-*I* and $[\alpha]_D^{25}$ +96° (*c* 1, hexane) for (2*S*, 5*S*)-*I*. For $C_9H_{16}O_2$ (156·2) calculated: 69·19% C, 10·32% H; found: 68·85% C, 9·95% H. IR spectrum: 1 017, 1 043 (C–O). ^1H and ^{13}C NMR spectra are identical to published data[13,12]. CD spectrum: 190 nm ($\Delta\varepsilon$ +0·35), 186 nm ($\Delta\varepsilon$ +0·75), 183 nm ($\Delta\varepsilon$ +0·70).

The authors are indebted to Dr S. Vašíčková for the measurement of IR *spectra, to K. Konečný for* GLC *analyses and to the Analytical Department of this Institute (Dr V. Pechanec, Head) for elemental analyses.*

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Translated by the author (P.M.).