Tetrahedron Vol. 43, No. 20, pp. 4635 to 4647, 1987
Printed in Great Britain

0040-4020/87 $3.00+.00
Pergamon Journals Ltd.

SYNTHESIS OF THE (4S,5R)-5-HYDROXY-DECAN-4-OLIDE (L-FACTOR) AND OF THE (R)-DECAN-4-OLIDE FROM A CHIRAL SULPHOXIDE

Pierfrancesco Bravo, Giuseppe Resnati, Florenza Viani, Alberto Arnone
CNR-Centro Studio Sostanze Organiche Naturali, Dipartimento di Chimica,
Politecnico, Piazza Leonardo da Vinci 32, I-20133 Milano, Italy.

Abstract - The condensation of optically pure (+)-R-n-hexyl 4-methylphenyl sulphoxide (2) on the succinic diester (8) produced the 4-oxo-5-sulphinyl decanoate 10 which was selectively reduced to the corresponding 4-hydroxy-5-sulphinyl decanoates 11. Starting from the (4S,5S,R_S) pure alcohol 11, a five-step sequence produced the (4S,5R)-5-hydroxy-decan-4-olide (17) (L-Factor) and a three-step sequence gave the (R)-decan-4-olide (22). In both cases final natural products were obtained in good overall yields and in optical pure form.

(*Received in UK* 31 *July* 1987)

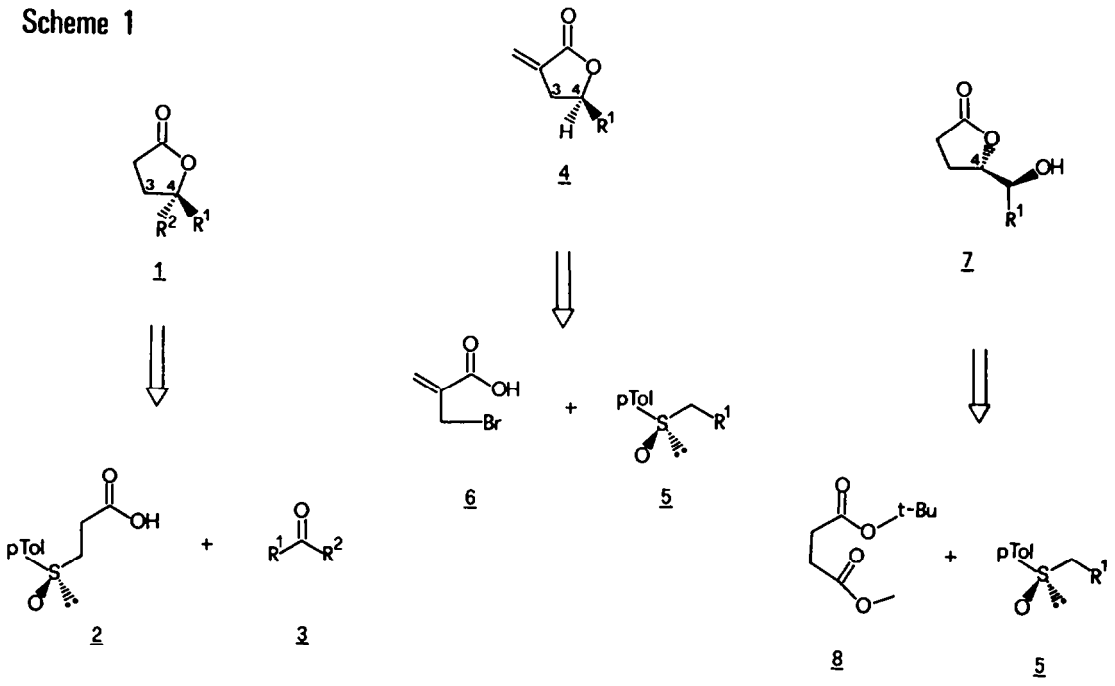
Structurally simple butanolides are widespread naturally occurring substances, they are often found in flavour, aroma components,[1] and in sex pheromones.[2] The biological activity of those products is strictly dipendent on the absolute configuration of the carbon atom on which the lactone is closed[3] and for that reason growing interest is being devoted to their asymmetric synthesis. Moreover, the 5-hydroxy-alkyl butanolides are usefull chiral building blocks[4] and particularly the (-)-(R)-4-hydroxymethyl butyrolactone has been extensively employed and various efficient protocols have been settled for introducing carbon chains and functional groups in its framework.[5]

Recently we also have been involved in the synthesis of enantiomerically pure γ-lactones by following the strategy of the chiral auxiliary group which, in our case, was the sulphinyl residue. γ-Lactones 1 have been obtained[6] through the condensation of the (+)-(R)-3-sulphinyl propionic acid (2) on carbonyl compounds 3 and α-methylene butyrolactones 4 were prepared[7] through the alkylation of the (+)-(R)-alkyl sulphoxides 5 with 2-(bromomethyl)acrylic acid (6) (Scheme 1). In both cases the four carbon backbone of the lactone ring was assembled by joining a three carbon unit with a one carbon fragment and the key step was the C_3 - C_4 bond forming reaction between two precursors having opposite donor and acceptor sites.[(a)]

Here we describe a new synthesis of naturally occurring δ-hydroxy butanolides of type 7. In this case the carbon backbone was assembled through a C - C bond formation between an α-sulphinyl carbanion and a carboxylic ester, and the two chiral carbon centers were obtained through the transfer of chirality from the enantiomerically pure sulphinyl group to the two contiguous carbon atoms. The same approach allowed to obtained also γ-lactone of type 1 by sacrifycing one of the two formed chiral centers. The (+)-(4S,5R)-4,5-dihydroxy decanoic acid γ-lactone, the so called "L-factor" which has been isolated from *Streptomices Griseus* cultures[9] and for which the autoregolatory activity for antracycline antibiotics biosynthesis has been initially claimed and afterwards discarded, and the (+)-(R)-4-hydroxy decanoic acid lactone, an allomone in the anal exudate of the thrips *Bagnalliella Yuccae*[10] have been synthetized in enantiomerically pure form.

(a) In the first case "d^3" and "a^1" synthons,[8] the homoenolate dianion from 2 and the carbonyl 3 were condensed, while in the second case an "a^3" and a "d^1" synthons, the electrophylic site β to the carboxylic acid and the anion α-to the sulphoxide respectively, were combined.

Scheme 1



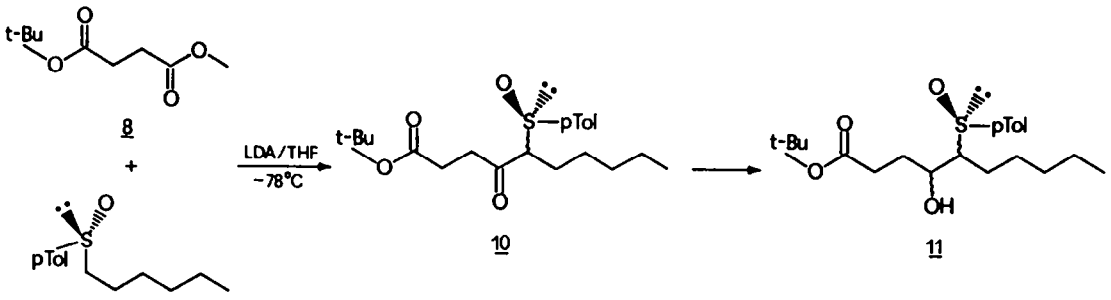
RESULTS AND DISCUSSION

Preparation of the Key Intermediates 11

(+)-R-n-Hexyl 4-methylphenyl suphoxide 9 was prepared in optically pure form by a modified Andersen procedure[11] from n-hexyl magnesium iodide and (-)-(1R,2S,5R)-menthyl (S)-4-methylphenylsulphinate. The lithium derivative of that sulphoxide, formed with lithium diisopropyl amide (LDA) in tetrahydrofuran (THF) solution, was reacted with t-butyl methyl succinate 8 to give, through a regioselective attack on the less hindered ester group, the (R_S)-t-butyl 4-oxo-5-(4-methylphenyl)sulphinyl decanoate (10) in 88 % chemical yields and as an about 6:4 mixture of the two diastereoisomers at the carbon atom. Although in other cases we succeded in isolating optically pure compounds from diastereoisomeric mixtures of α-substituted-β-keto sulphoxides,[12] no attempt was made in that case, and the two diastereoisomers were submitted to the reductive process as crude mixture obtained from the work up of the condensation.

The asymmetric reduction of the prochiral carbonyl group of keto-esters has been studied extensively because it is the key step for the facile synthesis of optically active lactones. On the other hand, while high and predictable diastereoselection can be obtained when reducing unsubstituted- or γ-substituted- β-keto sulphoxides,[13,14] lower diastereoselection, generally due to the chirality and to the chemical nature of the substituent, has been reported to occur in the reduction of α-substituted- β -keto sulphoxides.[15] In both cases the nature of the hydride species and of the solvent used as well as the presence of chelating metal salts do have a great influence on the diastereoselection of the process. The reduction of the carbonyl group of the β-keto sulphoxide 10 was therefore performed with different hydride species, in protic and aprotic medium and with or without chelating metals in order to force the reaction to proceed towards the desired diastereoisomer. A few results are summarized in Scheme 2. When di-isobutyl aluminium hydride (DIBAH) was employed in THF at -78° C both diastereoisomeric ketones were reduced with moderate to high diastereoselection (chemical yields 79 %, d.e. 40:1 for (5R,R_S)-10 in favour of the (4S,5R,R_S)-secondary alcohol 11 and 4:1 for (5S,R_S)-10 in favour of (4S,5S,R_S)-11). The preference for the entrance of the hydride from the re face of the carbonyl, accounting for the stereochemical results, is the one generally observed in the unchelated reduction of β-keto sulphoxides.[10,11] This preference is changed and lower diastereoselection is obtained, when the substrates were allowed to chelate with coordinating

Scheme 2



Medium	Diastereoselection			
	4S,5R,R_S	4R,5R,R_S	4S,5S,R_S	4R,5S,R_S
DIBAH/THF	40	1	48	11
DIBAH/$ZnCl_2$/THF	40	6	21	33
$NaBH_4$/NH_3(aq)/MeOH	2	11	37	50

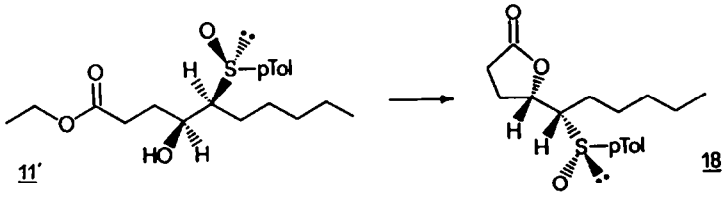
metals ($ZnCl_2$ or $CdCl_2$) at room temperature, and afterwards were reduced with DIBAH at -78° C (d.e. 1:1.6 for (5S,R_S)-10 and 7:1 for (5R,R_S)-10). By employing sodium borohydride in methanol in the presence of aqueous ammonia the prevailing products (87 % of the mixture) have now the same (S) absolute configuration at the sulphinyl substituted carbon and opposite configuration at the carbon of the secondary alcohol. That implies that under the basic and protic conditions used, the two (5S,R_S)-10 and (5R,R_S)-10 isomeric ketones do equilibrate very rapidly[10] and that the former stereoisomer is reduced at a much faster rate then the latter one, but the hydride transfer occurs now at both faces of the ketone with comparable rates.

Anyway, since all obtained compounds posses the optically pure auxiliary sulphinyl group, they can be easily isolated from the crude mixture in pure form by flash chromatography and crystallization. All the four diastereoisomeric t-butyl 4-hydroxy-5-(4-methylphenyl) sulphinyl decanoates (11) were in fact obtained in pure form so that all four possible diastereoisomeric-δ-hydroxy- γ-lactones should be accesible.

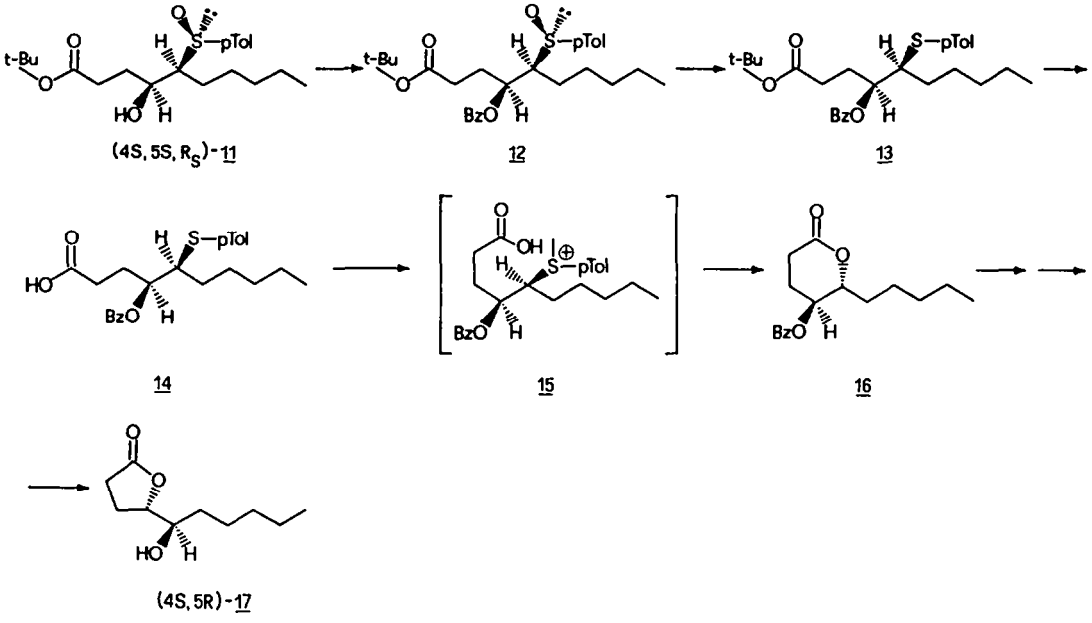
Synthesis of the so called "L-Factors" 17

(4S,5S,R_S)-t-Butyl 4-hydroxy-5-(4-methylphenyl)sulphinyl decanoate (11), obtained as a crystalline compound in 38 % yields by reducing the β-keto sulphoxides 10 with DIBAH in THF, was treated with benzyl bromide in dimethylformamide (DMF) in the presence of sodium hydride and the benzyl-protected hydroxy sulphoxide 12 was isolated in 85 % yields (Scheme 3).

In same preliminary experiments, the diethyl succinate (8') was employed as starting material instead of the mixed ester (8). Condensation with the sulphoxide 9 followed by reduction with DIBAH produced 4-hydroxy-5-sulphinyl decanoic acids ethyl esters (11'). However, when the benzylation of the hydroxyl group of these ethyl esters (11') was attempted, an intramolecular transesterification by action of the secondary alcohol on the ethyl ester prevailed and brought exclusively to the 4-hydroxy-5-(4-methylphenyl)sulphinyl-decan-4-olide (18) (see Experimental). Deoxygenation of the sulphoxide group of 12 by sodium iodide and trifluoroacetic anhydride[16] in acetone at -40° C gave the (4S,5S)-t-buthyl 4-benzyloxy-5-(4-methylphenyl)thio decanoate (13) in



Scheme 3

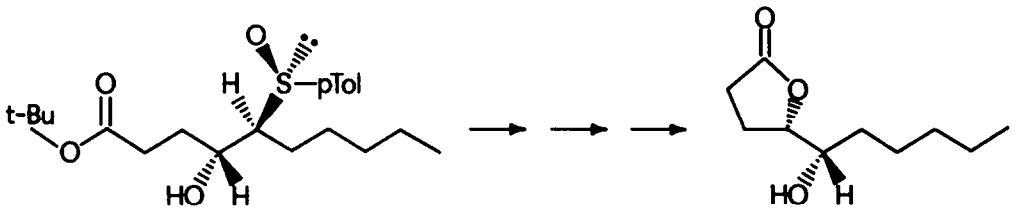


71 % overall yields from 11.[b] The corresponding (4S,5S)-4-benzyloxy-5-(4-methylphenyl)thio decanoic acids 14 formed in 89 % yields by heating the t-butyl ester 13 in acetic acid/ water/ dioxane solution.[c] Finally, the (4S,5R)-4-benzyloxy-5-hydroxy-decanoic acid lactone (16) was obtained in 84 % yield through a two steps sequence. The tolylthio group of (4S,5S)-14 was methylated regioselectively with trimethyloxonium tetrafluoroborate in dichloromethane/nitromethane at room temperature. The solvent was eliminated under vacuum and substituted by anhydrous dimethylformamide; afterwards the carboxylate anion was generated by adding potassium t-butoxide at low temperature (-40° C). A clean intramolecular attack of the carboxylate anion on the sulphonium group occurred and a single diastereoisomerically pure δ-lactone, the (4S,5R)-4-benzyloxy-5-hydroxy-decanoic acid lactone (16) formed through an S_N2 mechanism. Complete maintenance of the chirality at the carbon center (by invertion) has already been observed in the formation of γ-lactones.[7] The invertion of chirality is assumed to take place similarly to what has been already proved in intermolecular reactions for sulphur and nitrogen nucleophiles and commonly accepted for oxygen nucleophyles in intramolecular processes. That δ-lactone 16 has been already prepared from 3,4,6-tri-O-acetyl-D-glucal and transformed into the corresponding (4S,5R)-γ-lactone 17, the naturally occurring "L factor", in 93 % yields, through nickel-Raney promoted debenzylation followed by a spontaneous ring restriction.[19]

The synthetic sequence above described and reported on Scheme 3 was repeated by using as starting material the (4R,5S,R$_S$)-t-butyl 4-hydroxy-5-(4-methylphenyl)sulphinyl decanoate 11.

[b] The same (4S,5S)-13 was obtained, although in lower chemical yields, also by inverting the order of these two reactions. On deoxygenating the free 4-hydroxy-t-butyl ester 11, the (4S,5S)-t-butyl 4-hydroxy-5-(4-methylphenyl) thio decanoate (19) formed in 70 % yields and benzylation of the crude product under standard conditions gave 13 in 26 % overall yields. This route didn' t work well also when the 4-hydroxy-5-sulphinyl decanoic acids ethyl esters (11') were employed (see Experimental).

[c] When trifluoroacetic acid under several reaction conditions was employed, only the (4S,5S)-5-(4-methylphenyl)thio decan-4-olide (21) was isolated.



(4R,5S,R_S)-11 (4R,5R)-17

obtained in 34 % yields from 4-oxo-5-sulphinyl decanoates 10 by $NaBH_4$ reduction in methanol and aqueous ammonia. The diastereoisomeric (+)-(4R,5R)-4-benzyloxy-decan-5-olide (16), which upon treatment with nickel-Raney should give the (4R,5R)-L-factor-17, was obtained in 52 % overall yields.

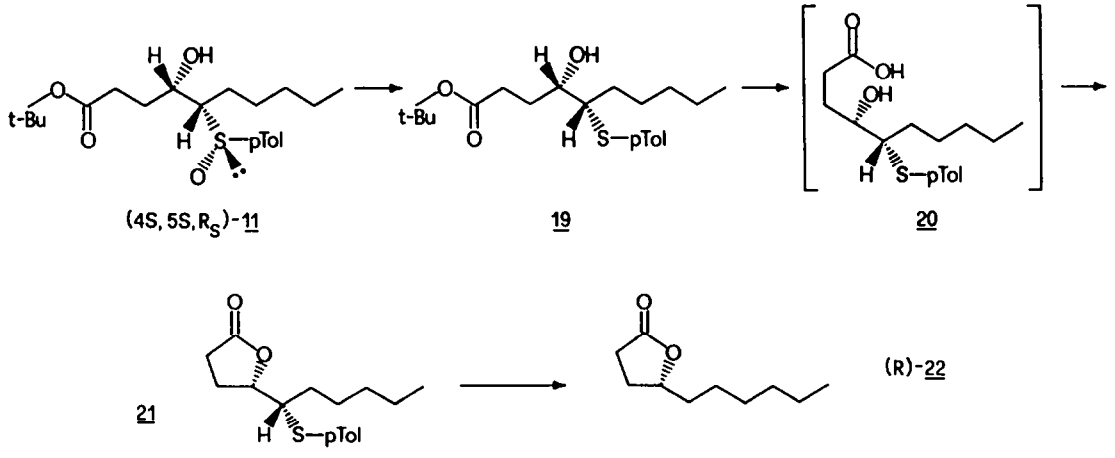
The (4R,5S)-L-factor and its (4S,5S) epimer, the two remaining diastereoisomers of this natural product, could be obtained from the (4R,5R,R_S)-hydroxy-sulphinyl decanoate 12 and from the (4S,5R,R_S)-isomer respectively, by applying the sequence of reactions reported in the Scheme 3. Similarly, the synthetic approach described by Mori,[20] which emploies the Sharpless epoxidation as a key step, allowed to obtain all the four diastereoisomers of L-factor, while the synthesis of Pougny[19] and that of Wightman,[21] which start from carbohydrate precursors, allowed to obtain only two isomers of this natural 5-hydroxy-butanolide. The overall chemical yields of the latter of these approaches starting from the chiral pool are however the highest.

Synthesis of γ-Decanolactone 22

The deoxygenation of the sulphinyl residue and the hydrolysis of the t-butyl ester moiety were accomplished in sequence starting from the (4S,5S,R_S)-t-butyl 4-hydroxy-5-(4-methylphenyl)sulphinyl-t-butyl decanoate 11 in the same conditions already described for synthesizing the "L-factor" from the benzyloxy t-butyl decanoates 12. The 4-hydroxy-5-(4-methylphenyl)thio decanoic acid 20 thus obtained spontaneously cyclized, already in the reaction medium, to the corresponding 4-hydroxy-5-(4-methylphenyl)thio decan-4-olide (21) (Scheme 4). Desulphurization with nickel-Raney in aqueous ethanol afforded the (+)-(R)-4-decanolactone (22), which was obtained in 38 % isolated global yields from 11.

The enantiomeric (-)-(S)-4-decanolactone 22 was obtained in comparable overall yields when the same three step procedure was applied on the diastereoisomer (4R,5S,R_S)-11. As the two t-butyl 4-hydroxy-5-sulphinyl decanoates 11 having the (4S) absolute configuration were isolated in 70 % yields when the epimeric mixture of t-butyl 4-oxo-5-sulphinyl decanoates 10 was reduced with DIBAH in THF, the sequence of reactions reported in Schemes 2 and 4 should give the

Scheme 4



(4S,5S,R_S)-11 19 20

(+)-(R)-allomone 22 in approximate 35 % overall yields starting from the simple (+)-(R)-n-hexyl sulphoxide 9.

The (R) absolute configuration was assigned to the dextrorotatory decan-4-olide (22) from the optical rotations of a great deal of similar butanolides.[6,22] Furthermore, a detailed analyses of ^{1}H and ^{13}C NMR spectra of diastereoisomeric decan-5-olides 16 allowed to establish the relative stereochemistries at the two chiral carbon atoms. The chemical correlations described above permitted thus to assign the absolute configurations at C-4 and at C-5 to the four diastereoisomeric 4-hydroxy-5-sulphinyl decanoates 11 and to all their transformation products 12-21. Eventually, these assignments were in agreement with the synthesis of (4S,5R)-decan-5-olide 16 realized starting from the chiral pool.[19]

Configuration and Conformation of (4R,5R)- δ -lactone 16 and of its (4S,5R) diastereoisomer.

The ^{1}H NMR spectra of (4R,5R)- δ -lactone 16 (cis isomer) and of (4S,5R)-16 (trans isomer) in $CDCl_3$ were similar (Table 1). For the δ-lactone protons each epimer exibited an ABMNXY pattern. The AB portion was assigned to H_2-2 since they presented a geminal coupling of 17.9 and 17.2 Hz,[23] the MN portion to H_3-2 (^{2}J = 14.3 and 14.0 Hz) and the XY portion to H-4 and H-5 ($^{3}J_{4,5}$ = 2.2 and 5.6 Hz), since they were vicinally coupled to H_2-3 and H_2-6, respectively. The ^{13}C NMR data (Table 1) were also in agreement with the proposed structures. In particular the presence of a δ-lactone ring was inferred from the chemical shift values of the C-1 carbonyl carbon atom (170.95 and 171.50).[23] The spectroscopic problem which faced us was to distinguish between the cis-trans epimers which is not easy in view of the conformation lability of the δ-lactone system. Indeed, this ring is reported[24] to exist in solution either in a half-chair or in a boat conformation or in a rapidly equilibrating mixture of the two, the planarity of the C-O-C(=O)C part of the ring being explained by resonance.[25] Thus in order to substantiate the deduction made from coupling costant analysis (see later), NOE difference experiments were performed in $CDCl_3$ and in acetone-d_6, since these usually provide unabiguous configurational information (Table 2). For the (4S,5R)-16-trans isomer irradiation of H-5, assumed as β, enhanced, among others, H-2 (2 %) and H-3 (0.5 %), irradiation of H-4 enhanced H-2 (0.5 %) and irradiation of H_2-6 enhanced H-3 (0.5 %). These results not only permitted to distinguish between the geminal C-2 and C-3 protons but also indicate that H-4 and H-5 are trans disposed. For the (4R,5R)-16-cis isomer irradiation of H-5 enhanced, among others, H-2 (0.5 %) and H-3 (3.5 %) while irradiation of 4-OCH_2 protons enhanced H-3 (1 %). H-5 and 4-OCH_2 protons are therefore trans disposed and, as a consequence, H-4 and H-5 are cis orientated. There has been considerable interest in the conformational properties of valerolactone derivatives since it

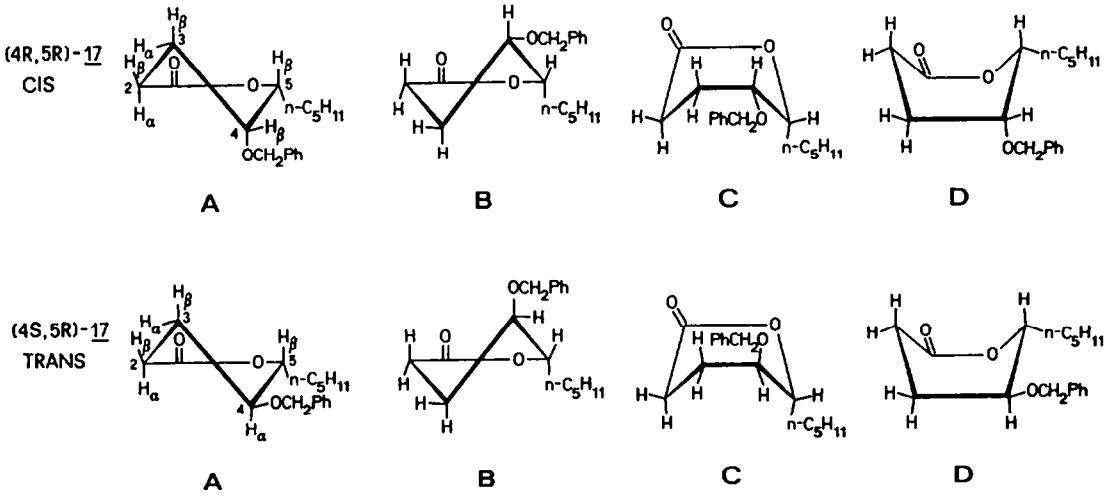


Table 1.- ^{1}H and ^{13}C NMR Chemical shifts (δ/ppm) and coupling constants for compounds (4R,5R)-16 (cis isomer) and of (4S,5R)-16 (trans isomer).

Carbon atom	(4R,5R)-16 (cis)	(4S,5R)-16 (trans)	Proton	(4R,5R)-16 (cis)	(4S,5R)-16 (trans)	J(Hz)	(4R,5R)-16 (cis)	(4S,5R)-16 (trans)
1	170.95 s	171.60 s	2α	2.67(2.51)[a]	2.48(2.41)[a]	2α,2β	17.9(17.7)[a]	17.2(17.4)[a]
2	25.45 t	26.57 t	2β	2.52(2.46)	2.73(2.65)	2α,3α	7.2(7.0)	5.6(6.2)
3	23.20 t	23.07 t	3α	2.23(2.27)	2.05(2.13)	2α,3β	11.0(10.0)	5.2(5.0)
4	70.01 d	73.27 d	3β	1.89(2.06)	2.00(2.04)	2α,4	~0(~0)	0.4(0.4)
5	82.86 d	81.61 d	4	3.68(3.82)	3.55(3.67)	2β,3α	3.5(4.4)	9.4(9.7)
6	31.25 t	33.42 t	5β	4.23(4.35)	4.31(4.32)	2β,3β	7.2(7.7)	7.7(7.2)
7	24.83 t	24.61 t	OCHa-4	4.67(4.72)	4.63(4.69)	2β,4	0.6(0.4)	0.4(0.4)
8	31.63 t	31.59 t	OCHb-4	4.45(4.49)	4.53(4.57)	3α,3β	14.3(14.3)	14.0(14.0)
9	22.54 t	22.53 t	H-6a	1.85(1.76)	1.69(1.72)	3α,4	4.1(3.8)	4.8(4.5)
10	14.02 q	14.01 q	H-6b	1.70(1.72)	1.64(1.61)	3β,4	2.9(3.3)	5.2(5.3)
4-OCH_2	70.63 t	70.90 t	H_2-7	1.4(1.4)	1.5(1.5)	3β,5	~0(~0)	0.6(0.7)
Ph	137.63 s	137.56 s	H_2-8	1.3(1.3)	1.3(1.3)	4,5β	2.2(2.0)	5.6(5.5)
	128.50 d	128.57 d	H_2-9	1.3(1.3)	1.3(1.3)	5,6a	7.8(8.1)	4.4(4.3)
	127.96 d	128.03 d	H_3-10	0.88(0.88)	0.89(0.88)	5,6b	5.9(6.1)	7.9(8.4)
	127.75 d	127.78 d	Ph	7.2-7.4(7.2-7.4)	7.3-7.4(7.3-7.5)	6a,6b	13.6 N.a.	13.6 N.a.

[a] Values in parentheses are chemical shifts and J in acetone-d6 N.a.=Not assigned.

is believed that the biological activity of these compounds is related to the conformation of the lactone ring.[26] In our case, the epimeric δ-lactones 16-cis and 16-trans can each assume the half-chair (A and B) and the boat (C and D) conformations illustrated in the Fig. or possibly an equilibrium mixture of the four. Since no NOE was observed in both compounds between C-2 and C-6 protons, the boat conformer C, which presents steric interactions between the axial bowsprit H_2-6 and the flagpole H-2 α, is highly improbable and this conformer will not be considered further. In the 16-cis δ-lactone the observed $^{3}J_{2,3}$ (11.0 Hz) and $^{3}J_{2,3}$ (3.5 Hz) strongly suggested an approximately staggered arrangement around the C(2)-C(3) bond, while the $^{3}J_{3\alpha,4\beta}$ (4.1 Hz) and $^{3}J_{3\beta,4\beta}$ (2.9 Hz) indicated that the C(4)-H bond bisects the C-3 methylene system. This situation can be accomodated in the half-chair A, the NOE between the 1,3-cis diaxially disposed H-3β, H-5β (3.5 %) being in agreement with this assignment. Moreover the smaller value observed between the W-type equatorially disposed H-2β, H-4β (^{4}J = 0.6 Hz) with respect to reference data[23,27] (^{4}J = 1.5-2.5 Hz) suggested a deformation of the W-system which can be explained if the δ-lactone ring adopts a flattened half-chair conformation in which C(3) becomes closer to the plane of the lactone group. The lack of NOE between H-3α and H_2-6 and the small NOE between H-2β and H-5β (0.5 %) confirmed that conformers B and D have little weight, if any. The 16-trans isomer exhibited coupling constants for the trans disposed C-2 and C-3 protons which are intermediate with respect to those observed for the 16-cis epimer, thus indicating a less conformational homogenity. Although an evaluation of the relative popolation of each conformer would require a knowledge of the coupling constants of the individual conformers, a qualitative description of the conformational state of this compounds can be given if we select the values of 11-13 and 1-3 Hz to represent the limiting trans diaxial and trans diequatorial constants.[23,26-28] Thus the values of 9.4 and 5.2 Hz observed for H-2β, H-3α and H-2α, H-3β indicate that these protons are mainly trans diaxially and trans diequatorially disposed as in conformers B and D while the value of 5.6 Hz for H-4α, H-5β suggests that conformer B, in which these protons are trans diequatorially orientated, is slightly preferred. Additional evidence for the proposed assignment of the relative configuration and prefered conformation of cis and trans δ-lactone 16 followed from NOE experiments performed on a 1:1 mixture of the two epimers. In fact the NOE observed between H-4 β,H-5β in the (4R,5R)-cis-δ-lactone 16 was three times greater than that observed between the corresponding H-4α, H-5β protons (4S,5R)-trans-δ-lactone 16 this fact confirming that in the cis compound these protons are spatially much closer than in the trans one.

Experimental

I.R. spectra were taken on a Perkin-Elmer 137 Infracord Spectrophotometer, ^1H and ^{13}C N.M.R. spectra on a Bruker CPX-300 spectrometer using tetramethylsilane as internal standard. NOE difference spectra were obtained by subtracting alternatively right-off resonance-free induction decays (f.i.d.s.) from right-on resonance-induced f.i.d.s. NOE values reported in the test have only qualitative significance. $|\alpha|_D^{20}$ values were obtained on a Jasco DIP-181 polarimeter. M.p.s are uncorrected and were obtained on a capillary apparatus; t.l.c. were run on silica gel 60 F_{254} Merck precoated plates. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from lithium aluminium hydride, and di-isopropylamine was distilled from calcium hydride and stored over molecular sieves (4 A). Dimethylformamide was stored over molecular sieves (4 A and 13 A). In all other cases commercially available reagent grade solvents were employed without further purification. A 2.6 M solution of n-butyllithium in hexanes (Aldrich) and a 1.0 M solution of DIBAH in n-hexane (Fluka) were employed; trimethyloxonium fluoborate and menthyl sulphinate (Fluka) were used as received.

t-Butyl methyl succinate (8)

In the teflon vessel of an autoclave (Berghof, PTFE 250 ml) liquid isobutylene (2-methyl-propene), cooled at -70° C (30 ml, 0.35 mol) was added under an argon atmosphere to a solution of mono methyl succinate (25 g, 0.189 mol), then conc. sulphuric acid (5 ml) in THF (85 ml) was dropped. The mixture was stirred for 5 min. at -20° C, then allowed to reach room temperature under stirring overnight. The reaction was poured in a saturated aqueous solution of $NaHCO_3/Na_2CO_3$ (250 ml) and extracted with ether (3 x 100 ml). The organic layers were dried over anhydrous sodium sulphate and the solvent was evaporated under reduced pressure to give 9.42 g (26.5 % yield of pure t-butyl methyl succinate (8) as a yellow oil.

(+)-(R)-n-hexyl-p-tolyl-sulphoxide (9)

A solution of n-hexyl-iodide (44.3 ml, 0.3 mol) in anhydrous ether (100 ml) was added dropwise to a stirred suspension of Mg, activated by adding a crystal of iodine (7.3 g, 0.3 mol) in the same solvent (50 ml). The solution was stirred for two additional hours, the ether was removed under reduced pressure and benzene (600 ml) was added.
The benzene solution of the Grignard reagent was cooled to 5-10° C and a solution of (-)-(1R,2S,5R)-menthyl(S)-p-toluene-sulphinate (50 g, 0.15 mmol) was added dropwise at that temperature. The mixture was stirred at room temperature for additional 30 min., a saturated aqueous solution of ammonium chloride (200 ml) was added while cooling with an ice-water bath and the pH of the mixture was adjusted to 3 by adding 10 N hydrochloric acid. The mixture was extracted with ether (3 x 300 ml); the combined organic layers were washed with a diluted solution of $NaHCO_3$ (2 x 50 ml), with water (50 ml) and dried over anhydrous sodium sulphate. Solvent removal under reduced pressure gave a residue which, upon flash chromatography on silica gel (eluent: n-hexane/ethyl acetate 60:40), gave 23.5 g (70 % yield) of pure (+)-(R)-n-hexyl p-tolyl sulphoxide (9) as a yellowish oil ^1H NMR ($CDCl_3$), δ:0.89 (3H, t, J 6.9 Hz, H_3-6), 1.2-1.7 (8H, m, H_2-2,-3,-4,-5), 2.45 (3H, br s, Me arom.), 2.77 (2H, m, $H_2$1), 7.32 and 7.52 (4H, m, Ph); $|\alpha|_D^{20}$ +175° (c = 1.0 in $CHCl_3$).

Condensation of (+)-(R)-n-hexyl-p-tolyl-sulphoxide (9) on methyl t-butyl succinate (8)

A solution of LDA (prepared from di-isopropylamine (7.5 ml, 53 mmol) and n-butyllithium (21 ml, 53 mmol)) in THF (52 ml) was cooled under Argon at -78° C and treated dropwise with a solution of (+)-(R)-9 (10 g, 48 mmol) in THF (26 ml). Methyl t-butyl succinate (8) (9.94 g, 53 mmol) was added at the same temperature to the yellow solution of the so formed α-sulphinyl anion. After the mixture had been stirred for 10 min. at -78° C, saturated aqueous solution of ammonium chloride was added (80 ml). The reaction mixture was extracted with ethyl acetate (3 x 200 ml), the collected organic layers were dried over anhydrous sodium sulphate, and the solvent was evaporated under reduced pressure. The residue was flash chromatographed (ethyl acetate/n-hexane 16:40) on silica gel to give 16.05 g (88 % yield) of a mixture (approximate ratio 55/45) of the two epimers at C(5) of t-butyl 5-(4-methylphenyl)sulphinyl-4-oxo-decanoate (10) as a yellowish oil. (Found C 65.8, H 8.7, $C_{21}H_{32}O_4S$ requires C 66.3, H 8.4); νmax (film) 2930, 1710, 1730, 1050 cm^{-1}; ^1H NMR ($CDCl_3$), δ :0.85 (3H, t, J 6.8 Hz, H_3-10), 1.0-2.0 (8H, m, H_2-6,-7,-8,-9), 1.41 and 1.42 (9H, s, t-Bu), 2.2-2.9 (4H, m, H_2-2 and -3), 2.41 (3H, br s, Me arom.), 3.62 and 3.77 (1H, m, H-5), 7.3-7.5 (4H, m, Ph).

Condensation of racemic n-hexyl p-tolyl sulphoxide (9) on diethyl succinate (8')

The reaction was realized as described above for methyl t-butyl succinate and after the same work up and flash chromatography (toluene/ethyl acetate 2:1) the ethyl 5-(4-methylphenyl)sulphinyl-4-oxo decanoate 10' was isolated in 90 % yield as an oil and as a mixture of the two epimers at the carbon atom. ^1H NMR ($CDCl_3$), δ :0.88 (3H, t, J 6.8 Hz, H_3-10), 1.0-2.0 (8H, m, H_2-6,-7,-8,-9), 1.23 (3H, t, J 7.0 Hz, CH_3CH_2), 2.1-2.9 (4H, m, H_2-2 and -3), 2.45 (3H, br s, Me arom.), 3.65 and 3.68 (1H, m, H-5), 4.10 and 4.12 (2H, q, J 7.0 Hz, OCH_2), 7.2-7.6 (4H, m, Ph).

Reduction of t-butyl 4-oxo-5-sulphinyl decanoate 10 (mixture of epimers) with DIBAH

A solution of the 4-oxo-5-sulphinyl decanoate 10 (mixture of the two epimers at C(5)) (5g, 13.2 mmol) in THF (40 ml) was cooled, under Argon, at -78° C and a solution of DIBAH in n-hexane (19.7 ml, 19.7 mmol) was added dropwise. After the mixture had been stirred for 5 min. at the

same temperature, a saturated aqueous solution of ammonium chloride was added (100 ml), then the pH was adjusted to 7 with a diluted solution of hydrochloric acid. The reaction mixture was extracted with ethyl acetate (3 x 300 ml), the collected organic phases were dried over anhydrous sodium sulphate, and the solvent was evaporated under reduced pressure. Flash chromatography of the residue on silica gel (eluent: n-hexane/ethyl acetate 7:3) allowed to obtain in 79 % overall yield the four diastereoisomers of t-butyl 4-hydroxy-5-(4-methylphenyl)sulphinyl decanoate (11) as single pure compounds. (+)-(4S,5R,R_S)-11: 32 % yield; m.p. 70-71° C (from di-isopropyl ether); (Found C 66.1, H 8.7, $C_{21}H_{34}O_4S$ requires C 65.9, H 8.9); R_f 0.36 (n-hexane/ethyl acetate 7:3); $[\alpha]_D^{20}$ +160° (c 0.70 in $CHCl_3$); νmax (nujol) 3280, 1730, 1010, 990 cm^{-1}; ^1H NMR ($CDCl_3$), δ:0.90 (3H, t, J 7.0 Hz, H_3-10), 1.0-1.8 (6H, m, H_2-7, -8, -9), 1.36 (9H, s, t-Bu), 1.45 and 1.83 (2H, m, H_2-3), 1.87 and 1.99 (2H, m, H_2-6), 2.17 and 2.32 (2H, m, H_2-2), 2.30 (1H, ddd, J 9.3, 4.5 and 1.5 Hz, H-5), 2.43 (3H, br s, Me arom.), 4.03 (1H, dddd, J 9.8, 3.6, 3.0 and 1.5 Hz, H-4), 4.16 (1H, dd, J 3.0 and 1.2 Hz, OH-4), 7.36 and 7.49 (4H, m, Ph); ^{13}C NMR ($CDCl_3$), δ:13.99 (q), 21.42 (q), 22.43 (t), 23.50 (t), 27.40 (t), 28.01 (q), 29.71 (t), 31.60 (t), 31.79 (t), 67.24 (d), 69.34 (d), 80.25 (s), 124.63 (d), 130.00 (d), 138.17 (s), 141.67 (s), 172.62 (s). (+)-(4R,5R,R_S)-11: 0.7 % yield; m.p. 68-69° C (from n-pentane); (Found C 65.3, H 8.6, $C_{21}H_{34}O_4S$ requires C 65.9, H 8.9); R_f 0.32 (n-hexane/ethyl acetate 7:3) $[\alpha]_D^{20}$ +159° (c 0.9 in $CHCl_3$) ν max (nujol) 3270, 1725, 990 cm^{-1}; ^1H NMR ($CDCl_3$), δ:0.83 (3H, t, J 6.9 Hz, H_3-10), 1.0-1.8 (8H, m, H_2-6, -7, -8, -9), 1.44 (9H, s, t-Bu), 1.80 and 1.95 (2H, m, H_2-3), 2.41 and 2.43 (2H, m, H_2-2), 2.42 (3H, br s, Me arom.), 2.76 (1H, ddd, J 7.8, 5.2 and 5.0 Hz, H-5), 4.12 (1H, dddd, J 10.0, 7.8, 3.1 and 2.7 Hz, H-4), 4.70 (1H, dd, J 3.1 and 1.1 Hz, OH-4), 7.33 and 7.59 (4H, m, Ph). (+)-(4R,5S,R_S)-11: 8.9 % yield; m.p. 88-89° C (from di-isopropyl ether); (Found C 65.1, H 9.1, $C_{21}H_{34}O_4S$ requires C 65.9, H 8.9); R_f 0.31 (n-hexane/ethyl acetate 7:3); $[\alpha]_D^{20}$ +93° (c 0.50 in $CHCl_3$), ν max (nujol) 3360, 1730, 1020, 1010 cm^{-1}; ^1H NMR ($CDCl_3$), δ:0.74 (3H, t, J 6.9 Hz, H_3-10), 0.9-1.7 (8H, m, H_2-6, -7, -8, -9), 1.46 (9H, s, t-Bu), 1.85 and 1.96 (2H, m, H_2-3), 2.41 (3H, br s, Me arom.), 2.45 (2H, m, H_2-2), 2.51 (1H, ddd, J 6.5, 5.5 and 2.5 Hz, H-5), 3.25 (1H, dd, J 3.3 and 0.8 Hz, OH-4), 4.27 (1H, dddd, J 9.5, 3.3, 3.2 and 2.5 Hz, H-4), 7.33 and 7.47 (4H, m, Ph). (+)-(4S,5S,R_S)-11: 38 % yield, m.p. 98-99° C (from di-isopropyl ether); (Found C 65.8, H 9.2, $C_{21}H_{34}O_4S$ requires C 65.9, H 8.9); R_f 0.26 (n-hexane/ethyl acetate); $[\alpha]_D^{20}$ +110° (c 0.55 in $CHCl_3$); ν max (nujol) 3400, 1720, 1030, 1015 cm^{-1}; ^1H NMR ($CDCl_3$), δ:0.80 (3H, t, J 6.9 Hz, H_3-10), 1.0-1.7 (8H, m, H_2-6, -7, -8, -9), 1.44 (9H, s, t-Bu), 1.94 and 1.98 (2H, m, H_2-3), 2.43 (3H, br s, Me arom.), 2.44 and 2.49 (2H, m, H_2-2), 2.65 (1H, ddd, J 7.0, 6.4 and 5.7 Hz, H-5), 3.94 (1H, dddd, J 8.3, 6.4, 5.0 and 4.2 Hz, H-4), 4.21 (1H, dd, J 5.0 and 0.5 Hz, OH-4), 7.34 and 7.47 (4H, m, Ph).

Reduction of ethyl 4-oxo-5-sulphinyl decanoate (10') (mixture of epimers) with DIBAH.

The reaction was realized as described above for the t-butyl ester 10 and after a similar work up and flash chromatography (n-hexane/ethyl ether 1:2) the ethyl 4-hydroxy-5-(4-methylphenyl) sulphinyl decanoates 11' were isolated in 82 % global yield. The ratio of the diastereoisomers was nearly the same reported above. The reported relative stereochemistries were assigned by comparing physical and spectral properties of ethyl esters 11' with those of t-butyl esters 11.(4S*, 5R* , R_S*)-ethyl 4-hydroxy-5-(4-methylphenyl)sulphinyl decanoate: R_f 0.38; ^1H NMR ($CDCl_3$), δ:0.95 (3H, t, J 7.0 Hz, H_3-10), 1.0-2.1 (10H, m, H_2-3,-6,-7,-8,-9), 1.23 (3H, t, J 7.0 Hz, CH_3-CH_2), 2.2-2.5 (3H, m, H_2-2 and H-5), 2.46 (3H, br s, Me arom.), 4.03 (2H, q, J 7.0 Hz, OCH_2), 4.07 (1H, m, H-4), 4.10 (1H, br, OH-4), 7.36 and 7.51 (4H, m, Ph). (4R*, 5S*, R_S*)-ethyl 4-hydroxy-5-(4-methylphenyl)sulphinyl decanoate: R_f 0.31; ^{1}NMR ($CDCl_3$), δ:0.70 (3H, t, J 6.9 Hz, H_3-10), 0.9-2.1 (10H, m, H_2-3,-6,-7,-8,-9), 1.27 (3H, t, J 7.0 Hz, CH_3-CH_2), 2.43 (3H, br s, Me arom.), 2.4-2.7 (3H, m, H_2-2 and H-5), 3.35 (1H, br, OH-4), 4.13 (2H, q, J 7.0 Hz, OCH_2), 4.27 (1H, m, H-4), 7.31 and 7.50 (4H, m, Ph). (4S*, 5S*, R_S*)-ethyl 4-hydroxy-5-(4-methylphenyl)sulphinyl decanoate: R_f 0.23; ^1H NMR ($CDCl_3$), δ:0.76 (3H, t, J 6.9, H_3-10), 1.0-2.1 (10H, m, H_2-3,-6,-7,-8,-9), 1.25 (3H, t, J 7.0 Hz, CH_3-CH_2), 2.44 (3H, br s, Me arom.), 2.4-2.8 (3H, m, H_2-2 and H-5), 4.00 (1H, m, H-4), 4.10 (1H, br, OH-4), 4.20 (2H, q, J 7.0 Hz, OCH_2), 7.33 and 7.48 (4H, m, Ph).

Reduction of t-butyl 4-oxo-5-sulphinyl decanoate 10 (mixture of epimers) with DIBAH in the presence of $CdCl_2$ or $ZnCl_2$

To a solution of 10 (5.0 g, 13.2 mmol) in THF (40 ml) at room temperature and under Argon atmosphere powdered $CdCl_2$ (dried on $CaCl_2$) (2.42 g, 13.2 mmol), was added and after stirring for 30 min., the suspension was cooled at -78° C and a solution of DIBAH (19.7 ml, 19.7 mmol) was dropped. After the described above work up, the residue (3.50 g) was flash chromatographed on silica gel to give the four diastereoisomeric 4-hydroxy-5-sulphinyl decanoates 11 in pure form and in 50 % overall yield. (+)-(4S,5R,R_S)-11: 20 % yield; (+)-(4R,5R,R_S)-11: 3 % yield; (+)-(4R,5S,R_S)-11: 16.5 % yield; (+)-(4S,5S,R_S)-11: 10.5 % yield.

Reduction of t-butyl 4-oxo-5-sulphinyl decanoate 10 (mixture of epimers) with $NaBH_4$

A solution of $NaBH_4$ (800 mg, 21.1 mmol) in CH_3OH/NH_3 aq (30 % solution) 9:1 (50 ml) was added dropwise at room temperature to a solution of the sulphinyl ketone 10 (7.0 g, 19.2 mmol) in $CH_3OH/$ NH_3 aq (30 % solution) 9:1 (50 ml). After the mixture had been stirred for 10 min., 1 N hydrochloric solution was added (to reach pH 7) and the solvents were evaporated off under reduced pressure. The residue (9.0 g) was diluted with water and worked up as described above. Flash chromatography gave the four diastereoisomeric t-butyl-4-hydroxy-5-sulphinyl decanoates 11 in pure form and in 68 % overall yield. (+)-(4S,5R,R_S)-11: 1.8 % yield; (+)-(4R,5R,R_S)-11: 7.4 % yield; (+)-(4R,5S,R_S)-11: 34 % yield; (+)-(4S,5S,R_S)-11:25 % yield.

Benzylation of t-butyl 4-hydroxy-5-(4-methylphenyl)sulphinyl decanoates (11)

A solution of (+)-(4R,5S,R_S)-4-hydroxy decanoate 11 (2.50 mmol) in DMF (6 ml) was dropped into a suspension of benzyl bromide (25.0 mmol) and oil free sodium hydride (5.0 mmol) in the same solvent (6 ml) at -10° C. After stirring at room temperature for 10 min., the mixture was poured into ice/water (80 ml) and extracted with ether (3 x 100 ml). The collected organic layers were dried over anhydrous sodium sulphate, the solvent was removed under reduced pressure and the residue was flash chromatographed (toluene/ethyl acetate 85:15) to give the (+)-(4R,5S,R_S)-t-butyl 4-benzyloxy-5-(4-methylphenyl)sulphinyl decanoate (12) in 88 % yield; m.p. 105-107° C (from n-pentane); (Found C 69.8, H 8.6, $C_{28}H_{40}O_4S$ requires C 71.2, H 8.5); $[\alpha]_D^{20}$ +59° (c 0.96 in $CHCl_3$); ν_{max} 1725, 1035, 1010 cm^{-1}; ^1H NMR ($CDCl_3$), δ:0.78 (3H, t, J 6.9 Hz, H_3-10), 0.9-1.4 (6H, m, H_2-7,-8,-9), 1.43 (9H, s,t-Bu), 1.56 and 1.70 (2H, m, H_2-6), 2.02 and 2.14 (2H, m, H_2-3), 2.38 (3H, br s, Me arom.), 2.40 (2H, m, H_2-2), 2.68 (1H, ddd, J 7.6, 4.9 and 3.7 Hz, H-5), 3.75 (1H, ddd, J 9.0, 3.9 and 3.7 Hz, H-4), 4.47 and 4.54 (2H, d, J 11.6 Hz, OCH_2-4), 7.2-7.4 (9H, m, Ph).
Similarly, starting from the diastereoisomeric (+)-(4S,5S,R_S)-11, the (+)-(4S,5S,R_S)-t-butyl 4-benzyloxy-5-(4-methylphenyl)sulphinyl decanoate (12) was obtained in 85 % yield; m.p. 74-75° C (from di-isopropyl ether/n-pentane); (Found C 69.7, H 8.4, $C_{28}H_{40}O_4S$ requires C 71.2, H 8.5); $[\alpha]_D^{20}$ +50° (c 0.95 in $CHCl_3$); ν_{max} (nujol) 1720, 1030, 1010 cm^{-1}; ^1H NMR ($CDCl_3$), δ:0.75 (3H, t, J 7.0 Hz, H_3-10), 0.8-1.8 (6H, m, H_2-7,-8,-9), 1.43 (9H, s, t-Bu), 1.43 and 1.79 (2H, m, H_2-6), 1.83 and 1.92 (2H, m, H_2-3), 2.33 (2H, m, H_2-2), 2.41 (3H, br s, Me arom.), 2.62 (1H, ddd, J 6.2, 5.5 and 5.5 Hz, H-5), 3.73 (1H, ddd, J 8.0, 6.2 and 3.7 Hz, H-4), 4.52 and 4.68 (2H, d, J 11.1 Hz, OCH_2-4), 7.2-7.5 (9H, m, Ph).

Attempted benzylation of (4S*, 5S*, R_S*)-ethyl 4-hydroxy-5-(4-methylphenyl)sulphinyl decanoate (11'). The procedure described above was employed and after flash chromatography the (4S*, 5S*, R_S*)-5-(4-methylphenyl)sulphinyl decan-4-olide (18) was exclusively obtained. ν_{max} (nujol) 1175, 1030 cm^{-1}; ^1H NMR ($CDCl_3$), δ:0.74 (3H, t, J 7.0 Hz, H_3-10), 0.8-1.2 (6H, m, H_2-7,-8,-9), 1.31 and 1.83 (2H, m, H_2-6), 2.01 and 2.35 (2H, m, H_2-3), 2.42 (3H, br s, Me arom.), 2.58 and 2.62 (2H, m, H_2-2), 2.71 (1H, ddd, J 7.7, 5.7 and 4.7 Hz, H-5), 4.88 (1H, ddd, J 8.9, 7.7 and 6.5, H-4), 7.34 and 7.48 (4H, m, Ph).

Deoxygenation of the sulphinyl group of t-butyl 4-benzyloxy-5-sulphinyl decanoates 12

Trifluoroacetic anhydride (1.1 ml, 7.6 mmol) was added via a syringe into a vigorously stirred solution of (+)-(4R,5S,R_S)-4-benzyloxy-5-sulphinyl decanoate 12 (0.72 g, 1.53 mmol) and of sodium iodide (0.68 g, 4.58 mmol) in acetone (50 ml) maintaining the temperature below -40° C. After stirring the reaction for 10 min. at -20° C, excess of saturated aqueous sodium sulphite and of sodium hydrogen carbonate were added dropwise in that order until no more iodine was present and until CO_2 evolution had ceased respectively. Acetone was evaporated off under reduced pressure and the mixture was extracted with ether (3 x 100 ml). The organic layers were dried over anhydrous sodium sulphate and the solvent was evaporated under reduced pressure. The residue was flash chromatographed (n-hexane/di-isopropyl ether 95:5) on silica gel and the (-)-(4R,5S)-t-butyl 4-benzyloxy-5-(4-methylphenyl)thio decanoate (13) was isolated as an oil in 88 % yield; $[\alpha]_D^{20}$ -4.1° (c 1.15 in $CHCl_3$); ν_{max} (film) 2920, 1730 cm^{-1}; ^1H NMR ($CDCl_3$), δ:0.88 (3H, t, J 6.8 Hz, H_3-10), 1.1-1.7 (8H, m, H_2-6,-7,-8,-9), 1.41 (9H, s, t-Bu), 1.88 and 1.99 (2H, m, H_2-3), 2.31 (3H, br s, Me arom.), 2.31 and 2.33 (2H, m, H_2-2), 3.15 (1H, ddd, J 9.0, 4.5 and 4.0 Hz, H-5), 3.56 (1H, ddd, J 8.5, 4.0 and 3.9 Hz, H-4), 4.43 and 4.56 (2H, d, J 11.2 Hz, OCH_2-4), 7.0-7.4 (9H, m, Ph).
Similarly, starting from the diastereoisomeric (+)-(4S,5S,R_S)-12, the (-)-(4S,5S)-t-butyl 4-benzyloxy-5-(4-methylphenyl)thio decanoate (13) was isolated in 83 % yield as a sticky liquid; $[\alpha]_D^{20}$ -30°(c 0.90 in $CHCl_3$); ν_{max} (film) 2960, 1730 cm^{-1}; ^{1} NMR ($CDCl_3$), δ:0.88 (3H, t, J 6.9 Hz, H_3-10), 1.2-1.5 (6H, m, H_2-7,-8,-9), 1.41 (9H, s, t-Bu), 1.76 and 1.82 (2H, m, H_2-6), 1.80 and 2.13 (2H, m, H_2-3), 2.18 and 2.33 (2H, m, H_2-2), 2.33 (3H, br s, Me arom.), 3.18 (1H, ddd, J 9.7, 3.9 and 3.3 Hz, H-5), 3.43 (1H, ddd, J 9.7, 3.3 and 2.8 Hz, H-4), 4.32 and 4.44 (2H, d, J 11.6 Hz, OCH_2-4), 7.0-7.3 (9H, m, Ph).

Deoxygenation of the sulphinyl group of t-butyl 4-hydroxy-5-sulphinyl decanoates (11)

A solution of trifluoroacetic acid (2.6 g, 12.2 mmol) in acetone (30 ml) was dropped into a vigorously stirred solution of (+)-(4R,5S,R_S)-4-hydroxy-5-sulphinyl decanoate (11) (2.34 g, 6.12 mmol) and of sodium iodide (2.75 g, 18.4 mmol) in the same solvent (55 ml) mantaining the temperature below -50° C. The reaction mixture was left for 10 min., during which time the temperature rose to -20° C. Excess of a saturated aqueous solution of sodium sulphite was added until the colour of iodine had faded, then an excess of a saturated aqueous solution of sodium hydrogen carbonate was added. Acetone was evaporated off under reduced pressure and the mixture was extracted with ether (3 x 200 ml). The collected extracts were evaporated under reduced pressure. At this stage TLC analyses (n-hexane/ethyl ether 9:1) revealed the presence of two products the lower R_f one corresponding to the desired (4R,5S)-t-butyl-4-hydroxy-5-(4-methylphenyl)thio decanoate (19), the higher R_f one being probably the trifluoroacetyl ester of (4R,5S)-19. The row mixture was therefore diluited with THF (30 ml) and 1.0 N sodium hydroxide was added (8 ml). After stirring 30 min. at room temperature, the solvent was evaporated under reduced pressure, water was added (20 ml) and the reaction product was extracted with ether (3 x 100 ml). The collected organic phases were dried over anhydrous sodium sulphate and TLC analyses at this stage showed the higher R_f product had disappeared.

The solvent was evaporated under reduced pressure and the residue was flash chromatographed (n-hexane/ethyl ether 85:15) to give the (4R,5S)-t-butyl 4-hydroxy-5-(4-methylphenyl)thio decanoate (19) in 82 % yield as a viscous oil; $[\alpha]^{20}_{365}$ +23° (c 1.0 in $CHCl_3$); ν_{max} (film)

3425, 1730 cm^{-1}; ^1H NMR ($CDCl_3$), δ:0.88 (3H, t, J 6.8 Hz, H_3-10), 1.2-1.5 (6H, m, H_2-7,-8,-9), 1.40 (9H, s, t-Bu), 1.50 and 1.67 (2H, m, H_2-6), 1.75 (2H, m, H_2-3), 2.32 (3H, br s, Me arom.), 2.33 and 2.40 (2H, m, H_2-2), 2.50 (1H, d, J 5.6 Hz, OH-4), 3.08 (1H, ddd, J 9.5, 3.8 and 3.5, H-5), 3.62 (1H, ddd, J 7.2, 5.9 and 3.5 Hz, H-4), 7.10 and 7.33 (4H, m, Ph).
Similarly, starting from the diastereoisomeric (+)-(4S,5S,R_S)-11, the (-)-(4S,5S)-t-butyl 4-hydroxy-5-(4-methylphenyl)thio decanoate (19) was isolated in 70 % yield as a viscous oil; $|\alpha|_D^{20}$ -20° (c 0.95 in $CHCl_3$); ν_{max} (film) 3425, 1730 cm^{-1}; ^1H NMR ($CDCl_3$), δ:0.89 (3H, t, J 6.8 Hz, H_3-10), 1.2-1.4 (6H, m, H_2-7,-8,-9), 1.43 (9H, s, t-Bu), 1.47 and 1.68 (2H, m, H_2-6), 1.72 and 1.91 (2H, m, H_2-3), 2.32 (3H, br s, Me arom.), 2.36 and 2.40 (2H, m, H_2-2) 2.85 (1H, d, J 4.5 Hz, OH-4), 2.91 (1H, ddd, J 9.1, 5.8 and 3.6 Hz, H-5), 3.54 (1H, ddd, J 9.0, 5.8 and 3.0 Hz, H-4), 7.10 and 7.33 (4H, m, Ph).

Deoxygenation of the sulphinyl group of ethyl 4-hydroxy-5-sulphinyl decanoates 11'

When (4S*, 5R*, R_S*)-ethyl 4-hydroxy-5-(4-methylphenyl)sulphinyl decanoate (11') was reacted and worked up as described above, before the basic treatment with 1.0 N sodium hydroxyde, only the (4S*, 5R*)-ethyl 4-trifluoroacetyloxy-5-(4-methylphenyl) sulphinyl decanoate was present. ^1H NMR ($CDCl_3$), δ:0.94 (3H, t, J 7.0 Hz, H_3-10), 1.0-1.8 (8H, m, H_2-6,-7,-8,-9), 1.24 (3H, t, J 7.0 Hz, CH_3CH_2), 1.9-2.4 (4H, m, H_2-2 and -3), 2.34 (3H, br s, Me arom.), 3.13 (1H, m, H-5), 4.10 (2H, q, J 7.0 Hz, OCH_2), 5.15 (1H, m, H-4), 7.12 and 7.33 (4H, m, Ph). On mild basic treatment of this product, hydrolyses of the trifluoroacetyl group occurred, but the exclusive isolated product was the (4S*, 5R*)-5-(4-methylphenyl)thio decan-4-olide (21) (which formed through an intramolecular attach of the free hydroxyl group on the ethyl ester or on the corresponding free acid formed in the basic treatment).
When the (4S*, 5S*, R_S*)-ethyl 4-hydroxy-5-(4-methylphenyl)sulphinyl decanoate (11) was similarly reacted and worked up, the corresponding (4S*, 5S*)-5-(4-methylphenyl)thio decanoate (21) was isolated along with the (4S*, 5S*) ethyl 4-hydroxy-5-(4-methylphenyl)thio decanoate (19'): ^1H NMR ($CDCl_3$), δ:0.90 (3H, t, J 6.8 Hz, H_3-10), 1.24 (3H, t, J 7.0 Hz, CH_3-CH_2), 1.3-2.0 (10H, m, H_2-3,-6,-7,-8,-9), 2.32 (3H, br s, Me arom.), 2.3-2.6 (2H, m, H_2-2), 2.84 (1H, d, J 4.5 Hz, OH-4), 2.92 (1H, m, H-5), 3.54 (1H, m, H-4), 4.12 (2H, q, J 7.0 Hz, OCH_2), 7.09 and 7.33 (4H, m, Ph). This last product however was not stable and tended to cyclize to the corresponding decan-4-olide on standing also at 0° C. The same occurred when the (4R*, 5S*, R_S*)-ethyl 4-hydroxy-5-(4-methylphenyl)sulphinyl decanoate (11') was similarly processed.

Benzylation of t-butyl 4-hydroxy-5-(4-methylphenyl)thio decanoate 19

A solution of the (4R,5S)-4-hydroxydecanoate 19 (2.00 g, 5.46 mmol) in DMF (2.0 ml) was dropped into a stirred suspension of benzyl bromide (8.17 ml, 5.46 mmol) and of oil free sodium hydride (10.92 mmol) in the same solvent (5.0 ml) maintaining the temperature below 10° C. After the reaction had been stirred for 10 min. at room temperature, the mixture was poured into ice/water (60 ml) and extracted with ether (3 x 100 ml). The collected organic phases were dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. Flash chromatography (n-hexane/di-isopropyl ether 95:5) of the residue gave the (-)-(4R,5S)-t-butyl 4-benzyloxy-5-(4-methylphenyl)thio decanoate (13) in 10 % yield and the (-)-(4R,5S)-5-(4-methylphenyl)thio -4-decanolide (21) in 88 % yield as a sticky liquid; $|\alpha|_D^{20}$ -34° (c 1.0 in $CHCl_3$); ν_{max} (film) 1775 cm^{-1}; ^1H NMR ($CDCl_3$), δ:0.90 (3H, t, J 6.9 Hz, H_3-10), 1.2-1.8 (8H, m, H_2-6,-7,-8,-9), 2.04 and 2.37 (2H, m, H_2-3), 2.33 (3H, br s, Me arom.), 2.53 and 2.56 (2H, m, H_2-2), 3.03 (1H, ddd, J 9.2, 7.4 and 3.6 Hz, H-5), 4.48 (1H, ddd, J 7.8, 7.4 and 7.0 Hz, H-4), 7.11 and 7.34 (4H, m, Ph).
When diastereoisomeric (4S,5S)-19 was similarly reacted, the (-)-(4S,5S)-t-butyl 4-benzyloxy-5-(4-methylphenyl)thio decanoate (13) was isolated in 26 % yield and the (-)-(4S,5S)-5-(4-methylphenyl)thio-4-decanolide (21) was isolated in 55 % yield as a viscous oil; $|\alpha|_D^{20}$ -27° (c 1.05 in $CHCl_3$); ν_{max} (film) 1775 cm^{-1}; ^1H NMR ($CDCl_3$), δ:0.89 (3H, t, J 6.9 Hz, H_3-10), 1.2-1.8 (8H, m, H_2-6,-7,-8,-9), 2.16 and 2.28 (2H, m, H_2-3), 2.33 (3H, br s, Me arom.), 2.55 and 2.58 (2H, m, H_2-2), 3.22 (1H, ddd, J 9.6, 4.0 and 3.8 Hz, H-5), 4.62 (1H, ddd, J 7.4, 7.4 and 4.0 Hz, H-4), 7.12 and 7.33 (4H, m, Ph).

Saponification of the t-butyl ester of 4-benzyloxy-5-tolylthio decanoates 13

A solution of (4R,5S)-t-butyl 4-benzyloxy-5-(4-methylphenyl)thio decanoate (13) (0.48 g, 1.0 mmol) in a mixture of acetic acid/water/1,4-dioxane 8:2:5 (5 ml) was refluxed under argon for ten hours. The solvent was evaporated off under reduced pressure, benzene (3 x 5 ml) was added to the residue and then evaporated to remove any residual acetic acid. The residue was flash chromatographed (n-hexane/ethyl ether/acetic acid 60:20:0.25) to give in 84 % yield the oily (+)-(4R,5S)-4-benzyloxy-5-(4-methylphenyl)thio decanoic acid (14); $|\alpha|_D^{20}$ +14.9° (c 1.15 in $CHCl_3$); ν_{max} (film) 3500-2500, 1710 cm^{-1}; ^1H NMR ($CDCl_3$), δ:0.88 (3H, t, J 6.8 Hz, H_3-10), 1.2-1.8 (8H, m, H_2-6,-7,-8,-9), 1.94 and 2.05 (2H, m, H_2-3), 2.32 (3H, br s, Me arom.), 2.38 and 2.40 (2H, m, H_2-2), 3.19 (1H, ddd, J 8.5, 4.5 and 4.0 Hz, H-5), 3.59 (1H, ddd, J 8.5, 4.0 and 4.0 Hz, H-4), 4.41 and 4.55 (2H, d, J 11.1 Hz, OCH_2-4), 7.0-7.4 (9H, m, Ph).
When the diastereoisomeric (4S,5S)-t-butyl 4-benzyloxy-5-tolylthio decanoate (13) was reacted in a similar manner, the (-)-4-benzyloxy-5-(4-methylphenyl)thio decanoic acid (14) was obtained as a viscous oil in 89 % yield: $|\alpha|_D^{20}$ -44.0° (c 0.70 in $CHCl_3$); ν_{max} (film) 3500-2500, 1710 cm^{-1}; ^1H NMR ($CDCl_3$), δ:0.89 (3H, t, J 6.8 Hz, H_3-10), 1.3-1.8 (8H, m, H_2-6,-7,-8,-9), 1.82 and 2.19 (2H, m, H_2-3), 2.31 and 2.43 (2H, m, H_2-2), 2.35 (3H, br s, Me arom.), 3.21 (1H, ddd, J 10.0, 3.5 and 3.0 Hz, H-5), 3.44 (1H, ddd, J 10.0, 3.0 and 2.5 Hz, H-4), 4.27 and 4.45 (2H, d, J 11.6 Hz, OCH_2-4), 7.1-7.3 (9H, m, Ph).

Table 2.-Some connectivities (%) established by NOE difference experiments in $CDCl_3$ for (4R,5R)-16 and (4S,5R)-16.

Proton irradiated	(4R,5R)-16(cis)	(4S,5R)-16(trans)
H-2α	OCH$_a$-4(0.5),OCH$_b$-4(0.5).	H-4α(0.5).
H-2β	H-5β(0.5).	H-5β(1.5),OCH$_a$-4(0.5),OCH$_b$-4(0.5).
H-3α	H-4β(2.5)[a],OCH$_a$-4(1.5)[a],OCH$_b$-4(1)[a].	H-4α(7),H-5β(2),H-6a(1),H-6b(1),OCH$_a$-4(2),OCH$_b$-4(1.5).
H-3β	H-4β(3.5)[a],H-5β(3.5)[a].	
H-4	H-3α(2.5),H-3β(2.5),H-5β(7.5),H-6a(1.5), H-6b(1.5),OCH$_a$-4(1),OCH$_b$-4(3.5).	H-2α(0.5),H-3α(2.5),H-3β(2.5),H-5β(2.5),H-6a(1.5), H-6b(1.5),OCH$_a$-4(2),OCH$_b$-4-(3).
H-5β	H-2β(0.5),H-3β(3.5),H-4β(7.5),H-6α(2.5),H-6b(2.5).	H-2β(2),H-3β(0.5)[a],H-4α(2.5),H-6a(1.5),H-6b(1.5).
H_2-6	H-4β(2.5)[a],H-5β(7)[a],OCH$_a$-4(0.3)[a],OCH$_b$-4(0.5)[a].	H-3α(0.5)[a],H-4α(5),H-5β(6).
OCH$_a$-4	H-2α(0.5),H-2β(0.5),H-3α(1),H-4β(1).	H-2β(0.2),H-3β(0.5),H-4α(2).
OCH$_b$-4	H-3α(1),H-4β(2.5).	H-3β(0.5),H-4α(3).

[a] In acetone-d6.

Lactonization of 4-benzyloxy-5-tolylthio decanoic acids 14

To a solution of the (4R,5S)-4-benzyloxy-5-tolylthio decanoic acid (14) (258 mg, 0.64 mmol) in methylene chloride/nitromethane (1:1 mixture, 8 ml), trimethyloxonium tetrafluoroborate (172 mg, 1.16 mmol) was added in one portion under argon and at -5° C. Stirring was maintained for 10 min. after reaching room temperature (10 min.). Solvent was removed under reduced pressure at 0° C and the crude sulphonium salt was dissolved in DMF (4 ml) and potassium t-butoxide (87 mg, 0.774 mmol) was added at -45° C. The temperature was left to raise at 10° C, stirring was continued for further 10 min, then a saturated aqueous solution of ammonium chloride (10 ml) and of water (30 ml) were added at -20° C. The reaction products were extracted with ether (3 x 40 ml), the organic layers were collected, dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. The residue was flash chromatographed (n-hexane/ethyl acetate 40:17) and the cis (4R,5R)-4-benzyloxy decan-5-olide (16) was isolated as an oil in 80 % yield; (Found C 72.8, H 8.5, $C_{17}H_{24}O_3$ requires C 73.9, H 8.7); $[\alpha]_D^{20}$ +15° (c 0.60 in $CHCl_3$); ν max (film) 1730 cm^{-1}; ^1H and ^{13}C NMR data are reported in the Tables 1 and 2.
When the diastereoisomeric trans (4S,5S)-4-benzyloxy-5-tolylthio decanoic acid (14) was similarly reacted, flash chromatography (n-hexane/ethyl acetate 40:10) of the row reaction products gave the (+)-(4S,5R)-4-benzyloxy-5-decan-5-olide (16) in 84 % yield as an oil; $[\alpha]_D^{20}$ +107° (c 0.64 in CCl_4) ($[\alpha]_D^{20}$ +106° c 0.7 in CCl_4 ref 19); ν_{max} (film) 1735 cm^{-1}; ^1H and ^{13}C NMR data are reported in the Tables 1 and 2.

Reductive desulphurization of 5-tolylthio-decan-4-olides 21

Raney-nickel (W2, 400 mg) was added to a solution of the (4R,5S)-5-(4-methylphenyl)thio-decan-4-olide (21) in ethanol (6 ml). The mixture was refluxed for 20 min., then filtered and nickel was washed with ether (3 x 20 ml). The collected organic layers were evaporated under reduced pressure and the residue was flash chromatographed (n-pentane/ethyl ether 60:40) to give (-)-(5)-decan-4-olide (22) in 91 % yield; $[\alpha]_D^{20}$ -30° (c 1.05 in $CHCl_3$); ν max (film) 1775 cm^{-1}; ^1H NMR ($CDCl_3$), δ :0.89 (3H, t, J 6.9 Hz, H_3-10), 1.2-1.7 (8H, m, H_2-6,-7,-8,-9), 1.61 and 1.74 (2H, m, H_2-5) 1.85 and 2.32 (2H, m, H_2-3), 2.50 and 2.56 (2H, m, H_2-2), 4.49 (1H, dddd, J 8.0, 7.8, 6.4 and 5.3 Hz, H-4); ^{13}C NMR ($CDCl_3$), δ:14.06 (q, C-10), 22.54 (t, C-9), 25.20 (t, C-6), 28.03 (t, C-3), 28.89 (t, C-2), 29.01 (t, C-7), 31.67 (t, C-8), 35.59 (t, C-5), 81.10 (d, C-4), 177.36 (s, C-1).
When the diastereoisomeric (4S,5S)-21 was similarly reacted the (+)-(R)-decan-4-olide (22) was obtained in 78 % yield; $[\alpha]_D^{20}$ +31° (c 1.2 in $CHCl_3$) other physical data were identical with those reported above.

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